

OK



Libertad y Orden

REPÚBLICA DE COLOMBIA
DIVISIÓN DE PROPIEDAD INDUSTRIAL

PI
PATENTE DE INVENCIÓN

PC
Industria y Comercio
SUPERINTENDENCIA

06-53412

TITULO: NUEVOS ANTAGONISTAS DEL RECEPTOR MUSCARÍNICO M₂ DE ACETILCOLINA.

CIP: A61K31/445, C07D211/56, A61P11/06

SOLICITANTE: GLAXO GROUP LIMITED

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra.

APODERADO: CARLOS R. OLARTE

BOGOTÁ, Junio 1 de 2006

Lpdko

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

03-07-2006

1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 S LICITANTE (71)	Nombre: <u>GLAXO GROUP LIMITED</u> Dirección: <u>Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN</u> Nacionalidad o Domicilio: <u>BRITANICA</u> Lugar de Constitución: <u>INGLATERRA</u> Teléfono: _____ Fax: _____ E-mail: _____		IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE APODERADO	Nombre: <u>CARLOS R. OLARTE</u> Dirección: <u>World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10</u> Teléfono: <u>601-7700</u> Fax: <u>601-7799</u> E-mail: <u>office@olarteraisbeck.com</u>		IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>79.782.747 Btá</u> <u>TP 74.295</u>
4 INVENTOR (ES) (72)	Nombre: <u>(1) JAKOB BUSCH-PETERSEN; (2) JIAN JIN; (3) MICHAEL R. PALOVICH; (4) WEI FU</u> Dirección: <u>(1,2 y 4) 709 Swedeland Road, King of Prussia, PA 19406, E.U.A.; (3) 1250 South Collegeville Road Collegeville, PA 19426, E.U.A.</u> Nacionalidad o Domicilio: <u>(1) Danes; (2 y 4) Chino; (3) Estadounidense</u>		
5 PCT (86) Solicitud Internacional No. <u>PCT/US2004/040668</u> Fecha <u>Diciembre 3, 2004</u> Publicación Internacional No. <u>WO 2005/055941</u> Fecha <u>Junio 23, 2005</u>			
6 Título (54) <u>NUEVOS ANTAGONISTAS DEL RECEPTOR MUSCARÍNICO M. DE ACETILCOLINA.</u>			
7 Clasificación Internacional (51) <u>A61K 31/445, C07D 211/56, A61P 11/06</u>			
8 Prioridad SI ☒ N ☐	(33) País de Origen <u>US</u>	(32) Fecha <u>Diciembre 3, 2003</u>	(31) Número de Solicitud <u>60/526,766</u>
9 Comprobante de pago No. <u>06 -41,020</u> Fecha <u>Junio 1, 2006</u>			

10

ANEX S

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☐

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso.

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

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

☒

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

☐

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

☐

Traducción del examen preliminar internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

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

☐

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

☐

Arte final 12 x 12.

☐

De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

☒

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

☒

Otros. Búsqueda Internacional

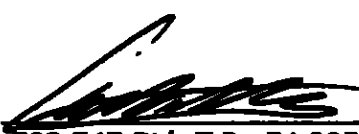
11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: 

C.C. 79.782.747 Btá T.P. 74.295

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

B
3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-053412- -00000-0000
Fec: 2008-08-02 18:45:24 Dep. 2020 NUECREACIONES
Tra. 11 PATENTENVO
Evo: 370 FABENACIONALI
Act 411 PRESENTACION Folios: 107

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 41,020
FECHA : JUNIO 1 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARTE RAISBESR	CONSIGNACION	BANCO POPULAR	050-00110-6	52332391	31/05/2006	3,738,000.00

***** CONCEPTO *****

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. _____

24
4

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

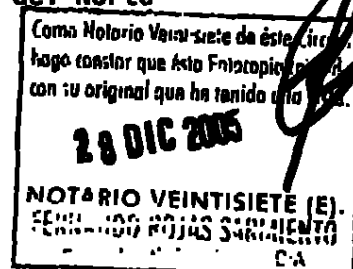
Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
 2. ha sido firmado por James Kerr Milligan
 3. Quien ejerce funciones de Notario público
 4. Lleva el sello del Notario público
- CERTIFICADO
5. En Londres
 6. El 14 agosto 2003
 7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
 8. No. G229474
 9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
 10. Firma legible de J. Garbrah- Por el Secretario de Estado



Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C

Marlen Neira C
MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Ingle
Resolución No. 2117 del 7 O.

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

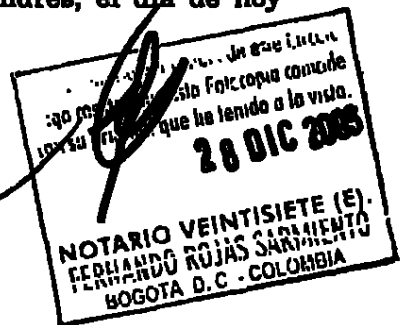
C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**GLAXO GROUP LIMITED**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en **Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra**;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debidamente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 8 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy vece de agosto del año dos mil tres.



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

2. Has been signed by James Kerr Milligan
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

Certified/Attesté
6. the/le 14 August 2003

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

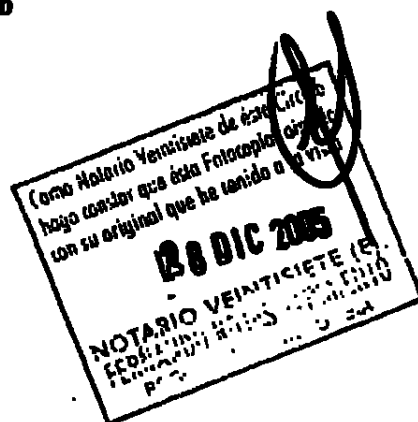
8. Number/sous No **G229474**

9. Stamp:
timbre:
10. Signature: J. Garbrah



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

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



OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

domiciliado en

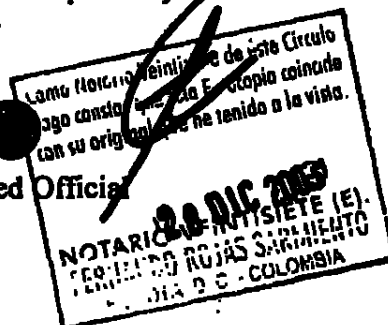
Glaxo Group Limited
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la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

Signature/Firma:


Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City/Country/Ciudad/Pais: Brentford, Middlesex, England



(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
23 June 2005 (23.06.2005)

PCT

(10) International Publication Number
WO 2005/055941 A2

(51) International Patent Classification⁷: A61K
(21) International Application Number:
PCT/US2004/040668
(22) International Filing Date: 3 December 2004 (03.12.2004)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
60/526,766 3 December 2003 (03.12.2003) US

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KR, 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).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations 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, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (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 patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations 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, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (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 patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— of inventorship (Rule 4.17(iv)) for US only

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.

(71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BUSCH-TERSEN, Jakob [DK/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). JIN, Jian [CN/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). MOORE, Michael, Lee [US/US]; 417 South Jackson Street, 1250 South Collegeville Road, Collegeville, PA 19426 (US). RIVERO, Ralph, A. [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). SHI, Dongchuan [CN/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US). WANG, Feng [CN/US]; 709 Swedeland Road, Swedeland Road, King of Prussia, PA 19406 (US). WANG, Yonghui [CN/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US).

(74) Agents: SIMON, Soma, G. et al.; GlaxoSmithKline, Corporate Intellectual Property, UW 2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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

(54) Title: NOVEL M₃ MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) Abstract: Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.

WO 2005/055941 A2

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Novel M₃ Muscarinic Acetylcholine Receptor Antagonists**FIELD OF THE INVENTION**

This invention relates to novel derivatives of cyclic quaternary ammonium salts, pharmaceutical compositions, processes for their preparation, and use thereof in treating M₃ muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M₁-M₅, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M₃ mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M₂ muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M₃ mAChRs {Costello, Evans, et al. 1999 72 /id} {Minette, Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M₃ mAChR-mediated hypermotility {Opřins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through

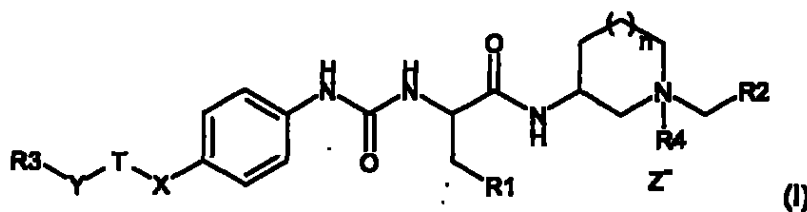
increased stimulation of M₃ mAChRs (Hegde & Eglen 1999 251 /id). Thus the identification of subtype-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M₃ mAChRs.

Conditions associated with an increase in stimulation of M₃ mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula I



wherein

n is 0 or 1;

When X is nitrogen or oxygen, Y is nothing;

When Y is nitrogen or oxygen, X is nothing;

T is a sulfonyl group (SO₂) or carbonyl group (CO) ;

When T=CO, X is oxygen or nitrogen;

Z' is selected from the group consisting of halo, CF₃COO⁻, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, C₃-C₈ alkenyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C₁-C₃ lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C₁-C₈ branched or unbranched alkyl,

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C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl and phenyl C₁-C₃ lower alkyl.

R₂ is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C₁-C₃ lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl and C₃-C₈ cycloalkyl lower alkyl and heterocycle rings;

R₃ is selected from the group consisting of an unsubstituted or substituted following group: phenyl, phenyl C₁-C₈ lower alkyl, thiophenyl, thiophenyl C₁-C₈ lower alkyl, furanyl, furanyl C₁-C₆ lower alkyl, pyridinyl, pyridinyl C₁-C₆ lower alkyl, imidazolyl, imidazolyl C₁-C₆ lower alkyl, naphthyl, naphthyl C₁-C₆ lower alkyl, quinolinyl, quinolinyl C₁-C₆ lower alkyl, indolyl, indolyl C₁-C₆ lower alkyl, benzothiophenyl, benzothiophenyl C₁-C₆ lower alkyl, benzofuranyl, benzofuranyl C₁-C₆ lower alkyl, benzimidazolyl, benzimidazolyl C₁-C₆ lower alkyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl C₁-C₈ lower alkyl, or C₃-C₈ alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, phenoxy, phenyl C₁-C₃ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl, phenyl C₁-C₃ lower alkyl, thiophenyl, thiophenyl C₁-C₃ lower alkyl, furanyl, furanyl C₁-C₃ lower alkyl, pyridinyl, pyridinyl C₁-C₃ lower alkyl, naphthyl, naphthyl C₁-C₃ lower alkyl, quinolinyl, quinolinyl C₁-C₃ lower alkyl, indolyl, indolyl C₁-C₃ lower alkyl, benzothiophenyl, benzothiophenyl C₁-C₃ lower alkyl, benzofuranyl, benzofuranyl C₁-C₃ lower alkyl, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ and NHCONHR₆;

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R4 is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl.

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DETAILED DESCRIPTION

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds that release the active parent drug according to Formula I - *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the *cis* (Z) and *trans* (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

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The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in Eur. J. Biochem., 158, 9 (1984).

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The term "C₁-C₈ alkyl" and "C₁-C₈ alkyl" is used herein includes both straight or branched chain radicals of 1 to 6 or 8 carbon atoms. By example this term includes, but is not limited to methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl,

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sec-butyl, isobutyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl and the like. "Lower alkyl" has the same meaning as C₁-C₈ alkyl.

Herein "C₁-C₈ alkoxy" includes straight and branched chain radicals of the likes of -O-CH₃, -O-CH₂CH₃, and the n-propoxy, isopropoxy, n-butoxy, 5 sec-butoxy, isobutoxy, *tert*-butoxy, pentoxy, and hexoxy, and the like.

"C₃-C₈-cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane, and the like.

"Halogen" or "halo" means F, Cl, Br, and I.

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The preferred compounds of Formula I include those compounds wherein:

n is 0 or 1;

When X is nitrogen or oxygen, Y is nothing;

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When Y is nitrogen or oxygen, X is nothing;

T is sulfonyl group SO₂ or carbonyl group CO;

R₁ is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, C₃-C₈ alkenyl, or unsubstituted or substituted phenyl C₁-C₃ lower alkyl; wherein, 20 when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl and phenyl C₁-C₃ lower alkyl; or R₂ and R₃ is -(CH₂)_j-, or -(CH₂)_j-Phenyl-(CH₂)_j-, wherein, j is an integer 25 from 3 to 8; i is an integer from 1 to 3.

R₂ is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C₁-C₈ alkoxy, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl, phenyl C₁-C₃ lower alkyl, phenylcarbonyl;

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R₃ is selected from the group consisting of an unsubstituted or substituted following group: phenyl C₁-C₆ lower alkyl, thiophenyl C₁-C₆ lower

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- alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzimidazolyl C1-C6 lower alkyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl C₁-C₆ lower alkyl, or C₃-C₈ alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, phenoxy, phenyl C₁-C₃ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl, phenyl C₁-C₃ lower alkyl, thiophenyl, thiophenyl C₁-C₃ lower alkyl, furanyl, furanyl C₁-C₃ lower alkyl, pyridinyl, pyridinyl C₁-C₃ lower alkyl, naphthyl, naphthyl C₁-C₃ lower alkyl, quinolinyl, quinolinyl C₁-C₃ lower alkyl, indolyl, indolyl C₁-C₃ lower alkyl, benzothiophenyl, benzothiophenyl C₁-C₃ lower alkyl, benzofuranyl, benzofuranyl C₁-C₃ lower alkyl, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ and NHCONHR₆;

- R₄ is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, or phenyl C₁-C₃ lower alkyl;

Even more preferred are those compounds where:

- n is 1;
 X is nitrogen or oxygen, Y is nothing;
 T is sulfonyl group SO₂;
 Z⁻ is selected from the group consisting of I⁻, Br⁻, Cl⁻, F⁻, CF₃COO⁻, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;
 R₄ is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl,

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R3 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C1-C8 branched or unbranched alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl C1-C6 lower alkyl, or C3-C8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C1-C8 alkoxy, phenoxy, phenyl C1-C3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C1-C8 branched or unbranched alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6 and NHCOR6;

R2 is selected from the group consisting of hydroxy, amino, halo, cyano, trifluoromethyl, C1-C8 alkoxy, C1-C8 alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

R1 is selected from the group consisting of C1-C8 branched or unbranched alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl lower alkyl, or C3-C8 alkenyl;

or R1 and R2 is $-(CH_2)_r-$, or $-(CH_2)_r$ -Phenyl- $(CH_2)_r-$.

The preferred compounds are selected from the group consisting of: *N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-{[(4-[(2,2,2-trifluoroethyl)sulfonyl]oxy)phenyl]amino}carbonyl}-L-tyrosinamide trifluoroacetate;

- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(5-methyl-2-thienyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 5 {[(4-methyl-2-thienyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(8-quinoliny)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- 10 *N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(3,4-bis(methyloxy)phenyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-
 tyrosinamide trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(2-bromophenyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 15 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(4-fluorophenyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 20 {[(phenylsulfonyl)oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(5-bromo-2-thienyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 25 {[(3-thienylsulfonyl)oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(2,5-dimethyl-3-thienyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl)-*N*-[[4-
 30 {[(2,2,2-trifluoroethyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;



- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(5-methyl-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(4-methyl-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(5-chloro-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(methanesulfonyl)oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(propylsulfonyl)oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[4-[(2-(acetamido)-4-methyl-1,3-thiazol-5-yl)sulfonyl]oxy]phenyl]amino]carbonyl]-*N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(4-(phenylsulfonyl)-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(5-chloro-2,1,3-benzoxadiazol-4-yl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(2-naphthalenylsulfonyl)oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[4-[(2,2,2-trifluoroethyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[4-[(5-methyl-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[4-[(4-methyl-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;

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- N*-[[(4-[(4-cyanophenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*L*-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(trifluoromethyl)phenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*L*-tyrosinamide
5 trifluoroacetate;
N-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(5-(3-isoxazolyl)-2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*L*-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(3-
10 fluorophenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*L*-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfonyl]oxy)phenyl]amino]carbonyl]-*L*-tyrosinamide trifluoroacetate;
15 *N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(5-methyl-4-isoxazolyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*L*-tyrosinamide trifluoroacetate;
N-[[(4-[(3,5-dimethyl-4-isoxazolyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*L*-tyrosinamide
20 trifluoroacetate;
N-[[(4-[(2,4-dichlorophenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*L*-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(4-[(trifluoromethyl)oxy]phenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*L*-tyrosinamide
25 trifluoroacetate;
N-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]oxy)phenyl]amino]carbonyl]-*L*-tyrosinamide trifluoroacetate;
N-[[(4-[(cyclohexylcarbonyl)oxy]phenyl]amino]carbonyl]-*N*-[(3*S*)-1-[(4-
30 fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*L*-tyrosinamide trifluoroacetate;

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- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[[(4-
[(cyclohexylcarbonyl)oxy]phenyl)amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- N*-[(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[[(4-
5 [(cyclohexylcarbonyl)oxy]phenyl)amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- N*-[(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[[(4-
[(cyclohexylcarbonyl)oxy]phenyl)amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- 10 *N*-[(3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidinyl]-*N*-[[(4-
[(cyclohexylcarbonyl)oxy]phenyl)amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- N*-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[[(4-[(2-
methylpropanoyl)oxy]phenyl)amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- 15 *N*-[(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[[(4-[(2-
methylpropanoyl)oxy]phenyl)amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[[(4-[(2-
methylpropanoyl)oxy]phenyl)amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[[(4-[(1-
20 methylethyl)amino]sulfonyl]phenyl)amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- N*-[(3*S*)-1-ethyl-1-[(3-hydroxyphenyl)methyl]-3-pyrrolidinyl]-*N*-[[(4-[(1-
methylethyl)amino]sulfonyl]phenyl)amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- 25 or any other pharmaceutically acceptable salt.

The most preferred compounds are selected from the group consisting
of:

- N*-[(3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidinyl]-*N*-[[(4-
[(2,5-dimethyl-3-thienyl)sulfonyl]oxy]phenyl)amino]carbonyl]-L-tyrosinamide
30 trifluoroacetate

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- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 {[(2,5-dimethyl-3-thienyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 5 {[(1-methylethyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[[4-[[6-
 chloro-3-methyl-1-benzothien-2-yl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-
 tyrosinamide trifluoroacetate;
- 10 *N*-[[4-[[2,5-dimethyl-3-thienyl)sulfonyl]oxy}phenyl]amino]carbonyl]-*N*-[(3*S*)-1-
 [(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-L-tyrosinamide
 trifluoroacetate;
- N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[4-[[1-
 methylethyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 15 trifluoroacetate;
- N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[4-[[1-
 methylethyl)sulfonyl]oxy}phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- 20 *N*-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[[4-[[1-
 methylethyl)amino]sulfonyl]phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate

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Methods of Preparation

Preparation

- The compounds of Formula (I) may be obtained by applying synthetic
 procedures, some of which are illustrated in the Schemes below. The synthesis
 30 provided for these Schemes is applicable for producing compounds of Formula
 (I) having a variety of different R₁, R₂, R₃ and R₄, which are reacted,
 employing substituents which are suitable protected, to achieve compatibility

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with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some Schemes are shown with specific compounds, this is merely for illustration purpose only.

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Preparation 1

Resin-bound amines **3** were prepared by reductive alkylation of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) with N-protected diamine HCl salts **2**, which were prepared from Boc-protected diamines **1** (Scheme 1). Reactions of **3** with Fmoc-protected amino acids, followed by removal of the protecting group, provided resin-bound intermediates **4**. 4-Hydroxyl aniline was coupled with resin-bound intermediates **4** to afford the corresponding resin-bound urea **5**, which was subsequently treated with potassium carbonate and thiophenol to give secondary amines. Reductive amination of secondary amine with aldehydes produced resin-bound tertiary amines **6**. Amines **6** were then reacted with a series of sulfonyl chlorides to give the corresponding resin-bound sulfonyl esters **7**, which were treated with alkyl halides (R₄Z) to give the corresponding resin-bound quaternary ammonium salts. Resin-bound quaternary ammonium salts were cleaved with 50% trifluoroacetic acid in dichloromethane to afford targeted compounds **8**.

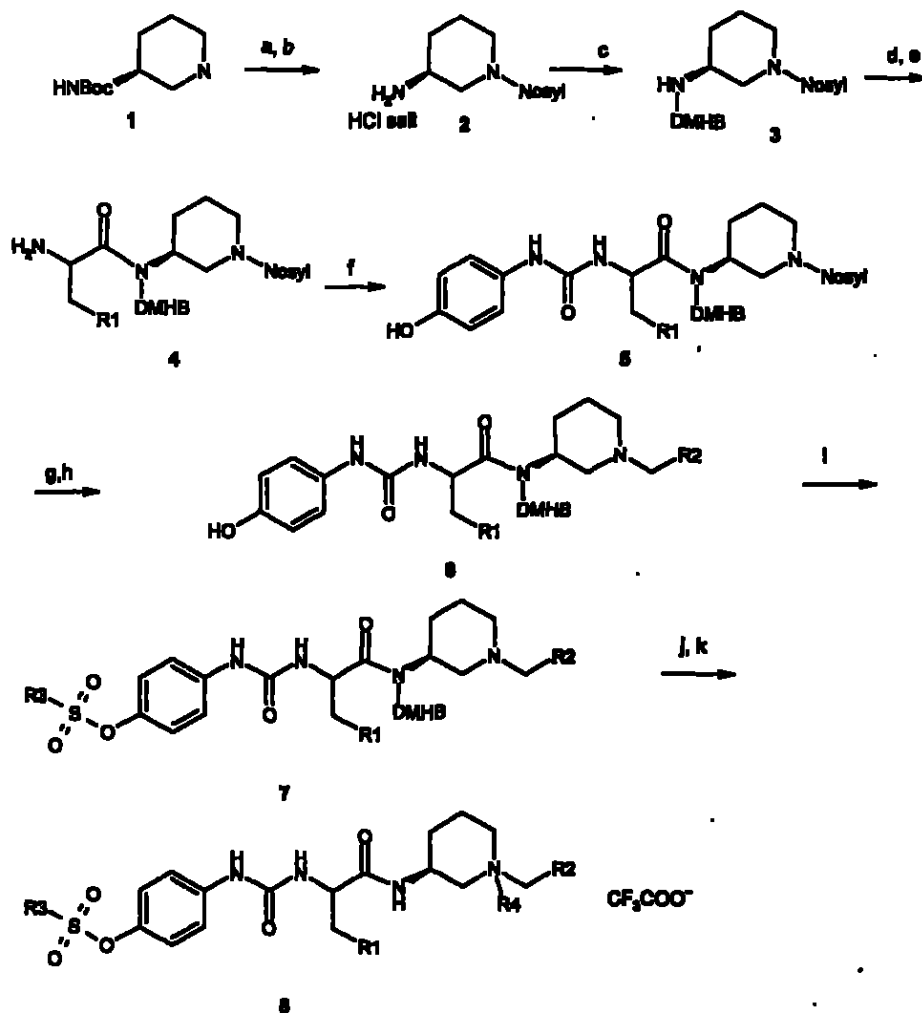
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Scheme 1



- Conditions: a) 2-nitrobenzenesulfonyl chloride (Nosyl-Cl), pyridine, CH₂Cl₂, 0 °C – rt; b) 4 M HCl in 1,4-dioxane, MeOH, rt; c) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin), Na(OAc)₃BH, diisopropylethylamine, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; d) Fmoc-protected amino acids, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; e) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; f) 4-nitrobenzene chloroformate, 4-hydroxyl aniline, tetrahydrofuran, diisopropylethylamine, dimethyl formamide, rt; g) K₂CO₃, PhSH, 1-methyl-2-pyrrolidinone, rt; h) R₂CHO, Na(OAc)₃BH, 10% acetic acid

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in 1-methyl-2-pyrrolidinone, rt; i) sulfonyl chloride, TEA, dichloromethane j)
R₄Z, acetonitrile, rt; k) 50% trifluoroacetic acid in dichloromethane, rt.

The following examples are provided as illustrative of the present invention but
not limiting in any way:

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Example 1

Preparation of N-((3S)-1-((3,4-bis(methoxy)phenyl)methyl)-1-methyl-3-
piperidinyl)-N-((4-((2,5-dimethyl-3-
thienyl)sulfonyloxy)phenyl)amino)carbonyl)-L-tyrosinamide
trifluoroacetate

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a) 3(S)-amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt

To a solution of 3(S)-(-)-(tert-butoxycarbonyl-amino)pyrrolidine (20.12 g,
108 mmol) in 250 mL of anhydrous methylene chloride at 0 °C was added 13.1
mL (162 mmol) of anhydrous pyridine, followed by slow addition of 25.2 g
15 (113.4 mmol) of 2-nitrobenzenesulfonyl chloride. The mixture was warmed to rt
over 1 h and stirred at rt for 16 h. The mixture was poured into 300 mL of 1 M
aqueous NaHCO₃ solution. After the resulting mixture was stirred at rt for 30
min, the organic layer was separated and washed with 500 mL of 1N aqueous
HCl solution twice. The resulting organic layer was dried over MgSO₄ and
20 concentrated *in vacuo*. The residue was used for the the next step without
further purification.

To a mixture of the above residue in 140 mL of anhydrous MeOH was
added 138 mL (544 mmol) of 4 M HCl in 1,4-dioxane solution. The mixture was
stirred at rt for 16 h, concentrated *in vacuo* and further dried in vacuum oven at
25 35 °C for 24 h to yield 3(S)-amino-N-(2-nitrobenzenesulfonyl) pyrrolidine HCl
salt as a yellow solid (30.5 g, 92% over the two steps): ¹H NMR (400 MHz, d₆-
DMSO) δ 8.63 (s, 3 H), 8.08-7.98 (m, 2 H), 7.96-7.83 (m, 2 H), 3.88-3.77 (m, 1
H), 3.68-3.56 (m, 2 H), 3.48-3.35 (m, 2 H), 2.28-2.16 (m, 1 H), 2.07-1.96 (m, 1
H).

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b) DMHB resin bound O-(1,1-dimethylethyl)-N-[(3S)-1-[(2-nitrophenyl)sulfonyl]-3-pyrrolidinyl]-L-tyrosinamide

To a mixture of 7.20 g (10.37 mmol, 1.44 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 156 mL of 10% acetic acid in anhydrous 1-methyl-2-pyrrolidinone was added 9.56 g (31.1 mmol) of 3(S)-amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt and 9.03 mL (51.84 mmol) of diisopropylethyl amine, followed by addition of 11.0 g (51.84 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 250 mL), CH₂Cl₂/MeOH (1:1, 3 x 250 mL) and MeOH (3 x 250 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. Elemental analysis N: 4.16, S: 3.12.

To a mixture of 800 mg (0.860 mmol, 1.075 mmol/g) of the above resin in 15 mL of anhydrous 1-methyl-2-pyrrolidinone was added 1.98 g (4.30 mmol) of Fmoc-Try(tBu)-OH and 117 mg (0.86 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 0.82 mL (5.16 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 25 mL), CH₂Cl₂/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 657 [M+H-tBu]⁺.

The above resin (0.860 mmol) was treated with 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution. After the mixture was shaken at rt for 15 min, the solution was drained and another 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution was added. The mixture was shaken at rt for another 15 min. The solution was drained and the resin was washed with DMF (3 x 25 mL), CH₂Cl₂/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h to afford DHMB resin bound O-(1,1-dimethylethyl)-N-[(3S)-1-[(2-nitrophenyl)sulfonyl]-3-pyrrolidinyl]-L-tyrosinamide (0.86 mmol). An analytical

28
24

amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 435 [M+H-tBu]⁺.

- 5 c) *N*-((3*S*)-1-[[3,4-bis(methoxy)phenyl]methyl]-1-methyl-3-piperidinyl)-*N*-
 10 [[4-[(2,5-dimethyl-3-thienyl)sulfonyloxy]phenyl]amino]carbonyl]-L-tyrosinamide

To a mixture of 1.1 g (9.26 mmol) of 4-hydroxyaniline in 20 ml anhydrous
 10 tetrahydrofuran was added 1.81 g (9.26 mmol) 4-nitrobenzylchloroformate.
 The reaction mixture was stirred at room temperature for half an hour and
 concentrated. Diisopropylethylamine (5 mL, 35.25 mmol), DMHB resin bound
O-(1,1-dimethylethyl)-*N*-((3*S*)-1-[(2-nitrophenyl)sulfonyl]-3-pyrrolidinyl)-L-
 tyrosinamide 4 (3 g, 2.4 mmol) and dimethyl formamide (25 mL) were added to
 15 reaction mixture and shaken overnight. The resin was washed with DMF (3 x
 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting
 urea resin 5 was dried in vacuum oven at 35 °C for 24 h. An analytical amount
 of resin was cleaved with 50% trifluoroacetic acid in dichloromethane for 2 h at
 rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 584.4 [M+H-
 20 tBu]⁺.

To a mixture of urea resin 5 (2.4 mmol) in 60 mL of 1-methyl-2-pyrrolidinone
 was added 2.5 g (18 mmol) of K₂CO₃ and 0.92 mL (9 mmol) of PhSH. After
 the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF
 (3 x 10 mL), H₂O (3 x 10 mL), DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10
 25 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at
 35 °C for 24 h. To a mixture of the above dry resin secondary amine 1 g (0.8
 mmol) in 40 mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution
 was added 997 mg (6 mmol) of 3,4-bis(methoxy)benzaldehyde and 1.272 g (6
 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken
 30 at rt for 72 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1,
 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin 6 was dried in vacuum

2/5

oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 550 [M+H-tBu]⁺.

To a mixture of resin-bound tertiary amines 6 (100 mg, 0.08mmol) in

- 5 10mL methylenechloride and triethyl amine (0.52 mL, 4 mmol) at 0°C was added 2,5-dimethyl-3-thiophenesulfonyl chloride (421.4 mg, 2 mmol). The reaction mixture was warmed to room temperature and shaken overnight. The resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL), MeOH (3 x 10 mL) and CH₂Cl₂ (3x10mL). The resulting resin was dried in
- 10 vacuum oven at 35 °C for 24 h.
- To a mixture of the above dry resin (0.08 mmol) in 3 mL of anhydrous acetonitrile was added 120 µL (1.918 mmol) of iodomethane. After the mixture was shaken at rt for 16 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL), MeOH (3 x 10 mL) and CH₂Cl₂ (3x10mL).
- 15 The resulting resin was dried in vacuum oven at 35 °C for 24 h. The dry resin was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using
- 20 a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H₂O (0.1% trifluoroacetic acid) and B = CH₃CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-[(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl]-*L*-tyrosinamide
- 25 trifluoroacetate (white powder, 32 mg, 54% over 6 steps): MS (ESI) 737.4 [M]⁺.

- Proceeding in a similar manner as described in example 1, but replacing 2,5-dimethyl-3-thiophenesulfonyl chloride with the appropriate sulfonyl chlorides and/or replacing 3,4-bis(methyloxy)benzaldehyde with the
- 30 appropriate aldehydes, the compounds listed in Tables 1 - 3 were prepared.

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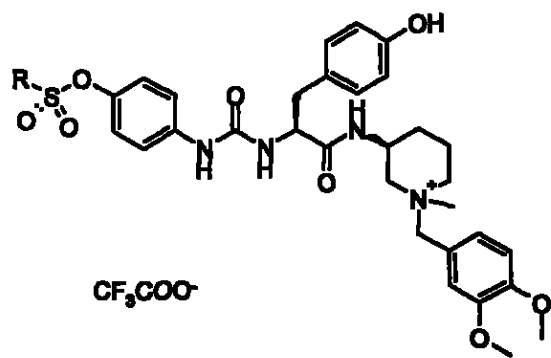
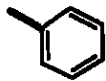
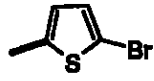


Table 1

Example	R	MS [M] ⁺
1		737
2		709
3		723
4		723
5		754
6		763
7		781
8		721

28
27

9		703
10		788
11		709
12		669

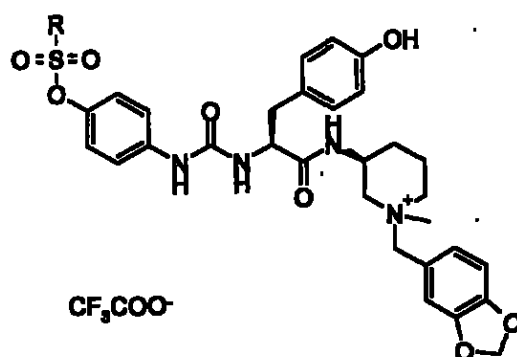
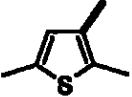
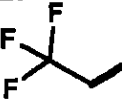
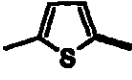
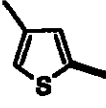
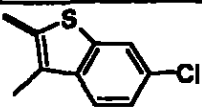
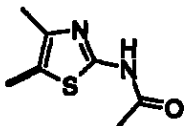
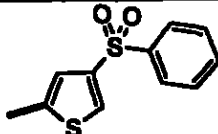
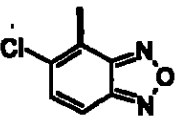
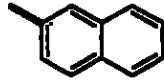


Table 2

Example	R	MS [M] ⁺
13		721
14		693
15		707
16		707
17		727

29
23

18		791
19		625
20		653
21		765
22		833
23		763
24		737
25		652

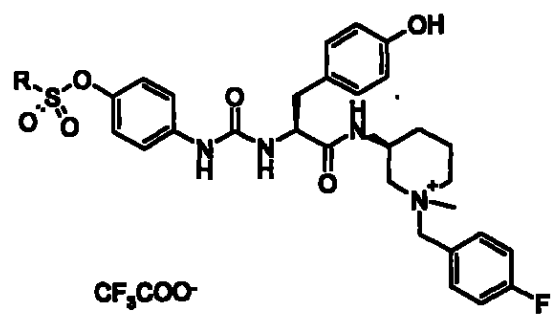
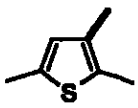
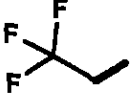
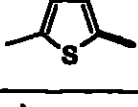
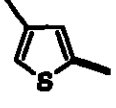
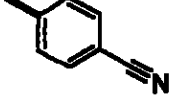
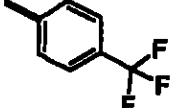
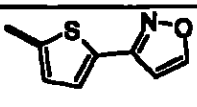
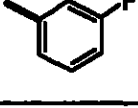
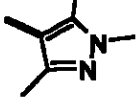
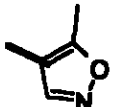
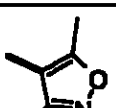


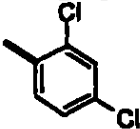
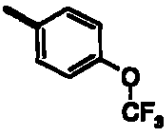
Table 3

Example	R	MS [M] ⁺
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30
29

26		695
27		667
28		681
29		681
30		686
31		729
32		734
33		679
34		693
35		688
36		680

31
30

37		729
38		745
39		665
40		627

Proceeding in a similar manner as described in example 1, but replacing sulfonyl chloride with acid chloride and/or replacing 3,4-bis(methyloxy)benzaldehyde with the appropriate aldehydes, the compounds listed in Tables 4-5 were prepared.

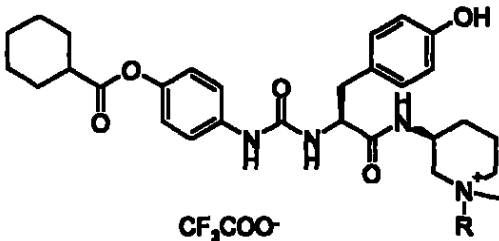
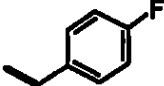
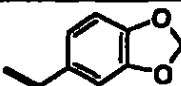
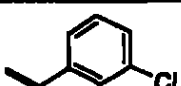
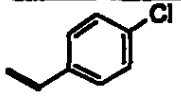
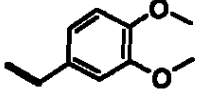


Table 4

Example	R	MS [M] ⁺
41		631
42		656
43		646

3/31

44		646
45		672

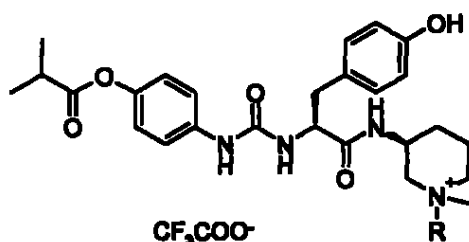
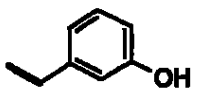
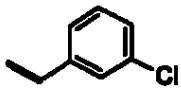
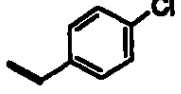


Table 5

Example	R	MS $[M]^+$
46		589
47		607
48		607

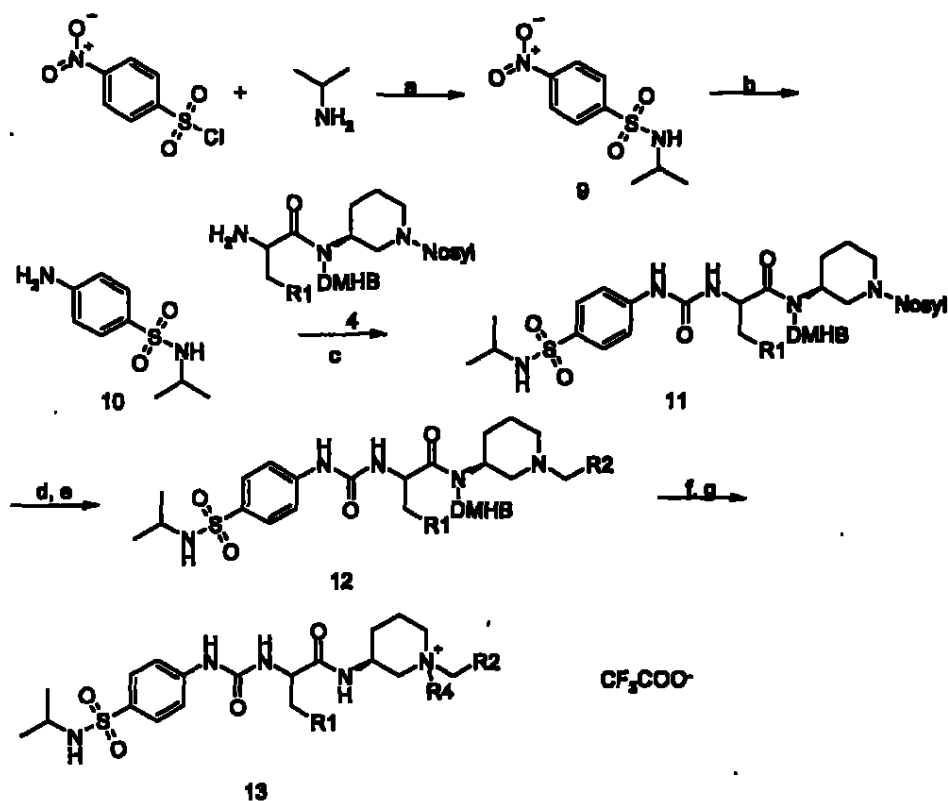
5

Preparation 2

4-Nitrobenzene sulfonyl chloride reacted with isopropyl amine to provide the isopropyl sulfonyl amide 9. The nitro group in 9 was converted to amine 10 via SnCl_2 . The amine was coupled with resin-bound amines 4 to afford the corresponding resin-bound ureas 11. The urea was subsequently treated with benzenethiolate to give secondary amine, which underwent reductive amination with appropriate aldehydes to produce tertiary amine 12. Amine 12 was then treated with alkyl halides to form the corresponding resin-bound quaternary

ammonium salts, which were cleaved with 50% trifluoroacetic acid in dichloromethane to afford targeted compounds 13.

Scheme 2



- 5 Conditions: a) Toluene 80°C b) SnCl₂, EtOH, 70°C; c) 4-nitrobenzene chloroformate, tetrahydrofuran, diisopropylethylamine, dimethyl formamide, rt; d) K₂CO₃, PhSH, 1-methyl-2-pyrrolidinone, rt; e) R₂CHO, Na(OAc)₃BH, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; f) R₄Z, acetonitrile, rt; g) 50% trifluoroacetic acid in dichloromethane, rt.
- 10 The following examples are provided as illustrative of the present invention but not limiting in any way:

Example 49

Preparation of N-[(3S)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidinyl]-N-[(4-[(1-methylethyl) amino]

- 15 sulfonyl]phenyl)amino]carbonyl]-L-tyrosinamide trifluoroacetate

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A solution of 4-nitrobenzenesulfonyl chloride (2000 mg, 9.05 mmol) in 20mL toluene was added dropwise to a solution of isopropylamine (1067 mg, 18.1 mmol) in 50mL toluene. The reaction mixture was heated to 80°C for 1 hour and cooled to room temperature. Water (25 mL) was added. The aqueous phase was extracted with ethyl acetate (3x50 mL). The combined organic phase was dried over MgSO₄, concentrated and run through a pad of silica gel eluting with hexane: ethyl acetate (1:1) to give amide (1800mg, 93%). MS (ESI) 245 [M+H]⁺.

To isopropyl amide 1400 mg, 5.71mmol) in 200 mL ethyl alcohol was added SnCl₂ (5420 mg, 28.6 mmol). The reaction mixture was stirred at 70°C for 3 hours. The reaction mixture was concentrated. Ethyl acetate 100 ml) and saturated NaHCO₃ (60 mL) were added. Sn salts was precipitated out after 30mins and filtered off. The organic phase was washed with brine, dried over MgSO₄ and concentrated to afford amine 10 (1100 mg, 90%). MS (ESI) 215 [M+H]⁺.

To a mixture of 198 mg (0.8 mmol) of 4-amino-N-(1-methylethyl) benzenesulfonamide in 3ml anhydrous tetrahydrofuran was added 169 mg (0.84 mmol) 4-nitrobenzenechloroformate. The reaction mixture was stirred at room temperature for half an hour and concentrated. Diisopropylethylamine (0.28 mL, 1.6 mmol), DMHB resin bound O-(1,1-dimethylethyl)-N-[(3S)-1-[(2-nitrophenyl)sulfonyl]-3-pyrroldinyl]-L-tyrosinamide 4 (400 mg, 0.32 mmol) and dimethyl formamide (5 mL) were added to reaction mixture and shaken overnight. The resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting urea resin 11 was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloromethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 689.6 [M+H-tBu]⁺.

To a mixture of urea resin 11 (0.32 mmol) in 4 mL of 1-methyl-2-pyrroldinone was added 332 mg (2.4 mmol) of K₂CO₃ and 0.12 mL (1.6 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with

35
34

DMF (3 x 10 mL), H₂O (3 x 10 mL), DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. The resulting solution was concentrated *in vacuo*: MS (ESI) 504.4 [M+H-tBu]⁺.

- 5 To a mixture of the above dry resin secondary amine (0.16 mmol) in 4mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution was added 282.8 mg (2.4 mmol) of 3-hydroxybenzaldehyde and 508.8 mg (2.4 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL) and
- 10 MeOH (3 x 10 mL). The resulting resin 12 was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 610.4 [M+H-tBu]⁺.
- To a mixture of resin-bound tertiary amines 12 (0.16 mmol) in
- 15 4mL of anhydrous acetonitrile was added 74 µL (1.2 mmol) of iodomethane. After the mixture was shaken at rt for 16 h, the resin was washed with DMF (3 x 10 mL), CH₂Cl₂/MeOH (1:1, 3 x 10 mL), MeOH (3 x 10 mL) and CH₂Cl₂ (3x10mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. The dry resin was treated with 4 mL of 50% trifluoroacetic acid in
- 20 dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2
- 25 min, hold for 1 min where A = H₂O (0.1% trifluoroacetic acid) and B = CH₃CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce of *N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-[[4-[(1-methylethyl)amino]sulfonyl]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate (white powder, 50 mg, 50% over 5 steps): MS (ESI) 624 [M]⁺.

Proceeding in a similar manner as described in example 49, but replacing 3-hydroxyl benzaldehyde with 1,3-benzodioxole-5-carbaldehyde, the compound listed in Tables 6 was prepared.

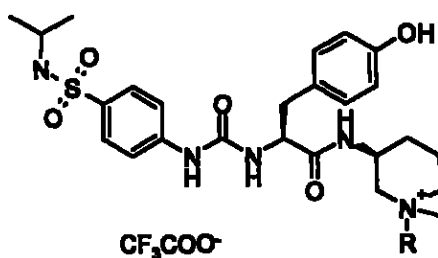


Table 6

Example	R	MS [M] ⁺
50		853

Proceeding in a similar manner as described in example 1, but replacing 1,1-dimethylethyl (3S)-3-piperidinylcarbamate with 1,1-dimethylethyl (3S)-3-pyrrolidinylcarbamate, and/or replacing 3,4-bis(methyloxy)benzaldehyde 3-hydroxyl benzaldehyde, and replacing methyl iodide with ethyl iodide to make the quaternary ammonium salt, the compound listed in Tables 7 was prepared.

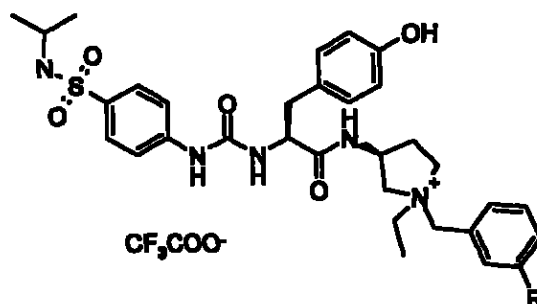


Table 7

Example	R	MS [M] ⁺
51	OH	624

BIOLOGICAL EXAMPLES

37
30

The inhibitory effects of compounds at the M₃ mAChR of the present invention are determined by the following *in vitro* and *in vivo* assays:

5 Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

1) 384-well FLIPR assay

A CHO (chinese hamster ovary) cell line stably expressing the human M₃ muscarinic acetylcholine receptor is grown in DMEM plus 10% FBS, 2 mM Glutamine and 200 ug/ml G418. Cells are detached for maintenance and for
10 plating in preparation for assays using either enzymatic or ion chelation methods. The day before the FLIPR (fluorometric imaging plate reader) assay, cells are detached, resuspended, counted, and plated to give 20,000 cells per 384 well in a 50 ul volume. The assay plates are black clear bottom plates, Becton Dickinson catalog number 35 3982. After overnight incubation of plated
15 cells at 37 degrees C in a tissue culture incubator, the assay is run the next day. To run the assay, media are aspirated, and cells are washed with 1x assay buffer (145mM NaCl, 2.5mM KCl, 10mM glucose, 10mM HEPES, 1.2 mM MgCl₂, 2.5mM CaCl₂, 2.5mM probenecid (pH 7.4.) Cells are then incubated with 50ul of Fluo-3 dye (4uM in assay buffer) for 80 – 90 minutes at 37 degrees
20 C. The calcium- sensitive dye allows cells to exhibit an increase in fluorescence upon response to ligand via release of calcium from intracellular calcium stores. Cells are washed with assay buffer, and then resuspended in 50ul assay buffer prior to use for experiments. Test compounds and antagonists are added in 25 ul volume, and plates are incubated at 37 degrees C for 5 -30 minutes. A
25 second addition is then made to each well, this time with the agonist challenge, acetylcholine. It is added in 25 ul volume on the FLIPR instrument. Calcium responses are measured by changes in fluorescent units. To measure the activity of inhibitors / antagonists, acetylcholine ligand is added at an EC₅₀ concentration, and the antagonist IC₅₀ can then be determined using dose
30 response dilution curves. The control antagonist used with M₃ is atropine.

2) 96-well FLIPR assay

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Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described. CHO cells stably expressing M₃ mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent Indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH₂ PO₄, 25 mM NaH CO₃, 1.0 mM CaCl₂, 1.1 mM MgCl₂, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound (1×10^{-11} – 1×10^{-5} M final in the assay) was added and the plates were incubated for 10 min, at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA; at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels. The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

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Methacholine-Induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice ($n = 6$ each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine. Mice were pretreated with 50 µl of

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compound (0.003-10 $\mu\text{g}/\text{mouse}$) in 50 μl of vehicle (10% DMSO) intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of
5 methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

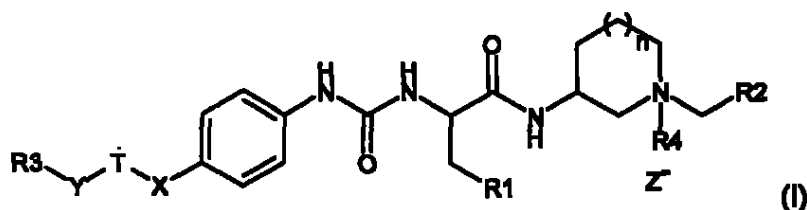
10 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred
15 embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and
20 not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

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What is claimed is:

1. A compound of formula I as indicated below:



5 wherein

n is 0 or 1;

When X is nitrogen or oxygen, Y is nothing;

When Y is nitrogen or oxygen, X is nothing;

T is a sulfonyl group (SO_2) or carbonyl group (CO);

10 When $T=CO$, X is oxygen or nitrogen;

Z' is selected from the group consisting of halo, CF_3COO^- , mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

R_1 is selected from the group consisting of C_1 - C_8 branched or unbranched alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl lower alkyl, C_3 - C_8 alkenyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C_1 - C_3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1 - C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1 - C_8 branched or unbranched alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl lower alkyl, phenyl and phenyl C_1 - C_3 lower alkyl.

R_2 is selected from the group consisting of C_1 - C_8 branched or unbranched alkyl, C_3 - C_8 cycloalkyl, C_3 - C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C_1 - C_3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1 - C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1 - C_8 branched or unbranched alkyl, C_3 - C_8 cycloalkyl and C_3 - C_8 cycloalkyl lower alkyl and heterocycle rings;

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R3 is selected from the group consisting of an unsubstituted or substituted following group: phenyl, phenyl C1-C6 lower alkyl, thiophenyl, thiophenyl C1-C6 lower alkyl, furanyl, furanyl C1-C6 lower alkyl, pyridinyl, pyridinyl C1-C6 lower alkyl, imidazolyl, imidazolyl C1-C6 lower alkyl, naphthyl, naphthyl C1-C6 lower alkyl, quinoliny, quinoliny C1-C6 lower alkyl, indolyl, indolyl C1-C6 lower alkyl, benzothienophenyl, benzothienophenyl C1-C6 lower alkyl, benzofuranyl, benzofuranyl C1-C6 lower alkyl, benzimidazolyl, benzimidazolyl C1-C6 lower alkyl, C1-C8 branched or unbranched alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl C1-C6 lower alkyl, or C3-C8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C1-C8 alkoxy, phenoxy, phenyl C1-C3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C1-C8 branched or unbranched alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinoliny, quinoliny C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothienophenyl, benzothienophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

R4 is selected from the group consisting of C1-C8 branched or unbranched alkyl, C3-C8 cycloalkyl, C3-C8 cycloalkyl lower alkyl.

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2. A. compound according to claim 1 selected from the group consisting of:
 n is 0 or 1;
 When X is nitrogen or oxygen, Y is nothing;
 When Y is nitrogen or oxygen, X is nothing;
 T is a sulfonyl group (SO2) or carbonyl group (CO) ;

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When T=CO, X is oxygen or nitrogen;

Z is selected from the group consisting of halo, CF₃COO⁻, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

R1 is selected from the group consisting of C₁-C₈ branched or
5 unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, C₃-C₈ alkenyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C₁-C₃ lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C₁-C₈ branched or unbranched alkyl,
10 C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl and phenyl C₁-C₃ lower alkyl.

R2 is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C₁-C₃ lower alkyl;
15 wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl and C₃-C₈ cycloalkyl lower alkyl and heterocycle rings;

R3 is selected from the group consisting of an unsubstituted or
20 substituted following group: phenyl, phenyl C₁-C₆ lower alkyl, thiophenyl, thiophenyl C₁-C₆ lower alkyl, furanyl, furanyl C₁-C₆ lower alkyl, pyridinyl, pyridinyl C₁-C₆ lower alkyl, imidazolyl, imidazolyl C₁-C₆ lower alkyl, naphthyl, naphthyl C₁-C₆ lower alkyl, quinolinyl, quinolinyl C₁-C₆ lower alkyl, indolyl, indolyl C₁-C₆ lower alkyl, benzothiophenyl, benzothiophenyl C₁-C₆ lower alkyl,
25 benzofuranyl, benzofuranyl C₁-C₆ lower alkyl, benzoimidazolyl, benzoimidazolyl C₁-C₆ lower alkyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl C₁-C₆ lower alkyl, or C₃-C₈ alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, phenoxy, phenyl C₁-C₃ alkoxy, halo,
30 hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy,

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- propylenedioxy, butylenedioxy, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl, phenyl C₁-C₃ lower alkyl, thlophenyl, thiophenyl C₁-C₃ lower alkyl, furanyl, furanyl C₁-C₃ lower alkyl, pyridinyl, pyridinyl C₁-C₃ lower alkyl, naphthyl, naphthyl C₁-C₃ lower alkyl, quinolinyl, quinolinyl C₁-C₃ lower alkyl, indolyl, Indolyl C₁-C₃ lower alkyl, benzothlophenyl, benzothlophenyl C₁-C₃ lower alkyl, benzofuranyl, benzofuranyl C₁-C₃ lower alkyl, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ and NHCONHR₆;
- 10 R₄ is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl.

or a pharmaceutically acceptable salt thereof.

- 15 3. A. compound according to claim 1 selected from the group consisting of:
- n is 0 or 1;
- When X is nitrogen or oxygen, Y is nothing;
- When Y is nitrogen or oxygen, X is nothing;
- 20 T is a sulfonyl group (SO₂) or carbonyl group (CO) ;
- When T=CO, X is oxygen or nitrogen;
- Z⁻ is selected from the group consisting of halo, CF₃COO⁻, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;
- R₁ is selected from the group consisting of C₁-C₈ branched or
- 25 unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, C₃-C₈ alkenyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C₁-C₃ lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C₁-C₈ branched or unbranched alkyl,
- 30 C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl and phenyl C₁-C₃ lower alkyl.

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R2 is selected from the group consisting of C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C₁-C₃ lower alkyl; wherein, when substituted, a group is substituted by one or more radicals
5 selected from the group consisting of C₁-C₈ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl and C₃-C₈ cycloalkyl lower alkyl and heterocycle rings;

R3 is selected from the group consisting of an unsubstituted or substituted following group: phenyl, phenyl C₁-C₈ lower alkyl, thiophenyl,
10 thiophenyl C₁-C₈ lower alkyl, furanyl, furanyl C₁-C₈ lower alkyl, pyridinyl, pyridinyl C₁-C₈ lower alkyl, imidazolyl, imidazolyl C₁-C₈ lower alkyl, naphthyl, naphthyl C₁-C₈ lower alkyl, quinolinyl, quinolinyl C₁-C₈ lower alkyl, indolyl, indolyl C₁-C₈ lower alkyl, benzothiophenyl, benzothiophenyl C₁-C₈ lower alkyl, benzofuranyl, benzofuranyl C₁-C₈ lower alkyl, benzimidazolyl,
15 benzoimidazolyl C₁-C₈ lower alkyl, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl C₁-C₈ lower alkyl, or C₃-C₈ alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C₁-C₈ alkoxy, phenoxy, phenyl C₁-C₃ alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy,
20 propylenedioxy, butylenedioxy, C₁-C₈ branched or unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl, phenyl, phenyl C₁-C₃ lower alkyl, thiophenyl, thiophenyl C₁-C₃ lower alkyl, furanyl, furanyl C₁-C₃ lower alkyl, pyridinyl, pyridinyl C₁-C₃ lower alkyl, naphthyl, naphthyl C₁-C₃ lower alkyl, quinolinyl, quinolinyl C₁-C₃ lower alkyl, indolyl, indolyl C₁-C₃ lower alkyl,
25 benzothiophenyl, benzothiophenyl C₁-C₃ lower alkyl, benzofuranyl, benzofuranyl C₁-C₃ lower alkyl, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ and NHCONHR₆;

R4 is selected from the group consisting of C₁-C₈ branched or
30 unbranched alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl lower alkyl.

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4.

or a pharmaceutically acceptable salt thereof.

4. A. compound according to claim 1 selected from the group consisting of:
- 5 *N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(2,2,2-trifluoroethyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(5-methyl-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide
 10 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(4-methyl-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 15 [(8-quinoliny)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(3,4-bis(methyloxy)phenyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-
 tyrosinamide trifluoroacetate;
- 20 *N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(2-bromophenyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(4-fluorophenyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide
 25 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(phenylsulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(5-bromo-2-thienyl)sulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide
 30 trifluoroacetate;
- N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidiniumyl)-*N*-[[4-
 [(3-thienylsulfonyl]oxy]phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;

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- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(2,5-dimethyl-3-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- 5 *N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinylumyl]-*N*-[[(4-[(2,2,2-trifluoroethyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(5-methyl-2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- 10 *N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(4-methyl-2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinylumyl]-*N*-[[(4-[(5-chloro-2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- 15 *N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[[(4-[(methanesulfonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinylumyl]-*N*-[[(4-[(propylsulfonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- 20 *N*-[[(4-[(2-(acetilamino)-4-methyl-1,3-thiazol-5-yl)sulfonyl]oxy)phenyl]amino]carbonyl]-*N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinylumyl]-*N*-[[(4-[(4-(phenylsulfonyl)-2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- 25 *N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinylumyl]-*N*-[[(4-[(5-chloro-2,1,3-benzoxadiazol-4-yl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinylumyl]-*N*-[[(4-[(2-naphthalenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
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- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[(4-
[(2,2,2-trifluoroethyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- 5 *N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(5-methyl-
2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(4-methyl-
2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(4-[(4-cyanophenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*N*-[(3*S*)-1-(4-
fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-L-tyrosinamide trifluoroacetate;
- 10 *N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(4-
(trifluoromethyl)phenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- N*-[(3*S*)-1-(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(5-(3-
isoxazolyl)-2-thienyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide
- 15 trifluoroacetate;
- N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(3-
fluorophenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- N*-[(3*S*)-1-(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(1,3,5-
trimethyl-1*H*-pyrazol-4-yl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide
- 20 trifluoroacetate;
- N*-[(3*S*)-1-(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(5-methyl-
4-isoxazolyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide
trifluoroacetate;
- 25 *N*-[(4-[(3,5-dimethyl-4-isoxazolyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*N*-[(3*S*)-
1-(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-L-tyrosinamide
trifluoroacetate;
- N*-[(4-[(2,4-dichlorophenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-*N*-[(3*S*)-1-(4-
fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-L-tyrosinamide trifluoroacetate;
- 30 *N*-[(3*S*)-1-(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl]-*N*-[(4-[(4-
[(trifluoromethyl)oxy]phenyl)sulfonyl]oxy)phenyl]amino]carbonyl]-L-tyrosinamide
trifluoroacetate;

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- N*-{[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[(4-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]oxy)phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-{[(4-[(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-*N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidinyl]-L-tyrosinamide trifluoroacetate;
- 5 *N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[(4-[(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[(4-[(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- 10 [(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[(4-[(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- 15 *N*-[(3*S*)-1-[(3,4-bis(methyloxy)phenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[(4-[(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- : [(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[(4-[(2-methylpropanoyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- 20 *N*-[(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[(4-[(2-methylpropanoyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidinyl]-*N*-[(4-[(2-methylpropanoyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[(4-[(1-methylethyl)amino]sulfonyl]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- 25 [(cyclohexylcarbonyl)oxy]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- N*-[(3*S*)-1-ethyl-1-[(3-hydroxyphenyl)methyl]-3-pyrrolidinyl]-*N*-[(4-[(1-methylethyl)amino]sulfonyl]phenyl]amino)carbonyl]-L-tyrosinamide trifluoroacetate;
- 30 or any other pharmaceutically acceptable salt.

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5. A compound according to claim 1 selected from the group consisting of:
N-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidinyl)-*N*-[[4-
 {(2,5-dimethyl-3-thienyl)sulfonyl]oxy}phenyl)amino]carbonyl]-L-tyrosinamide
 trifluoroacetate
- 5 *N*-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidinyl)-*N*-[[4-
 {(2,5-dimethyl-3-thienyl)sulfonyl]oxy}phenyl)amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
N-((3*S*)-1-[[3,4-bis(methyloxy)phenyl]methyl]-1-methyl-3-piperidinyl)-*N*-[[4-
 {(1-methylethyl)sulfonyl]oxy}phenyl)amino]carbonyl]-L-tyrosinamide
 10 trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidinyl]-*N*-[[4-[(6-
 chloro-3-methyl-1-benzothien-2-yl) sulfonyl]oxy}phenyl)amino] carbonyl]-L-
 tyrosinamide trifluoroacetate;
N-[[4-[(2,5-dimethyl-3-thienyl)sulfonyl]oxy}phenyl)amino]carbonyl]-*N*-[(3*S*)-1-
 15 [(4-fluorophenyl)methyl]-1-methyl-3-piperidinyl]-L-tyrosinamide
 trifluoroacetate;
N-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidinyl)-*N*-[[4-[(1-
 methylethyl)sulfonyl]oxy}phenyl)amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
 20 *N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidinyl)-*N*-[[4-[(1-
 methylethyl)sulfonyl]oxy}phenyl)amino]carbonyl]-L-tyrosinamide
 trifluoroacetate;
N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidinyl)-*N*-[[4-[(1-
 methylethyl) amino] sulfonyl]phenyl)amino]carbonyl]-L-tyrosinamide
 25 trifluoroacetate
 or any other pharmaceutically acceptable salt, or non-salt form thereof.

6. A Pharmaceutical composition for the treatment of muscarinic
 acetylcholine receptor mediated diseases comprising a compound according to
 30 claim 1 and a pharmaceutically acceptable carrier thereof.

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7. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof comprising administering a safe and effective amount of a compound according to claim 1.
- 5 8. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor, comprising administering a safe and effective amount of a compound according to claim 1.
9. A method according to claim 8 wherein the disease is selected from the
10 group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.
10. A method according to claim 9 wherein administration is via inhalation
15 via the mouth or nose.
11. A method according to claim 10 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.
- 20 12. A method according to claim 11 wherein the compound is administered to a human and has a duration of action of 12 hours or more for a 1 mg dose.
13. A method according to claim 12 wherein the compound has a duration of
25 action of 24 hours or more.
14. A method according to claim 13 wherein the compound has a duration of action of 36 hours or more.

NUEVOS ANTAGONISTAS DEL RECEPTOR MUSCARÍNICO M₂ DE ACETILCOLINA

CAMPO DE LA INVENCION

5 Esta invención se refiere a nuevos derivados de sales cíclicas de amonio cuaternario, a composiciones farmacéuticas, a procesos para su preparación, y a su uso en el tratamiento de enfermedades mediadas por el receptor muscarínico M₂ de acetilcolina.

ANTECEDENTES DE LA INVENCION

10 La acetilcolina liberada a partir de neuronas colinérgicas en los sistemas nerviosos central y periférico afecta a muchos procesos biológicos diferentes a través de la interacción con dos clases principales de receptores de acetilcolina - los receptores nicotínicos y los receptores muscarínicos de acetilcolina. Los receptores muscarínicos de acetilcolina (mAChR) pertenecen a la superfamilia de receptores
15 acoplados a proteína-G que tienen siete dominios transmembrana. Hay cinco subtipos de mAChR, denominados M₁-M₅, y cada uno es el producto de un gen distinto. Cada uno de estos cinco subtipos presenta propiedades farmacológicas únicas. Los receptores muscarínicos de acetilcolina están ampliamente distribuidos en los órganos de los vertebrados, y estos receptores pueden mediar tanto acciones inhibidoras como excitadoras. Por ejemplo, los mAChR M₃ median las repuestas contráctiles en el músculo liso que se encuentra en las vías respiratorias, en la vejiga y el tracto gastrointestinal. Como revisiones, véase {Brown 1989 247 /id}.

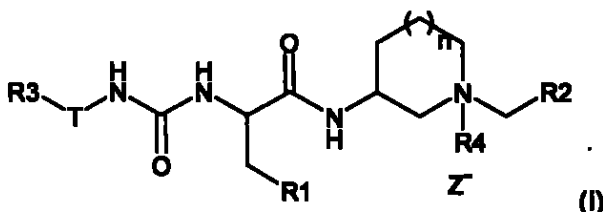
20 En varios estados patofisiológicos diferentes se ha detectado una disfunción del receptor muscarínico de acetilcolina. Por ejemplo, en el asma y en la enfermedad pulmonar obstructiva crónica (COPD), las afecciones inflamatorias llevan a la pérdida de la función del autorreceptor muscarínico M₂ de acetilcolina en los nervios parasimpáticos que abastecen al músculo liso pulmonar, originando un aumento de la liberación de acetilcolina tras la estimulación del nervio vago. Esta disfunción del mAChR da como resultado una hiperreactividad de las vías respiratorias mediada
25 por la mayor estimulación de los mAChR M₃ {Costello, Evans, et al. 1999 72 /id}{Minette, Lammers, et al. 1989 248 /id}. De manera similar, la inflamación del tracto gastrointestinal en la enfermedad inflamatoria del intestino (IBD) da como resultado la hipermovilidad mediada por mAChR M₃ {Oprins, Meijer, et al. 2000 245 /id}. También se ha demostrado que la incontinencia debida a la hipercontractilidad
30 de la vejiga está mediada por un aumento de la estimulación de mAChR M₃ {Hedge
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& Eglen 1999 251 /id). De esta manera, la identificación de antagonistas de mAChR con selectividad de subtipo puede ser útil para utilizar dichos antagonistas como agentes terapéuticos en estas enfermedades mediadas por mAChR.

A pesar de la gran cantidad de indicios que respaldan el uso de la terapia contra receptores muscarínicos para el tratamiento de una diversidad de estados de enfermedad, en la clínica se usan relativamente pocos compuestos antimuscarínicos. De esta manera, sigue existiendo la necesidad de nuevos compuestos que sean capaces de causar el bloqueo de mAChR M₃. Las afecciones asociadas con un aumento en la estimulación de mAChR M₃, tales como asma, COPD, IBD e incontinencia urinaria, mejorarían mediante el uso de compuestos que son inhibidores de la unión a mAChR.

SUMARIO DE LA INVENCIÓN

Esta invención se refiere a compuestos de Fórmula I



15 donde

n es 0 ó 1;

cuando X es nitrógeno u oxígeno, Y no es nada;

cuando Y es nitrógeno u oxígeno, X no es nada;

T es un grupo sulfonilo (SO₂) o carbonilo (CO);

20

cuando T=CO, X es oxígeno o nitrógeno;

Z se selecciona entre el grupo compuesto por halo, CF₃COO⁻, mesilato, tosilato, o cualquier otro contralón farmacéuticamente aceptable;

R1 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, alquenilo C₃-C₈, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxí, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo y fenil-alquilo inferior C₁-C₃.

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R2 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo no sustituido o

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sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxil, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈ y cicloalquil C₃-C₈-alquilo inferior y anillos heterocíclicos;

R3 se selecciona entre el grupo compuesto por uno de los siguientes grupos no sustituidos o sustituidos: fenilo, fenil-alquilo inferior C₁-C₈, tiofenilo, tiofenil-alquilo inferior C₁-C₈, furanilo, furanil-alquilo inferior C₁-C₈, piridinilo, piridinil-alquilo inferior C₁-C₈, imidazolilo, imidazolil-alquilo inferior C₁-C₈, naftilo, naftil-alquilo inferior C₁-C₈, quinolinilo, quinolinil-alquilo inferior C₁-C₈, indolilo, indolil-alquilo inferior C₁-C₈, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₈, benzofuranilo, benzofuranil-alquilo inferior C₁-C₈, benzimidazolilo, benzimidazolil-alquilo inferior C₁-C₈, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior C₁-C₈, o alqueno C₃-C₈; donde, cuando está sustituido, un grupo está sustituido por uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, fenoxi, fenil-alcoxi C₁-C₃, halo, hidroxil, amino, ciano, trifluorometilo, metilendioxil, etilendioxil, propilendioxil, butilendioxil, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, tiofenilo, tiofenil-alquilo inferior C₁-C₃, furanilo, furanil-alquilo inferior C₁-C₃, piridinilo, piridinil-alquilo inferior C₁-C₃, naftilo, naftil-alquilo inferior C₁-C₃, quinolinilo, quinolinil-alquilo inferior C₁-C₃, indolilo, indolil-alquilo inferior C₁-C₃, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₃, benzofuranilo, benzofuranil-alquilo inferior C₁-C₃, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ y NHCONHR₆;

R4 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈ o cicloalquil C₃-C₈-alquilo inferior.

DESCRIPCIÓN DETALLADA

La presente invención incluye todos los hidratos, solvatos, complejos y profármacos de los compuestos de esta invención. Los profármacos son cualquier compuesto unido covalentemente que libera el fármaco parental activo de acuerdo con la Fórmula I - In vivo. Si en un compuesto de la presente invención está presente un centro quiral u otra forma de un centro isomérico, deben considerarse incluidas en la presente invención todas las formas de tal isómero o de tales isómeros, incluyendo los enantiómeros y diastereoisómeros. Los compuestos de la invención que contienen un centro quiral pueden usarse como una mezcla racémica, una

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mezcla enriquecida enantioméricamente, o la mezcla racémica puede separarse usando técnicas bien conocidas y puede usarse un enantiómero individual solo. En los casos en los que los compuestos tienen dobles enlaces carbono-carbono insaturados, dentro del alcance de esta invención se incluyen tanto los isómeros cis (Z) como los isómeros trans (E). En los casos en los que los compuestos pueden existir en formas tautoméricas, tales como los tautómeros ceto-enol, todas las formas tautoméricas se consideran incluidas en esta invención, tanto si existen en equilibrio o como si están predominantemente en una forma.

El significado de cualquier sustituyente en cualquier aparición en la Fórmula I o en cualquier subfórmula de la misma es independiente de su significado, o del significado de cualquier otro sustituyente, en cualquier otra aparición, salvo que se especifique lo contrario.

Las abreviaturas y los símbolos usados habitualmente en las técnicas de péptidos y químicas se usan este documento para describir los compuestos de la presente invención. En general, las abreviaturas de los aminoácidos siguen la Nomenclatura Bioquímica de la Junta de la Comisión IUPAC-IUB como se describe en Eur. J. Biochem., 158, 9 (1984).

Las expresiones "alquilo C₁-C₈" y "alquilo C₁-C₆" usadas en este documento incluyen radicales tanto de cadena lineal como de cadena ramificada de 1 a 8 u 8 átomos de carbono. Por ejemplo, esta expresión incluye, pero sin limitación, metilo, etilo, n-propilo, isopropilo, n-butilo, sec-butilo, isobutilo, *tert*-butilo, pentilo, hexilo, heptilo, octilo y similares. "Alquilo inferior" tiene el mismo significado que "alquilo C₁-C₄".

En este documento, "alcoxi C₁-C₆" incluye radicales de cadena lineal y ramificada de los tipos -O-CH₃, -O-CH₂CH₃, y n-propoxi, isopropoxi, n-butoxi, sec-butoxi, isobutoxi, *tert*-butoxi, pentoxi, y hexoxi, y similares.

Se entiende que "cicloalquilo C₃-C₆", como se aplica en este documento, incluye ciclopropano, ciclobutano, ciclopentano y ciclohexano, y similares, sustituidos y no sustituidos.

"Halógeno" o "halo" significa F, Cl, Br y I.

Los compuestos preferidos de Fórmula I incluyen los compuestos en los que:

- n es 0 ó 1;
- cuando X es nitrógeno u oxígeno, Y no es nada;

cuando Y es nitrógeno u oxígeno, X no es nada;

T es un grupo sulfonilo (SO₂) o carbonilo (CO);

R1 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, alquenilo C₃-C₈, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxil, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo y fenil-alquilo inferior C₁-C₃;

o R2 y R3 es -(CH₂)_j, o -(CH₂)_j-Fenil-(CH₂)_i; donde j es un número entero de 3 a 8; e i es un número entero de 1 a 3.

R2 se selecciona entre el grupo compuesto por hidrógeno, hidroxil, amino, halo, ciano, trifluorometilo, alcoxi C₁-C₈, alquilo C₁-C₈, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, fenilcarbonilo;

R3 se selecciona entre el grupo compuesto por uno de los siguientes grupos no sustituidos o sustituidos: fenil-alquilo inferior C₁-C₈, tiofenil-alquilo inferior C₁-C₈, furanil-alquilo inferior C₁-C₈, piridinil-alquilo inferior C₁-C₈, imidazolil-alquilo inferior C₁-C₈, naftil-alquilo inferior C₁-C₈, quinolinil-alquilo inferior C₁-C₈, indolil-alquilo inferior C₁-C₈, benzotiofenil-alquilo inferior C₁-C₈, benzofuranil-alquilo inferior C₁-C₈, benzimidazolil-alquilo inferior C₁-C₈, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior C₁-C₈, o alquenilo C₃-C₈; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, fenoxil, fenil-alcoxi C₁-C₃, halo, hidroxil, amino, ciano, trifluorometilo, metilenodioxil, etilenodioxil, propilenodioxil, butilenodioxil, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, tiofenilo, tiofenil-alquilo inferior C₁-C₃, furanilo, furanil-alquilo inferior C₁-C₃, piridinilo, piridinil-alquilo inferior C₁-C₃, naftilo, naftil-alquilo inferior C₁-C₃, quinolinilo, quinolinil-alquilo inferior C₁-C₃, indolilo, indolil-alquilo inferior C₁-C₃, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₃, benzofuranilo, benzofuranil-alquilo inferior C₁-C₃, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ y NHCONHR₆;

R4 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, o fenil-alquilo inferior C₁-C₃.

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Incluso son más preferidos los compuestos en los que:

n es 1;

cuando X es nitrógeno u oxígeno, Y no es nada;

T es un grupo sulfonilo SO₂;

- 5 Z se selecciona entre el grupo compuesto por I⁻, Br⁻, Cl⁻, F⁻, CF₃COO⁻, mesilato, tosilato o cualquier otro contraión farmacéuticamente aceptable;

R4 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior;

- R3 se selecciona entre el grupo compuesto por uno de los siguientes grupos
10 no sustituidos o sustituidos: fenil-alquilo inferior C₁-C₈, tiofenil-alquilo inferior C₁-C₈, furanil-alquilo inferior C₁-C₈, piridinil-alquilo inferior C₁-C₈, imidazolil-alquilo inferior C₁-C₈, naftil-alquilo inferior C₁-C₈, quinolinil-alquilo inferior C₁-C₈, indolil-alquilo inferior C₁-C₈, benzotiofenil-alquilo inferior C₁-C₈, benzofuranil-alquilo inferior C₁-C₈, benzoimidazolil-alquilo inferior C₁-C₈, alquilo C₁-C₈ ramificado o no ramificado, cl-
15 cloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior C₁-C₈, o alquenilo C₃-C₈; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, fenoxi, fenil-alcoxi C₁-C₃, halo, hidroxil, amino, ciano, trifluorometilo, metilenodioxil, etilenodioxil, propilenodioxil, butilenodioxil, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-
20 C₈-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, tiofenilo, tiofenil-alquilo inferior C₁-C₃, furanilo, furanil-alquilo inferior C₁-C₃, piridinilo, piridinil-alquilo inferior C₁-C₃, naftilo, naftil-alquilo inferior C₁-C₃, quinolinilo, quinolinil-alquilo inferior C₁-C₃, indolilo, indolil-alquilo inferior C₁-C₃, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₃, benzofuranilo, benzofuranil-alquilo inferior C₁-C₃, COOH, COR₆, COOR₆, CONHR₆,
25 CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆ y NHCOR₆;

R2 se selecciona entre el grupo compuesto por hidrógeno, hidroxil, amino, halo, ciano, trifluorometilo, alcoxi C₁-C₈, alquilo C₁-C₈, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, fenilcarbonilo;

- R1 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no
30 ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, o alquenilo C₃-C₈;
o R1 y R2 es -(CH₂)_r, o -(CH₂)_r-Fenil-(CH₂)_r.

Los compuestos preferidos se seleccionan entre el grupo compuesto por: trifluoroacetato de N-((3S)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinilo)-N-[[4-[(2,2,2-trifluoroetil)sulfonil]oxi]fenil]amino)carbonil)-L-tirosinamida;

- trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[5-metil-2-tienil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[4-metil-2-tienil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
5 trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[8-quinolinilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[3,4-bis(metiloxi)fenil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
10 [[4-[[2-bromofenil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[4-fluorofenil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[fenilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
15 trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[5-bromo-2-tienil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
[[4-[[3-tienilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[[4-
20 [[2,5-dimetil-3-tienil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[[4-
[[2,2,2-trifluoroetil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[[4-
[[5-metil-2-tienil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
25 trifluoroacetato de *N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[[4-
[[4-metil-2-tienil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[[4-
[[5-cloro-2-tienil)sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[[4-
30 [[metilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[[4-
[[propilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-([4-[[2-(acetilamino)-4-metil-1,3-tiazol-5-
il)sulfonil]oxi]fenil]amino]carbonil)-*N*-((3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-
35 piperidinioil)-L-tirosinamida;

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- trifluoroacetato de *N*-[[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[[(4-
[(4-(fenilsulfonil)-2-tienil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[[(4-
[(5-cloro-2,1,3-benzoxadiazol-4-il)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- 5 trifluoroacetato de *N*-[[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[[(4-
[(2-naftalenilsulfonil)oxi]fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[[(4-
[(2,2,2-trifluoroetil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(5-
10 metil-2-tienil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(4-
metil-2-tienil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(4-[(4-cianofenil)sulfonil]oxi)fenil]amino)carbonil]-*N*-[[(3*S*)-1-
[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-L-tirosinamida;
- 15 trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(4-
(trifluorometil)fenil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(5-
(3-isoxazolil)-2-tienil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(3-
20 fluorofenil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-
[(1,3,5-trimetil-1*H*-pirazol-4-il)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(5-
metil-4-isoxazolil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- 25 trifluoroacetato de *N*-[[(4-[(3,5-dimetil-4-isoxazolil)sulfonil]oxi)fenil]amino)carbonil]-
N-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(4-[(2,4-diclorofenil)sulfonil]oxi)fenil]amino)carbonil]-*N*-[[(3*S*)-
1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(4-
30 [(trifluorometil)oxi]fenil)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(1-
metil-1*H*-imidazol-4-il)sulfonil]oxi)fenil]amino)carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[[(4-[(ciclohexilcarbonil)oxi)fenil]amino)carbonil]-*N*-[[(3*S*)-1-[(4-
fluorofenil)metil]-1-metil-3-piperidinioil]-L-tirosinamida;

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- trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-clorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 5 trifluoroacetato de *N*-[(3*S*)-1-[(3-clorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(3-hidroxifenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(2-metilpropanoil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 10 trifluoroacetato de *N*-[(3*S*)-1-[(3-clorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(2-metilpropanoil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-clorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(2-metilpropanoil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 15 trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[[(4-[(1-metiletil)amino]sulfonil)fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-etil-1-[(3-hidroxifenil)metil]-3-pirrolidinioil]-*N*-[[(4-[(1-metiletil)amino]sulfonil)fenil)amino]carbonil]-*L*-tirosinamida;
- o cualquier otra sal farmacéuticamente aceptable.
- 20 Los compuestos más preferidos se seleccionan entre el grupo compuesto por:
- trifluoroacetato de *N*-[(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(2,5-dimetil-3-tienil)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(2,5-dimetil-3-tienil)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 25 trifluoroacetato de *N*-[(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(1-metiletil)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[[(4-[(6-cloro-3-metil-1-benzotien-2-il)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 30 trifluoroacetato de *N*-[[(4-[(2,5-dimetil-3-tienil)sulfonil]oxi]fenil)amino]carbonil]-*N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(1-metiletil)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[[(4-[(1-metiletil)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
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trifluoroacetato de *N*-{(3*S*)-1-[(3-hidroxifenil)metil]-1-metil-3-piperidinilo}-*N*-[(4-[(1-metiletil)amino] sulfonil]fenil)amino]carbonil]-L-tirosinamida.

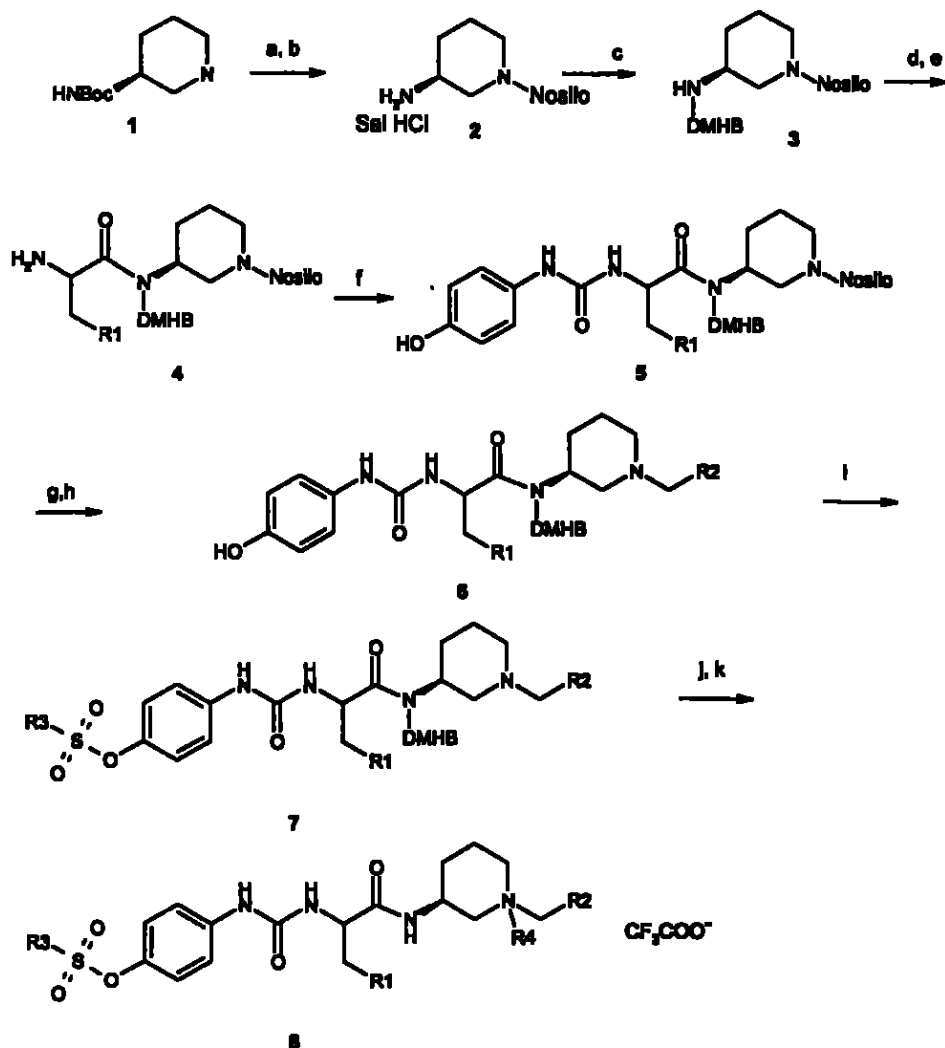
Métodos de Preparación

Preparación

- 5 Los compuestos de Fórmula (I) pueden obtenerse aplicando procedimientos de síntesis, algunos de los cuales se ilustran en los siguientes Esquemas. La síntesis proporcionada por estos Esquemas es aplicable para la producción de compuestos de Fórmula (I) que tienen diversos R1, R2, R3 y R4 diferentes, que se hacen reaccionar, empleando sustituyentes que están convenientemente protegidos, para conseguir compatibilidad con las reacciones indicadas en este documento. La desprotección posterior, en estos casos, produce compuestos que tienen la naturaleza descrita en general. Aunque algunos Esquemas se muestran con compuestos específicos, esto es simplemente con fines ilustrativos.

Preparación 1

- 15 Se prepararon aminas 3 unidas a resina por alquilación reductora de 2,6-dimetoxi-4-poliestirenobenciloxi-benzaldehído (resina DMHB) con sales 2 HCl de diamina protegida con N, que se prepararon a partir de diaminas 1 protegidas con Boc (Esquema 1). Las reacciones de 3 con aminoácidos protegidos con Fmoc, seguido de la eliminación del grupo protector, proporcionaron intermedios 4 unidos a resina. Se acopló 4-hidroxi anilina con los intermedios 4 unidos a resina para producir la correspondiente urea 5 unida a resina, que posteriormente se trató con carbonato potásico y tiofenol para dar aminas secundarias. La aminación reductora de las aminas secundarias con aldehídos produjo aminas terciarias 6 unidas a resina. Las aminas 6 se trataron después con una serie de cloruros de sulfonilo para dar los correspondientes sulfonil ésteres 7 unidos a resina, que se trataron con haluros de alquilo (R4Z) para dar las correspondientes sales de amonio cuaternario unidas a resina. Las sales de amonio cuaternario unidas a resina se escindieron con ácido trifluoroacético al 50% en diclorometano para producir los compuestos diana 8.



- Condiciones: a) cloruro de 2-nitrobencenosulfonilo (Nosil-Cl), piridina, CH₂Cl₂, 0°C – t.a; b) HCl 4 M en 1,4-dioxano, MeOH, t.a; c) 2,6-dimetoxi-4-poliestirenobenciloxi-benzaldehído (resina DMHB), Na(OAc)₃BH, diisopropiletilamina, ácido acético al 10% en 1-metil-2-pirrolidinona, t.a; d) aminoácidos protegidos con Fmoc, 1,3-diisopropilcarbodiimida, 1-hidroxil-7-azabenzotriazol, 1-metil-2-pirrolidinona, t.a; e) piperidina al 20% en 1-metil-2-pirrolidinona, t.a; f) clorofornato de 4-nitrobenceno, 4-hidroxilanilina, tetrahidrofurano, diisopropiletilamina, dimetilformamida, t.a; g) K₂CO₃, PhSH, 1-metil-2-pirrolidinona, t.a; h) R₂CHO, Na(OAc)₃BH, ácido acético al 10% en 1-metil-2-pirrolidinona, t.a; i) cloruro de sulfonilo, TEA, diclorometano; j) R₄Z, acetonitrilo, t.a; k) ácido trifluoroacético al 50% en diclorometano, t.a.

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Los siguientes ejemplos se proporcionan como ilustrativos de la presente invención pero no la limitan de manera alguna:

Ejemplo 1

Preparación de trifluoroacetato de N-((3S)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinol)-N-[[4-[[2,5-dimetil-3-tienil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida

a) sal HCl de 3(S)-amino-N-(2-nitrobencenosulfonil)pirrolidina

A una solución de 3(S)-(-)-(terc-butoxicarbonil-amino)pirrolidina (20,12 g, 108 mmol) en 250 ml de cloruro de metileno anhidro a 0°C se le añadieron 13,1 ml (162 mmol) de piridina anhidra, seguido de la adición lenta de 25,2 g (113,4 mmol) de cloruro de 2-nitrobencenosulfonilo. La mezcla se calentó a t.a durante 1 h y se agitó a t.a durante 16 h. La mezcla se vertió en 300 ml de solución acuosa de NaHCO₃ 1 M. Después de agitar la mezcla resultante a t.a durante 30 min, la capa orgánica se separó y se lavó dos veces con 500 ml de solución acuosa de HCl 1 N. La capa orgánica resultante se secó sobre MgSO₄ y se concentró al vacío. El residuo se usó para la siguiente etapa sin purificación adicional.

A una mezcla del residuo anterior en 140 ml de MeOH anhidro se le añadieron 136 ml (544 mmol) de HCl 4 M en solución de 1,4-dioxano. La mezcla se agitó a t.a durante 16 h, se concentró al vacío y se secó adicionalmente en un homo de vacío a 35°C durante 24 h para producir la sal HCl de 3(S)-amino-N-(2-nitrobencenosulfonil)pirrolidina en forma de un sólido amarillo (30,5 g, 92% tras las dos etapas): ¹H RMN (400 MHz, d₆-DMSO) δ 8,63 (s, 3 H), 8,08-7,98 (m, 2 H), 7,96-7,83 (m, 2 H), 3,88-3,77 (m, 1 H), 3,66-3,56 (m, 2 H), 3,46-3,35 (m, 2 H), 2,28-2,16 (m, 1 H), 2,07-1,96 (m, 1 H).

b) O-(1,1-dimetiletil)-N-[(3S)-1-[(2-nitrofenil)sulfonil]-3-pirrolidinil]-L-tirosinamida unida a resina DMHB.

A una mezcla de 7,20 g (10,37 mmol, 1,44 mmol/g) de 2,6-dimetoxi-4-pollestirenobenciloxi-benzaldehído (resina DMHB) en 156 ml de ácido acético al 10% en 1-metil-2-pirrolidinona anhidra se le añadieron 9,56 g (31,1 mmol) de sal HCl de 3(S)-amino-N-(2-nitrobencenosulfonil)pirrolidina y 9,03 ml (51,84 mmol) de diisopropiletilamina, seguido de la adición de 11,0 g (51,84 mmol) de triacetoxiborohidruro sódico. Después, la mezcla resultante se agitó a t.a durante 72 h, la resina se lavó con DMF (3 x 250 ml), CH₂Cl₂/MeOH (1:1, 3 x 250 ml) y MeOH (3 x 250 ml). La resina resultante se secó en un homo de vacío a 35°C durante 24 h. Análisis elemental N: 4,16, S: 3,12.

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A una mezcla de 800 mg (0,860 mmol, 1,075 mmol/g) de la resina anterior en 15 ml de 1-metil-2-pirrolidinona anhidra se le añadieron 1,98 g (4,30 mmol) de Fmoc-Tri(tBu)-OH y 117 mg (0,86 mmol) de 1-hidroxi-7-azabenzotriazol, seguido de la adición de 0,82 ml (5,16 mmol) de 1,3-diisopropilcarbodiimida. Después, la mezcla resultante se agitó a t.a durante 24 h, la resina se lavó con DMF (3 x 25 ml), CH₂Cl₂/MeOH (1:1, 3 x 25 ml) y MeOH (3 x 25 ml). La resina resultante se secó en un horno de vacío a 35°C durante 24 h. Se escindió una cantidad analítica de resina con ácido trifluoroacético al 50% en dicloroetano durante 2 h a t.a. La solución resultante se concentró al vacío: MS (ESI) 657 [M+H-tBu]⁺.

La resina anterior (0,860 mmol) se trató con 15 ml de piperidina al 20% en solución de 1-metil-2-pirrolidinona anhidra. Después, la mezcla se agitó a t.a durante 15 min, la solución se drenó y se añadieron otros 15 ml de piperidina al 20% en solución de 1-metil-2-pirrolidinona anhidra. La mezcla se agitó a t.a durante 15 min más. La solución se drenó y la resina se lavó con DMF (3 x 25 ml), CH₂Cl₂/MeOH (1:1, 3 x 25 ml) y MeOH (3 x 25 ml). La resina resultante se secó en un horno de vacío a 35°C durante 24 h para dar O-(1,1-dimetiletil)-N-[(3S)-1-[(2-nitrofenil)sulfonil]-3-pirrolidinil]-L-tirosinamida unida a resina DHMB (0,86 mmol). Se escindió una cantidad analítica de resina con ácido trifluoroacético al 50% en dicloroetano durante 2 h a t.a. La solución resultante se concentró al vacío: MS (ESI) 435 [M+H-tBu]⁺.

c) N-[(3S)-1-[[3,4-bis(metiloil)fenil]metil]-1-metil-3-piperidinolil]-N-[[4-[(2,5-dimetil-3-tienil)sulfonil]oxil)fenil]amino]carbonil]-L-tirosinamida

A una mezcla de 1,1 g (9,26 mmol) de 4-hidroxilanilina en 20 ml de tetrahydrofurano anhidro se le añadieron 1,81g (9,26 mmol) de 4-nitrobencenocloroformiato. La mezcla de reacción se agitó a temperatura ambiente durante media hora y se concentró. Se añadieron diisopropiletilamina (5 ml, 35,25 mmol), O-(1,1-dimetiletil)-N-[(3S)-1-[(2-nitrofenil)sulfonil]-3-pirrolidinil]-L-tirosinamida 4 unida a resina DMHB (3 g, 2,4 mmol) y dimetilformamida (25 ml) a la mezcla de reacción y se agitaron durante una noche. La resina se lavó con DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml) y MeOH (3 x 10 ml). La resina 5 de urea resultante se secó en un horno de vacío a 35°C durante 24 h. Se escindió una cantidad analítica de resina con ácido trifluoroacético al 50% en diclorometano durante 2 h a t.a. La solución resultante se concentró al vacío: MS (ESI) 584,4 [M+H-tBu]⁺.

A una mezcla de resina 5 de urea (2,4 mmol) en 60 ml de 1-metil-2-pirrolidinona se le añadieron 2,5 g (18 mmol) de K₂CO₃ y 0,92 ml (9 mmol) de

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PhSH. Después, la mezcla resultante se agitó a t.a durante 2 h, la resina se lavó con DMF (3 x 10 ml), H₂O (3 x 10 ml), DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml) y MeOH (3 x 10 ml). La resina resultante se secó en un horno de vacío a 35°C durante 24 h. A una mezcla de la amina secundaria de la resina seca anterior de 1 g (0,8 mmol) en 40 ml de HOAc al 10% en solución de 1-metil-2-pirrolidinona anhidra se le añadieron 997 mg (6 mmol) de 3,4-bis(metiloxi)benzaldehído y 1,272 g (6 mmol) de triacetoxiborohidruro sódico. Después, la mezcla resultante se agitó a t.a durante 72 h, la resina se lavó con DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml) y MeOH (3 x 10 ml). La resina resultante 6 se secó en un horno de vacío a 35°C durante 24 h. Se escindió una cantidad analítica de resina con ácido trifluoroacético al 50% en dicloroetano durante 2 h a t.a. La solución resultante se concentró al vacío: MS (ESI) 550 [M+H-tBu]⁺.

A una mezcla de aminas 6 terciarias unidas a resina (100 mg, 0,08 mmol) en 10 ml de cloruro de metileno y trietilamina (0,52 ml, 4 mmol) a 0°C se le añadió cloruro de 2,5-dimetil-3-tiofenosulfonilo (421,4 mg, 2 mmol). La mezcla de reacción se calentó a temperatura ambiente y se agitó durante una noche. La resina se lavó con DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml), MeOH (3 x 10 ml) y CH₂Cl₂ (3x10 ml). La resina resultante se secó en un horno de vacío a 35°C durante 24 h.

A una mezcla de la resina seca anterior (0,08 mmol) en 3 ml de acetonitrilo anhidro se le añadieron 120 µl (1,918 mmol) de yodometano. Después, la mezcla se agitó a t.a durante 16 h, la resina se lavó con DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml), MeOH (3 x 10 ml) y CH₂Cl₂ (3x10 ml). La resina resultante se secó en un horno de vacío a 35°C durante 24 h. La resina seca se trató con 4 ml de ácido trifluoroacético al 50% en dicloroetano a t.a durante 2 h. Después de recoger la solución de escisión, la resina se trató con 4 ml más de ácido trifluoroacético al 50% en dicloroetano a t.a durante 10 min. Las soluciones de escisión combinadas se concentraron al vacío. El residuo se purificó usando un sistema de HPLC semi-preparativo Gilson con una columna YMC ODS-A (C-18) de 50 mm por 20 mm de DI, eluyendo con 10% de B a 90% de B en 3.2 min, mantenido durante 1 min, donde A = H₂O (ácido trifluoroacético al 0,1%) y B = CH₃CN (ácido trifluoroacético al 0,1%) bombeado a 25 ml/min, para producir trifluoroacetato de N-[(4-[(etiloxi)carbonil]fenil)amino)carbonil]-N-[(3S)-1-[(4-hidroxifenil)metil]-1-metil-3-pirrolidinioil]-L-tirosinamida (polvo blanco, 32 mg, 54% tras 6 etapas): MS (ESI) 737,4 [M]⁺.

68
64

Procediendo de una manera similar a la descrita en el ejemplo 1, pero sustituyendo cloruro de 2,5-dimetil-3-tiofenosulfonilo por los cloruros de sulfonilo apropiados y/o sustituyendo 3,4-bis(metilo)benzaldehído por los aldehídos apropiados, se prepararon los compuestos indicados en las Tablas 1 - 3.

5

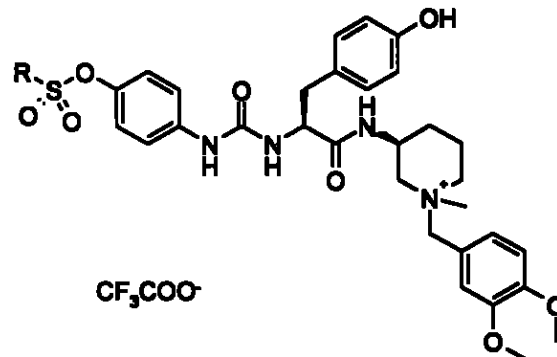
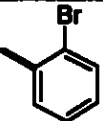
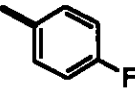
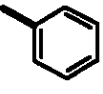
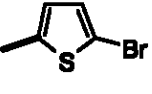
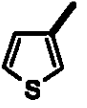


Tabla 1

Ejemplo	R	MS [M] ⁺
1		737
2		709
3		723
4		723
5		754
6		763

6/5
65

7		781
8		721
9		703
10		788
11		709
12		669

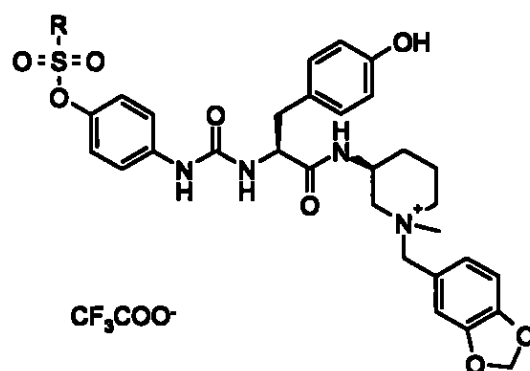
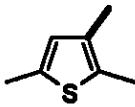
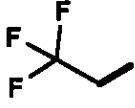
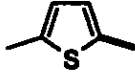
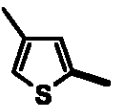
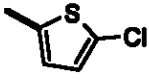
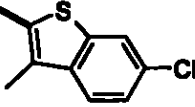
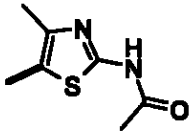
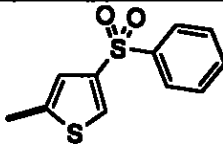
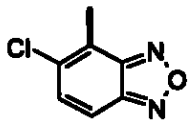
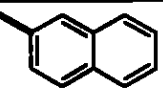
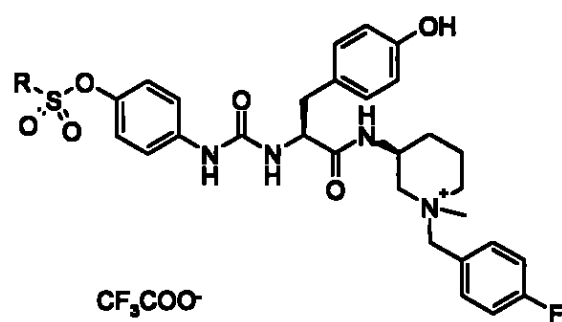


Tabla 2

Ejemplo	R	MS $[M]^+$
13		721
14		693
15		707

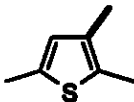
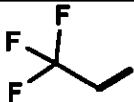
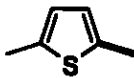
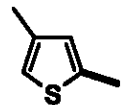
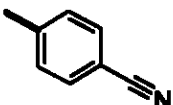
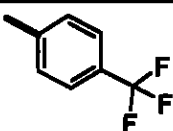
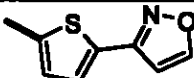
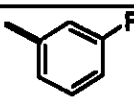
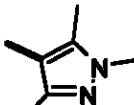
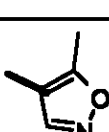
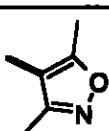
6A
66

16		707
17		727
18		791
19		825
20		853
21		765
22		833
23		763
24		737
25		852

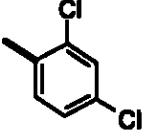
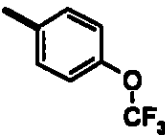
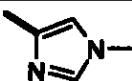


68
67

Tabla 3

Ejemplo	R	MS [M] ⁺
26		695
27		667
28		681
29		681
30		686
31		729
32		734
33		679
34		693
35		686
36		680

69
68

37		729
38		745
39		665
40		627

5 Procediendo de una manera similar a la descrita en el ejemplo 1, pero sustituyendo cloruro de sulfonilo por cloruro de ácido y/o sustituyendo 3,4-bis(metiloxi)benzaldehído por los aldehídos apropiados, se prepararon los compuestos indicados en las Tablas 4-5.

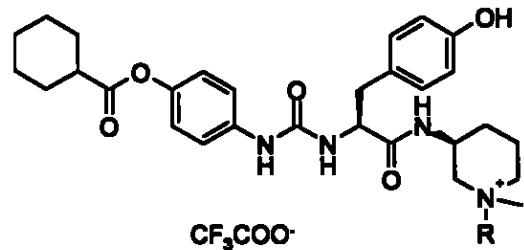
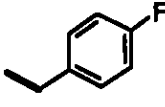
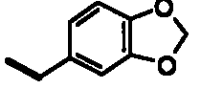
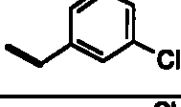
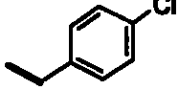
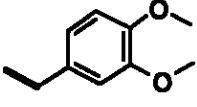


Tabla 4

Ejemplo	R	MS $[M]^+$
41		631
42		656
43		646
44		648

45		672
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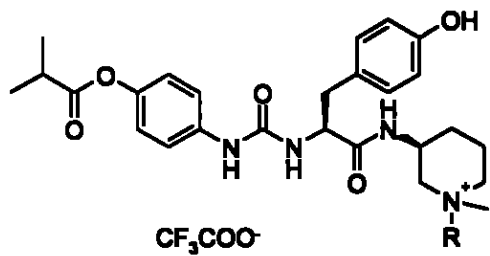
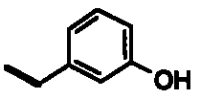
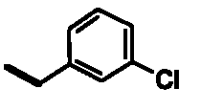
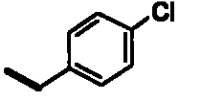


Tabla 5

Ejemplo	R	MS [M] ⁺
46		589
47		607
48		607

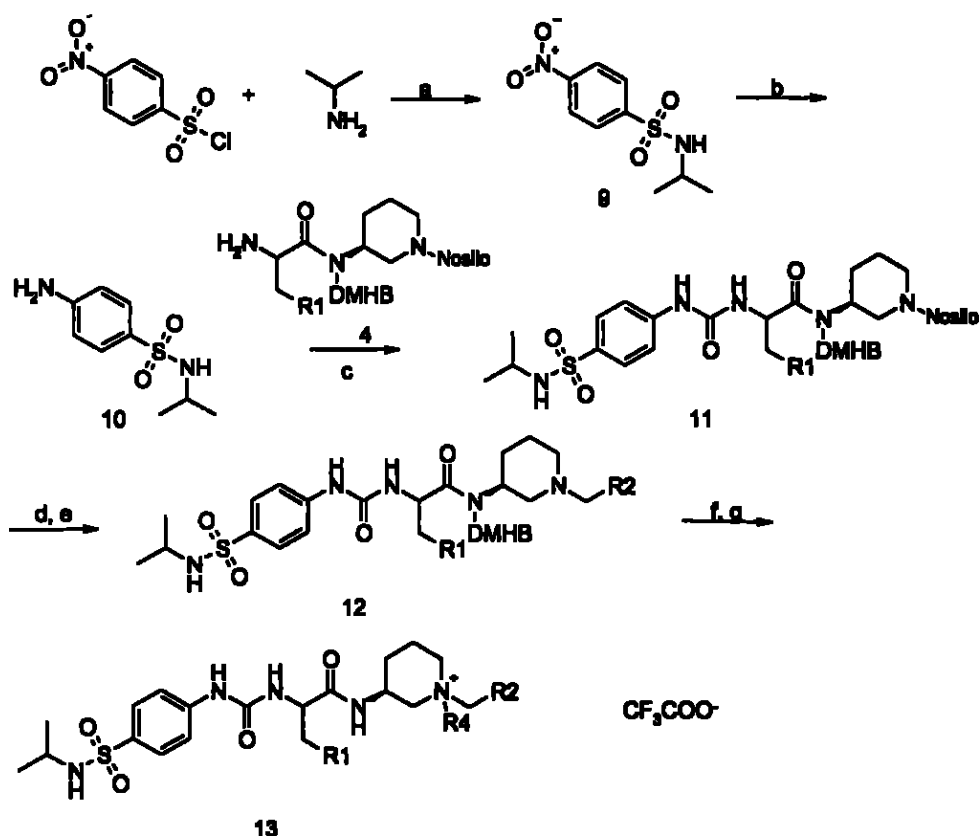
5 Preparación 2

Se hizo reaccionar cloruro de 4-nitrobenzenosulfonilo con isopropilamina para proporcionar la isopropilsulfonilamida 9. El grupo nitro de 9 se convirtió en la amina 10 mediante SnCl₂. La amina se acopló con aminas 4 unidas a resina para producir las ureas 11 unidas a resina correspondientes. La urea se trató posteriormente con benzenotiolato para dar una amina secundaria, que se sometió a aminación reductora con los aldehídos apropiados para producir la amina terciaria 12. Después, la amina 12 se trató con haluros de alquilo para formar las sales de amonio cuaternario unidas a resina correspondientes, que se escindieron con ácido trifluoroacético al 50% en diclorometano para dar los compuestos diana 13.

15

Esquema 2

70



Condiciones: a) Tolueno 80°C b) SnCl₂, EtOH, 70°C; c) cloroformiato de 4-nitrobenceno, tetrahidrofurano, diisopropiletilamina, dimetilformamida, t.a; d) K₂CO₃, PhSH, 1-metil-2-pirrolidinona, t.a; e) R₂CHO, Na(OAc)₃BH, ácido acético al 10% en 1-metil-2-pirrolidinona, t.a; f) R₄Z, acetonitrilo, t.a; g) ácido trifluoroacético al 50% en diclorometano, t.a.

Los siguientes ejemplos se proporcionan como ilustrativos de la presente invención pero no la limitan de manera alguna:

Ejemplo 49

10 Preparación de trifluoroacetato de N-((3S)-1-((3-hidroxifenil)metil)-1-metil-3-piperidinol)-N-((4-((1-metiletil)amino)sulfonil)fenil)amino)carbonil)-L-tirosinamida

Una solución de cloruro de 4-nitrobencenosulfonilo (2000 mg, 9,05 mmol) en 20 ml tolueno se añadió gota a gota a una solución de isopropilamina (1067 mg, 18,1 mmol) en 50 ml de tolueno. La mezcla de reacción se calentó a 80°C durante 1 hora y se enfrió a temperatura ambiente. Se añadió agua (25 ml). La fase acuosa se extrajo con acetato de etilo (3x50 ml). La fase orgánica combinada se secó sobre

72
71

MgSO₄, se concentró y se procesó a través de una capa de gel de sílice eluyendo con hexano:acetato de etilo (1:1) para dar amida (1800 mg, 93%). MS (ESI) 245 [M+H]⁺.

5 A Isopropilamida (1400 mg, 5,71mmol) en 200 ml de alcohol etílico se le añadió SnCl₂ (5420 mg, 28,6 mmol). La mezcla de reacción se agitó a 70°C durante 3 horas. La mezcla de reacción se concentró. Se añadieron acetato de etilo (100 ml) y NaHCO₃ saturado (60 ml). Se hicieron precipitar las sales de Sn después de 30 minutos y se retiraron por filtración. La fase orgánica se lavó con salmuera, se secó sobre MgSO₄ y se concentró para dar la amina 10 (1100 mg, 90%). MS (ESI)
10 215 [M+H]⁺.

A una mezcla de 196 mg (0,8 mmol) de 4-amino-N-(1-metiletil)bencenosulfonamida en 3 ml de tetrahidrofurano anhidro se le añadieron 169 mg (0,84 mmol) 4-nitrobencenocloroformiato. La mezcla de reacción se agitó a temperatura ambiente durante media hora y se concentró. Se añadieron diisopropi-
15 letilamina (0,28 ml, 1,6 mmol), O-(1,1-dimetiletil)-N-((3S)-1-[(2-nitrofenil)sulfonil]-3-pirrolidinil)-L-tirosinamida 4 unida a resina DMHB (400 mg, 0,32 mmol) y dimetilformamida (5 ml) a la mezcla de reacción y se agitó durante una noche. La resina se lavó con DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml) y MeOH (3 x 10 ml). La resina de urea 11 resultante se secó en un horno de vacío a 35°C durante 24 h. Se
20 escindió una cantidad analítica de resina con ácido trifluoroacético al 50% en diclorometano durante 2 h a t.a. La solución resultante se concentró al vacío: MS (ESI) 689.6 [M+H-tBu]⁺.

A una mezcla de resina de urea 11 (0,32 mmol) en 4 ml de 1-metil-2-pirrolidinona se le añadieron 332 mg (2,4 mmol) de K₂CO₃ y 0,12 ml (1,6 mmol) de
25 PhSH. Después, la mezcla resultante se agitó a t.a durante 2 h, la resina se lavó con DMF (3 x 10 ml), H₂O (3 x 10 ml), DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml) y MeOH (3 x 10 ml). La resina resultante se secó en un horno de vacío a 35°C durante 24 h. La solución resultante se concentró al vacío: MS (ESI) 504.4 [M+H-tBu]⁺.

30 A una mezcla de la amina secundaria de la resina seca anterior (0,16 mmol) en 4 ml de HOAc al 10% en solución de 1-metil-2-pirrolidinona anhidra se le añadieron 292,8 mg (2,4 mmol) de 3-hidroxilbenzaldehído y 508,8 mg (2,4 mmol) de triacetoxiborohidruro sódico. Después, la mezcla resultante se agitó a t.a durante 24 h, y la resina se lavó con DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml) y MeOH (3 x
35 10 ml). La resina 12 resultante se secó en un horno de vacío a 35°C durante 24 h.

73
72

Se escindió una cantidad analítica de resina con ácido trifluoroacético al 50% en dicloroetano durante 2 h a t.a. La solución resultante se concentró al vacío: MS (ESI) 610,4 [M+H-tBu]⁺.

5 A una mezcla de aminas terciarias 12 unidas a resina (0,16 mmol) en 4 ml de acetonitrilo anhidro se le añadieron 74 µl (1,2 mmol) de yodometano. Después, la mezcla se agitó a t.a durante 16 h, la resina se lavó con DMF (3 x 10 ml), CH₂Cl₂/MeOH (1:1, 3 x 10 ml), MeOH (3 x 10 ml) y CH₂Cl₂ (3x10 ml). La resina re-
sultante se secó en un horno de vacío a 35°C durante 24 h. La resina seca se trató con 4 ml de ácido trifluoroacético al 50% en dicloroetano a t.a durante 2 h. Después
10 de recoger la solución de escisión, la resina se trató con 4 ml más de ácido trifluoroacético al 50% en dicloroetano a t.a durante 10 min. Las soluciones de escisión combinadas se concentraron al vacío. El residuo se purificó usando un sistema de HPLC semi-preparativo Gilson con una columna YMC ODS-A (C-18) de 50 mm por 20 mm de DI, eluyendo con 10% de B a 90% de B en 3,2 min, mantenido durante 1
15 min, donde A = H₂O (ácido trifluoroacético al 0,1%) y B = CH₃CN (ácido trifluoroacético al 0,1%) bombeado a 25 ml/min, para producir trifluoroacetato de *N*-{(3*S*)-1-[(3-hidroxifenil)metil]-1-metil-3-piperidinioil}-*N*-[[4-[(1-metiletil)amino]sulfonil]fenil] amino]carbonil]-L-tirosinamida (polvo blanco, 50 mg, 50% tras 5 etapas): MS (ESI) 624 [M]⁺.

20 Procediendo de una manera similar a la descrita en el ejemplo 49, pero sustituyendo 3-hidroxil benzaldehído con 1,3-benzodioxol-5-carbaldehído, se preparó el compuesto indicado en la Tabla 6.

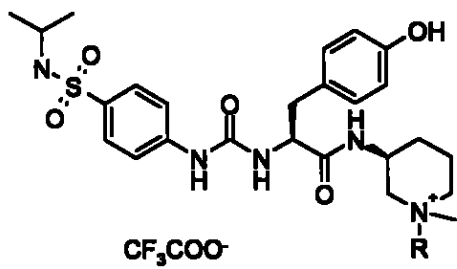


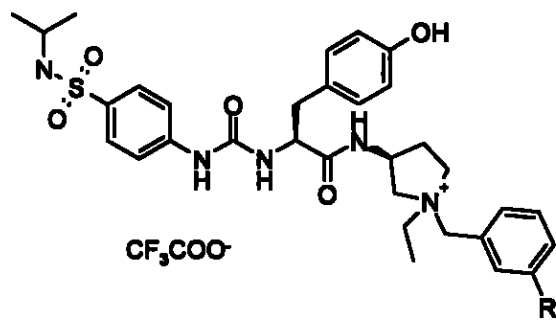
Tabla 6

Ejemplo	R	MS [M] ⁺
50		653

25 Procediendo de una manera similar a la descrita en el ejemplo 1, pero sustituyendo 1,1-dimetiletil (3*S*)-3-piperidinilcarbamato por 1,1-dimetiletil (3*S*)-3-

74
23

pirrolidinilcarbarnato, y/o sustituyendo 3,4-bis(metiloxi)benzaldehído por 3-hidroxi-benzaldehído, y sustituyendo yoduro de metilo por yoduro de etilo para preparar la sal de amonio cuaternario, se preparó el compuesto indicado en la Tabla 7.



5

Tabla 7

Ejemplo	R	MS [M] ⁺
51	OH	624

EJEMPLOS BIOLÓGICOS

Los efectos inhibidores de mAChR M₃ de los compuestos de la presente invención se determinan por medio de los siguientes ensayos *in vitro* e *in vivo*:

10 Análisis de la Inhibición de la Activación de Receptores por medio de la Movilización de Calcio:

1) Ensayo FLIPR de 384 pocillos

Se cultiva una línea de células CHO (ovario de hámster chino) que expresa de manera estable el receptor muscarínico M₃ humano de acetilcolina en DMEM
15 más FBS al 10%, Glutamina 2 mM y G418 a una concentración de 200 µg/ml. Se separan células para su mantenimiento y para su cultivo en placas para la preparación de ensayos usando métodos enzimáticos o de quelación de iones. El día antes del ensayo FLIPR (lector de placas de formación de imágenes fluorométricas), las células se separan, se resuspenden, se cuentan y se cultivan en placas para dar
20 20.000 células por placa de 384 pocillos en un volumen de 50 µl. Las placas de ensayo son placas de fondo transparente negro, Becton Dickinson número de catálogo 35 3962. Después de una noche de incubación de las células cultivadas en placas a 37 grados centígrados en un incubador de cultivo de tejidos, el ensayo se realiza al día siguiente. Para realizar el ensayo, el medio se aspira y las células se lavan
25 1 vez con tampón de ensayo (NaCl 145 mM, KCl 2,5 mM, glucosa 10 mM, HEPES 10 mM, MgCl₂ 1,2 mM, CaCl₂ 2,5 mM y probenecid 2,5 mM (pH 7,4). Después, las células se incuban con 50 µl de colorante Fluo-3 (4 µM en tampón de en-

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sayo) durante 60 – 90 minutos a 37 grados centígrados. El colorante sensible a calcio permite que las células muestren un aumento de la fluorescencia tras la respuesta al ligando por medio de la liberación de calcio desde los depósitos de calcio intracelulares. Las células se lavan con tampón de ensayo y después se resuspenden en 50 µl de tampón de ensayo antes del uso para los experimentos. Los compuestos de ensayo y los antagonistas se añaden en un volumen de 25 µl y las placas se incuban a 37 grados centígrados durante 5-30 minutos. Después se realiza una segunda adición a cada pocillo, esta vez con exposición al agonista, acetilcolina. Ésta se añade en un volumen de 25 µl sobre el instrumento FLIPR. Las respuestas de calcio se miden por cambios en unidades de fluorescencia. Para medir la actividad de los inhibidores/antagonistas, se añade ligando acetilcolina a una concentración CE_{50} y después se determina la CI_{50} del antagonista usando curvas de dilución dosis-respuesta. El antagonista de control usado con M3 es atropina.

15 2) Ensayo FLIPR de 96 pocillos

Se analizó la estimulación de mAChR expresados en células CHO controlando la movilización de calcio activada por receptores como se ha descrito previamente. Se cultivaron células CHO que expresaban de manera estable mAChR M₃ en placas de 96 pocillos de pared negra/fondo transparente. Después de 18 a 24 horas, el medio se aspiró y se reemplazó por 100 µl de medio de carga (EMEM con sales de Earl, BSA de calidad RIA al 0,1% (Sigma, St. Louis MO), y colorante indicador fluorescente Fluo-3-acetoximetil éster 4 µM (Fluo-3 AM, Molecular Probes, Eugene, OR) y se incubó durante 1 hora a 37°C. Después se aspiró el medio que contenía el colorante, se reemplazó por medio nuevo (sin Fluo-3 AM) y las células se incubaron durante 10 minutos a 37°C. Las células después se lavaron 3 veces y se incubaron durante 10 minutos a 37°C en 100 µl de tampón de ensayo (gelatina al 0,1% (Sigma), NaCl 120 mM, KCl 4,6 mM, KH_2PO_4 1 mM, $NaHCO_3$ 25 mM, $CaCl_2$ 1,0 mM, $MgCl_2$ 1,1 mM, glucosa 11 mM y HEPES 20 mM (pH 7,4)). Se añadieron 50 µl de compuesto (concentración final en el ensayo 1×10^{-11} – 1×10^{-5} M) y las placas se incubaron durante 10 minutos a 37°C. Las placas después se pusieron en un lector de placas de intensidad de luz fluorescente (FLIPR, Molecular Probes) donde las células cargadas de colorante se expusieron a una luz de excitación (488 nm) de un láser de argón de 6 vatios. Las células se activaron añadiendo 50 µl de acetilcolina (concentración final 0,1-10 nM), preparada en tampón que contenía BSA al 0,1%, a una velocidad de 50 µl/seg. La movilización de calcio, controlada

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como un cambio en la concentración citosólica de calcio, se midió como un cambio en la intensidad de emisión de 566 nm. El cambio en la intensidad de emisión está relacionado directamente con los niveles citosólicos de calcio. La fluorescencia emitida de los 96 pocillos se mide simultáneamente usando una cámara CCD enfriada.

- 5 Los puntos de datos se recogen cada segundo. Estos datos después se representaron y se analizaron usando el software GraphPad PRISM.

Broncodilatación inducida por metacolina

- La capacidad de respuesta de las vías respiratorias a metacolina se determinó en ratones BalbC despiertos, no encerrados ($n = 6$ en cada grupo). Se usó
10 pretismografía barométrica para medir los aumentos de las pausas (Penh), una medida sin unidades que, como se ha demostrado, se correlaciona con los cambios en la resistencia de las vías respiratorias que se producen durante la exposición bronquial a metacolina. Los ratones se pretrataron con 50 μ l de compuesto (0,003-10 μ g/ratón) en 50 μ l de vehículo (DMSO al 10%) por vía intranasal, y después se
15 pusieron en la cámara de pletismografía. Una vez en la cámara, los ratones se dejaron equilibrar durante 10 minutos antes de tomar una medición Penh inicial durante 5 minutos. Los ratones después se expusieron a un aerosol de metacolina (10 mg/ml) durante 2 minutos. Penh se registró de manera continua durante 7 minutos desde el comienzo de la administración del aerosol de metacolina, y continuando 5
20 minutos posteriormente. Los datos para cada ratón se analizaron y se representaron usando el software GraphPad PRISM.

- Todas las publicaciones, incluyendo aunque sin limitación las patentes y solicitudes de patente, citadas en esta memoria descriptiva se incorporan en este documento como referencia como si se indicara que cada publicación individual se
25 incorpora específica e individualmente como referencia en este documento como si se explicara con detalle.

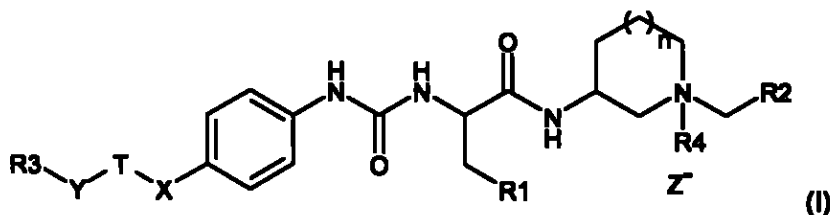
- La descripción anterior describe con detalle la invención incluyendo las realizaciones preferidas de la misma. Las modificaciones y mejoras de las realizaciones descritas específicamente en este documento están dentro del alcance de las
30 siguientes reivindicaciones. Se cree que un especialista en la técnica puede, sin mayor elaboración, usando la descripción anterior, utilizar la presente invención en toda su extensión. Por lo tanto, los Ejemplos de este documento deben considerarse simplemente ilustrativos y no deben considerarse de manera alguna una limitación del alcance de la presente invención. Las realizaciones de la invención en las

que se reivindica una propiedad o privilegio exclusivo se definen de la siguiente manera.

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REIVINDICACIONES

- Un compuesto de fórmula I como se indica a continuación:



- en la que

n es 0 ó 1;

cuando X es nitrógeno u oxígeno, Y no es nada;

cuando Y es nitrógeno u oxígeno, X no es nada;

T es un grupo sulfonilo (SO₂) o carbonilo (CO);

- cuando T=CO, X es oxígeno o nitrógeno;

Z se selecciona entre el grupo compuesto por halo, CF₃COO⁻, mesilato, tosilato, o cualquier otro contraión farmacéuticamente aceptable;

- R1 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, alquenilo C₃-C₈, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxí, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo y fenil-alquilo inferior C₁-C₃.

- R2 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxí, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈ y cicloalquil C₃-C₈-alquilo inferior y anillos heterocíclicos;

- R3 se selecciona entre el grupo compuesto por uno de los siguientes grupos no sustituidos o sustituidos: fenilo, fenil-alquilo inferior C₁-C₈, tiofenilo, tiofenil-alquilo inferior C₁-C₈, furanilo, furanil-alquilo inferior C₁-C₈, piridinilo, piridinil-alquilo inferior C₁-C₈, imidazolilo, imidazolil-alquilo inferior C₁-C₈, naftilo, naftil-alquilo inferior C₁-C₈, quinolinilo, quinolinil-alquilo inferior C₁-C₈, indolilo, indolil-alquilo inferior C₁-C₈, ben-

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- zotiofenilo, benzotiofenil-alquilo inferior C₁-C₈, benzofuranilo, benzofuranil-alquilo inferior C₁-C₈, benzoimidazolilo, benzoimidazolil-alquilo inferior C₁-C₈, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior C₁-C₈, o alquenilo C₃-C₈; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, fenoxi, fenil-alcoxi C₁-C₃, halo, hidroxil, amino, ciano, trifluorometilo, metilenodioxil, etilenodioxil, propilenodioxil, butilenodioxil, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, tiofenilo, tiofenil-alquilo inferior C₁-C₃, furanilo, furanil-alquilo inferior C₁-C₃, piridinilo, piridinil-alquilo inferior C₁-C₃, naftilo, naftil-alquilo inferior C₁-C₃, quinolinilo, quinolinil-alquilo inferior C₁-C₃, indolilo, indolil-alquilo inferior C₁-C₃, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₃, benzofuranilo, benzofuranil-alquilo inferior C₁-C₃, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ y NHCONHR₆;
- 15 R₄ se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈ o cicloalquil C₃-C₈-alquilo inferior.

2. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:
- 20 n es 0 ó 1;
- cuando X es nitrógeno u oxígeno, Y no es nada;
- cuando Y es nitrógeno u oxígeno, X no es nada;
- T es un grupo sulfonilo (SO₂) o carbonilo (CO);
- Z⁻ se selecciona entre el grupo compuesto por halo, CF₃COO⁻, mesilato, tosilato, o cualquier otro contraión farmacéuticamente aceptable;
- 25 R₁ se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, alquenilo C₃-C₈, fenilo sustituido o no sustituido o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxil, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo y fenil-alquilo inferior C₁-C₃;
- 30 R₂ se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está
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sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₆, halo, hidroxilo, amino, ciano, trifluorometilo, alquilo C₁-C₆ ramificado o no ramificado, cicloalquilo C₃-C₆ y cicloalquil C₃-C₆-alquilo inferior y anillos heterocíclicos;

- 5 R3 se selecciona entre el grupo compuesto por uno de los siguientes grupos no sustituidos o sustituidos: fenilo, fenil-alquilo inferior C₁-C₆, tiofenilo, tiofenil-alquilo inferior C₁-C₆, furanilo, furanil-alquilo inferior C₁-C₆, piridinilo, piridinil-alquilo inferior C₁-C₆, imidazolilo, imidazolil-alquilo inferior C₁-C₆, naftilo, naftil-alquilo inferior C₁-C₆, quinolinilo, quinolinil-alquilo inferior C₁-C₆, indolilo, indolil-alquilo inferior C₁-C₆, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₆, benzofuranilo, benzofuranil-alquilo inferior C₁-C₆, benzoimidazolilo, benzoimidazolil-alquilo inferior C₁-C₆, alquilo C₁-C₆ ramificado o no ramificado, cicloalquilo C₃-C₆, cicloalquil C₃-C₆-alquilo inferior C₁-C₆, o alquenilo C₃-C₆; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₆, fenoxi, fenil-alcoxi C₁-C₃, halo, hidroxilo, amino, ciano, trifluorometilo, metilenodioxilo, etilenodioxilo, propilenodioxilo, butilenodioxilo, alquilo C₁-C₆ ramificado o no ramificado, cicloalquilo C₃-C₆, cicloalquil C₃-C₆-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, tiofenilo, tiofenil-alquilo inferior C₁-C₃, furanilo, furanil-alquilo inferior C₁-C₃, piridinilo, piridinil-alquilo inferior C₁-C₃, naftilo, naftil-alquilo inferior C₁-C₃, quinolinilo, quinolinil-alquilo inferior C₁-C₃, indolilo, indolil-alquilo inferior C₁-C₃, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₃, benzofuranilo, benzofuranil-alquilo inferior C₁-C₃, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ y NHCONHR₆;
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- 25 R4 se selecciona entre el grupo compuesto por alquilo C₁-C₆ ramificado o no ramificado, cicloalquilo C₃-C₆ o cicloalquil C₃-C₆-alquilo inferior; o una sal farmacéuticamente aceptable del mismo.

3. Un compuesto de acuerdo con la reivindicación 1, seleccionado entre el grupo compuesto por:

- 30 n es 0 ó 1;
cuando X es nitrógeno u oxígeno, Y no es nada;
cuando Y es nitrógeno u oxígeno, X no es nada;
T es un grupo sulfonilo (SO₂) o carbonilo (CO);
cuando T=CO, X es oxígeno o nitrógeno;

Z' se selecciona entre el grupo compuesto por halo, CF_3COO^- , mesilato, tosilato, o cualquier otro contraión farmacéuticamente aceptable;

R1 se selecciona entre el grupo compuesto por alquilo $\text{C}_1\text{-C}_8$ ramificado o no ramificado, cicloalquilo $\text{C}_3\text{-C}_8$, cicloalquil $\text{C}_3\text{-C}_8$ -alquilo inferior, alquenilo $\text{C}_3\text{-C}_8$, fenilo sustituido o no sustituido o fenil no sustituido o sustituido-alquilo inferior $\text{C}_1\text{-C}_3$; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi $\text{C}_1\text{-C}_8$, halo, hidroxil, amino, ciano, trifluorometilo, alquilo $\text{C}_1\text{-C}_8$ ramificado o no ramificado, cicloalquilo $\text{C}_3\text{-C}_8$, cicloalquil $\text{C}_3\text{-C}_8$ -alquilo inferior, fenilo y fenil-alquilo inferior $\text{C}_1\text{-C}_3$;

R2 se selecciona entre el grupo compuesto por alquilo $\text{C}_1\text{-C}_8$ ramificado o no ramificado, cicloalquilo $\text{C}_3\text{-C}_8$, cicloalquil $\text{C}_3\text{-C}_8$ -alquilo inferior, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior $\text{C}_1\text{-C}_3$; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi $\text{C}_1\text{-C}_8$, halo, hidroxil, amino, ciano, trifluorometilo, alquilo $\text{C}_1\text{-C}_8$ ramificado o no ramificado, cicloalquilo $\text{C}_3\text{-C}_8$ y cicloalquil $\text{C}_3\text{-C}_8$ -alquilo inferior y anillos heterocíclicos;

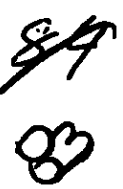
R3 se selecciona entre el grupo compuesto por uno de los siguientes grupos no sustituidos o sustituidos: fenilo, fenil-alquilo inferior $\text{C}_1\text{-C}_8$, tiofenilo, tiofenil-alquilo inferior $\text{C}_1\text{-C}_8$, furanilo, furanil-alquilo inferior $\text{C}_1\text{-C}_8$, piridinilo, piridinil-alquilo inferior $\text{C}_1\text{-C}_8$, imidazolilo, imidazolil-alquilo inferior $\text{C}_1\text{-C}_8$, naftilo, naftil-alquilo inferior $\text{C}_1\text{-C}_8$, quinolinilo, quinolinil-alquilo inferior $\text{C}_1\text{-C}_8$, indolilo, indolil-alquilo inferior $\text{C}_1\text{-C}_8$, benzotiofenilo, benzotiofenil-alquilo inferior $\text{C}_1\text{-C}_8$, benzofuranilo, benzofuranil-alquilo inferior $\text{C}_1\text{-C}_8$, benzoimidazolilo, benzoimidazolil-alquilo inferior $\text{C}_1\text{-C}_8$, alquilo $\text{C}_1\text{-C}_8$ ramificado o no ramificado, cicloalquilo $\text{C}_3\text{-C}_8$, cicloalquil $\text{C}_3\text{-C}_8$ -alquilo inferior $\text{C}_1\text{-C}_8$, o alquenilo $\text{C}_3\text{-C}_8$; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi $\text{C}_1\text{-C}_8$, fenoxi, fenil-alcoxi $\text{C}_1\text{-C}_3$, halo, hidroxil, amino, ciano, trifluorometilo, metilenodioxil, etilenodioxil, propilenodioxil, butilenodioxil, alquilo $\text{C}_1\text{-C}_8$ ramificado o no ramificado, cicloalquilo $\text{C}_3\text{-C}_8$, cicloalquil $\text{C}_3\text{-C}_8$ -alquilo inferior, fenilo, fenil-alquilo inferior $\text{C}_1\text{-C}_3$, tiofenilo, tiofenil-alquilo inferior $\text{C}_1\text{-C}_3$, furanilo, furanil-alquilo inferior $\text{C}_1\text{-C}_3$, piridinilo, piridinil-alquilo inferior $\text{C}_1\text{-C}_3$, naftilo, naftil-alquilo inferior $\text{C}_1\text{-C}_3$, quinolinilo, quinolinil-alquilo inferior $\text{C}_1\text{-C}_3$, indolilo, indolil-alquilo inferior $\text{C}_1\text{-C}_3$, benzotiofenilo, benzotiofenil-alquilo inferior $\text{C}_1\text{-C}_3$, benzofuranilo, benzofuranil-alquilo inferior $\text{C}_1\text{-C}_3$, COOH , COR_6 , COOR_6 , CONHR_6 , $\text{CON(R}_6)_2$, COG , NHR_6 , $\text{N(R}_6)_2$, G , OCOR_6 , OCONHR_6 , NHCOR_6 , $\text{N(R}_6)_2\text{COR}_6$, NHCOOR_6 y NHCONHR_6 ;

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R4 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈ o cicloalquilo C₃-C₈-alquilo inferior; o una sal farmacéuticamente aceptable del mismo.

- 5 4. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[[4-[[[2,2,2-trifluoroetil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
10 [[4-[[[5-metil-2-tienil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[4-[[[4-metil-2-tienil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[4-[[[8-quinolinilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
15 trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[4-[[[3,4-bis(metiloxy)fenil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[4-[[[2-bromofenil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
20 [[4-[[[4-fluorofenil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[4-[[[fenilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[4-[[[5-bromo-2-tienil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
25 trifluoroacetato de *N*-((3*S*)-1-[[3,4-bis(metiloxy)fenil]metil]-1-metil-3-piperidinol)-*N*-
[[4-[[[3-tienilsulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinol]-*N*-[[4-
[[[2,5-dimetil-3-tienil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinol]-*N*-[[4-
30 [[[2,2,2-trifluoroetil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinol]-*N*-[[4-
[[[5-metil-2-tienil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;
trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinol]-*N*-[[4-
[[[4-metil-2-tienil]sulfonil]oxi]fenil]amino]carbonil]-L-tirosinamida;

- trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[4-
 {[(5-cloro-2-tienil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[4-
 {[(metilsulfonil)oxi]fenil]amino]carbonil]-L-tirosinamida;
- 5 trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[4-
 {[(propilsulfonil)oxi]fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[4-{[2-(acetilamino)-4-metil-1,3-tiazol-5-
 il]sulfonil]oxi}fenil]amino]carbonil]-*N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-
 piperidinioil]-L-tirosinamida;
- 10 trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[4-
 {[(4-(fenilsulfonil)-2-tienil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[4-
 {[(5-cloro-2,1,3-benzoxadiazol-4-il)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[4-
 15 {[(2-naftalenilsulfonil)oxi]fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil]-*N*-[4-
 {[(2,2,2-trifluoroetil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[4-[(5-
 metil-2-tienil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- 20 trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[4-[(4-
 metil-2-tienil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[4-[(4-cianofenil)sulfonil]oxi}fenil]amino]carbonil]-*N*-[(3*S*)-1-
 [(4-fluorofenil)metil]-1-metil-3-piperidinioil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[4-[(4-
 25 (trifluorometil)fenil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[4-[(5-
 (3-isoxazolil)-2-tienil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[4-[(3-
 fluorofenil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- 30 trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[4-
 {[(1,3,5-trimetil-1*H*-pirazol-4-il)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-*N*-[4-[(5-
 metil-4-isoxazolil)sulfonil]oxi}fenil]amino]carbonil]-L-tirosinamida;
- trifluoroacetato de *N*-[4-[(3,5-dimetil-4-isoxazolil)sulfonil]oxi}fenil]amino]carbonil]-
 35 *N*-[(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil]-L-tirosinamida;



- trifluoroacetato de *N*-[[(4-[(2,4-diclorofenil)sulfonil]oxi]fenil)amino]carbonil]-*N*-{(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil}-*L*-tirosinamida;
- trifluoroacetato de *N*-{(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(trifluorometil)oxi]fenil)sulfonil]oxi]fenil]amino]carbonil]-*L*-tirosinamida;
- 5 trifluoroacetato de *N*-{(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(1-metil-1*H*-imidazol-4-il)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*N*-{(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil}-*L*-tirosinamida;
- trifluoroacetato de *N*-{(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil}-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 10 trifluoroacetato de *N*-{(3*S*)-1-[(4-clorofenil)metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-{(3*S*)-1-[(3-clorofenil)metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 15 trifluoroacetato de *N*-{(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(ciclohexilcarbonil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-{(3*S*)-1-[(3-hidroxifenil)metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(2-metilpropanoil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-{(3*S*)-1-[(3-clorofenil)metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(2-metilpropanoil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- 20 trifluoroacetato de *N*-{(3*S*)-1-[(4-clorofenil)metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(2-metilpropanoil)oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-{(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil}-*N*-[[(4-[(1-metiletil)amino]sulfonil]fenil)amino]carbonil]-*L*-tirosinamida;
- 25 trifluoroacetato de *N*-{(3*S*)-1-etil-1-[(3-hidroxifenil)metil]-3-pirrolidinioil}-*N*-[[(4-[(1-metiletil)amino]sulfonil]fenil)amino]carbonil]-*L*-tirosinamida;
- o cualquier otra sal farmacéuticamente aceptable.

5. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:

- 30 trifluoroacetato de *N*-{(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(2,5-dimetil-3-tienil)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;
- trifluoroacetato de *N*-{(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil}-*N*-[[(4-[(2,5-dimetil-3-tienil)sulfonil]oxi]fenil)amino]carbonil]-*L*-tirosinamida;

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- trifluoroacetato de *N*-{(3*S*)-1-[[3,4-bis(metiloxi)fenil]metil]-1-metil-3-piperidinioil)-*N*-
 {[(4-[(1-metiletil)sulfonil]oxi)fenil]amino]carbonil}-*L*-tirosinamida;
 trifluoroacetato de *N*-{(3*S*)-1-(1,3-benzodioxol-5-ilmetil)-1-metil-3-piperidinioil)-*N*-[(4-
 [(6-cloro-3-metil-1-benzotien-2-il)sulfonil]oxi)fenil]amino]carbonil}-*L*-tirosinamida;
 5 trifluoroacetato de *N*-[(4-[(2,5-dimetil-3-tienil)sulfonil]oxi)fenil]amino]carbonil)-*N*-
 {(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil)-*L*-tirosinamida;
 trifluoroacetato de *N*-{(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil)-*N*-[(4-[(1-
 metiletil)sulfonil]oxi)fenil]amino]carbonil}-*L*-tirosinamida;
 trifluoroacetato de *N*-{(3*S*)-1-[(4-fluorofenil)metil]-1-metil-3-piperidinioil)-*N*-[(4-[(1-
 10 metiletil)sulfonil]oxi)fenil]amino]carbonil}-*L*-tirosinamida;
 trifluoroacetato de *N*-{(3*S*)-1-[(3-hidroxifenil)metil]-1-metil-3-piperidinioil)-*N*-[(4-[(1-
 metiletil)amino]sulfonil]fenil]amino]carbonil}-*L*-tirosinamida
 o cualquier otra sal farmacéuticamente aceptable, o forma distinta de sal de
 los mismos.
- 15
6. Una composición farmacéutica para el tratamiento de enfermedades media-
 das por el receptor muscarínico de acetilcolina, que comprende un compuesto de
 acuerdo con la reivindicación 1 y un vehículo farmacéuticamente aceptable del mis-
 mo.
- 20
7. Una composición farmacéutica para el tratamiento de enfermedades media-
 das por el receptor muscarínico de acetilcolina, que comprende un compuesto de
 acuerdo con la reivindicación 1 y un vehículo farmacéuticamente aceptable del mis-
 mo.
- 25
8. Un método para inhibir la unión de acetilcolina a sus receptores en un mamí-
 fero en necesidad del mismo, que comprende administrar una cantidad segura y
 eficaz de un compuesto de acuerdo con la reivindicación 1.
- 30
9. Un método de tratamiento de una enfermedad mediada por el receptor mus-
 carínico de acetilcolina, donde la acetilcolina se une a dicho receptor, que com-
 prende administrar una cantidad segura y eficaz de un compuesto de acuerdo con
 la reivindicación 1.

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10. Un método de acuerdo con la reivindicación 8, en el que la enfermedad se selecciona entre el grupo compuesto por enfermedad pulmonar obstructiva crónica, bronquitis crónica, asma, obstrucción respiratoria crónica, fibrosis pulmonar, enfisema pulmonar y rinitis alérgica.
- 5
11. Un método de acuerdo con la reivindicación 9, en el que la administración se realiza por inhalación a través de la boca o la nariz.
12. Un método de acuerdo con la reivindicación 10, en el que la administración
- 10 se realiza por medio de un dispensador de medicamentos seleccionado entre un inhalador de polvo seco con depósito, un inhalador de polvo seco multi-dosis o un inhalador de dosis medida.
13. Un método de acuerdo con la reivindicación 11, en el que el compuesto se
- 15 administra a un ser humano y tiene una duración de acción de 12 horas o más para una dosis de 1 mg.
14. Un método de acuerdo con la reivindicación 12, en el que el compuesto tiene una duración de acción de 24 horas o más.
- 20
15. Un método de acuerdo con la reivindicación 13, en el que el compuesto tiene una duración de acción de 36 horas o más.

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RESUMEN DE LA DESCRIPCIÓN

Se proporcionan antagonistas del receptor muscarínico de acetilcolina y métodos de uso de los mismos.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

SIMON, Soma, G.
GlaxoSmithKline
Corporate Intellectual Property,
UW 2220
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA 19406-0939
United States of America

Date of mailing (day/month/year)

20 September 2005 (20.09.2005)

Applicant's or agent's file reference

PU60604

IMPORTANT NOTIFICATION

International application No.

PCT/US2004/040668

International filing date (day/month/year)

03 December 2004 (03.12.2004)

1. The following indications appeared on record concerning:



the applicant



the inventor



the agent



the common representative

Name and Address

State of Nationality

CN

State of Residence

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

FU, Wei
709 Swedeland Road
King of Prussia, PA 19406
United States of America

State of Nationality

CN

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person shown in Box II has been added as an applicant for US only.

4. A copy of this notification has been sent to:



the receiving Office



the designated Offices concerned



the International Searching Authority



the elected Offices concerned



the International Preliminary Examining Authority



other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer

Kishan SINGH RAM

Telephone No. (41-22) 338 8450

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SIMON, Soma, G.
GlaxoSmithKline
Corporate Intellectual Property,
UW 2220
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA 19408-0939
United States of America

Date of mailing (day/month/year)

20 September 2005 (20.09.2005)

Applicant's or agent's file reference

PU60604

IMPORTANT NOTIFICATION

International application No.

PCT/US2004/040668

International filing date (day/month/year)

03 December 2004 (03.12.2004)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality

US

State of Residence

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

PALOVICH, Michael, R.
709 Swedeland Road
King of Prussia, PA 19408
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person shown in Box II has been added as an applicant for US only.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer

Kishan SINGH RAM

Telephone No. (41-22) 338 8450

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SIMON, Soma, G.
GlaxoSmithKline
Corporate Intellectual Property,
UW 2220
709 Swadeland Road
P.O. Box 1539
King of Prussia, PA 19406-0939
United States of America

Date of mailing (day/month/year) 20 September 2005 (20.09.2005)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PU60604	
International application No. PCT/US2004/040668	International filing date (day/month/year) 03 December 2004 (03.12.2004)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address WANG, Yonghui 709 Swadeland Road King of Prussia, PA 19406 United States of America	State of Nationality CN	State of Residence 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 CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

The person shown in Box 1 has been deleted from the record of this application.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.87.40	Authorized officer José APPAVE Telephone No. (41-22) 338 8163
--	---

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

SIMON, Soma, G.
GlaxoSmithKline
Corporate Intellectual Property,
UW 2220
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA 19406-0939
United States of America

Date of mailing (day/month/year)

20 September 2005 (20.09.2005)

Applicant's or agent's file reference

PU60604

IMPORTANT NOTIFICATION

International application No.

PCT/US2004/040888

International filing date (day/month/year)

03 December 2004 (03.12.2004)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

WANG, Feng
709 Swedeland Road
Swedeland Road
King of Prussia, PA 19406
United States of America

State of Nationality

CN

State of Residence

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

CN

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person shown in Box 1 has been deleted from the record of this application.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer

Kishan SINGH RAM

Telephone No. (41-22) 338 8460

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SIMON, Soma, G.
GlaxoSmithKline
Corporate Intellectual Property,
UW 2220
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA 19406-0939
United States of America

Date of mailing (day/month/year) 20 September 2005 (20.09.2005)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PU60604	
International application No. PCT/US2004/040668	International filing date (day/month/year) 03 December 2004 (03.12.2004)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address SHI, Dongchuan 709 Swedeland Road King of Prussia, PA 19406 United States of America	State of Nationality CN	State of Residence 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 CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

The person shown in Box 1 has been deleted from the record of this application.

4. A copy of this notification has been sent to:

☒ the receiving Office	☒ the designated Offices concerned
☒ the International Searching Authority	☐ the elected Offices concerned
☐ the International Preliminary Examining Authority	☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.87.40	Authorized officer Kishan SINGH RAM Telephone No. (41-22) 338 8450
--	--

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SIMON, Soma, G.
GlaxoSmithKline
Corporate Intellectual Property,
UW 2220
709 Swedeland Road
P.O. Box 1539
King of Prussia, PA 19406-0939
United States of America

Date of mailing (day/month/year) 20 September 2005 (20.09.2005)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PU60604	
International application No. PCT/US2004/040668	International filing date (day/month/year) 03 December 2004 (03.12.2004)

1. The following indications appeared on record concerning:		
☒ the applicant	☒ the inventor	☐ the agent ☐ the common representative
Name and Address RIVERO, Ralph, A. 1250 South Collegeville Road Collegeville, PA 19426 United States of America	State of Nationality US	State of Residence 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 US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary: The person shown in Box 1 has been deleted from the record of this application.		
4. A copy of this notification has been sent to:		
☒ the receiving Office	☒ the designated Offices concerned	
☒ the International Searching Authority	☐ the elected Offices concerned	
☐ the International Preliminary Examining Authority	☐ other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Kishan SINGH RAM
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 8450

PATENT COOPERATION TREATY

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GlaxoSmithKline
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UW 2220
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United States of America

Date of mailing (day/month/year)

20 September 2005 (20.09.2005) ..

Applicant's or agent's file reference

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IMPORTANT NOTIFICATION

International application No.

PCT/US2004/040668

International filing date (day/month/year)

03 December 2004 (03.12.2004)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

MOORE, Michael, Lee
417 South Jackson Street
1250 South Collegeville Road
Collegeville, PA 19426
United States of America

State of Nationality

US

State of Residence

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

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The applicant shown in Box 1 has been deleted from the record of this applicant.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87.40

Authorized officer

Kishan SINGH RAM

Telephone No. (41-22) 338 8460

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 June 2005 (23.06.2005)

PCT

(10) International Publication Number
WO 2005/055941 A3(51) International Patent Classification: A61K 31/445,
C07D 211/56(21) International Application Number:
PCT/US2004/040668(22) International Filing Date:
3 December 2004 (03.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/526,766 3 December 2003 (03.12.2003) US(71) Applicant (for all designated States except US): GLAXO
GROUP LIMITED [GB/GB]; Glaxo Wellcome House,
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(72) Inventors; and

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WANG, Yonghui [CN/US]; 709 Swedeland Road, King of
Prussia, PA 19406 (US). FU, Wei [CN/US]; 709 Swede-
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Prussia, PA 19406 (US).(74) Agents: SIMON, Soma, G. et al.; GlaxoSmithKline,
Corporate Intellectual Property, UFW 2220, 709 Swedeland
Road, P.O. Box 1539, King of Prussia, PA 19406-0939
(US).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GH, GM, GR, GU, HT, 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, KR, LS, MW, MZ, NA, SD, SI, 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).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations 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, GR, GU, HT, 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, UZ, VC, VN, YU, ZA, ZM,
ZW, ARIPO patents (BW, GH, GM, KE, LS, MW, MZ, NA,
SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (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 patents (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG)— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations 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, GR, GU, HT, 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, UZ, VC, VN, YU, ZA,
ZM, ZW, ARIPO patents (BW, GH, GM, KE, LS, MW, MZ,
NA, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (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 patents (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG)

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments(88) Date of publication of the international search report:
16 February 2006For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.(54) Title: NOVEL M₃ MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) Abstract: Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.

WO 2005/055941 A3

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/40668

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/443, C07D 211/56

US CL : 514/329; 546/223

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/329; 546/223

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 practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/48099 A1 (MERCK PATENT GMBH) 20 June 2002 (20.06.2002), see pages 54-61, piperidinyl species.	1-6

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"T" earlier application or patent 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

"I" 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

"A" document member of the same patent family

Date of the actual completion of the international search

17 November 2005 (17.11.2005)

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Date of mailing of the international search report

13 DEC 2005

Author: [Signature]

Gina Chung

Telephone No. 571-272-1600

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/40668

96

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

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 additional fees, this Authority did not invite payment of any additional fees.
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.: 1-14, α -1 piperidinium compounds

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/40668

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97

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
Group I, claims 1-3, 6-14 in part and 4-5, drawn to piperidinium compounds i.e. $n=1$ and their composition.

Group II, claims 1-3, 6-14 in part when $n=0$, drawn to pyrrolidiny compounds and their composition.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: prior art indicated that the pyrrolidinium core and the piperidinium core do not share any technical features as to link the two groups together for the utility. The piperidinium core are evidenced to have chemotactic activity (see CA 138304060) while the pyrrolidinium core have plant growth regulatory activity (see CA 94:121072).

Continuation of B. FIELDS SEARCHED Item 3:

CAS—structure
East/West

PATENT CO PERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SOMA G. SIMON
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, UW2220
709 SWEDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 13 DEC 2005	
Applicant's or agent's file reference PU60604	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US04/40668	International filing date (day/month/year) 03 December 2004 (03.12.2004)
Applicant GLAXO GROUP LIMITED	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is notified, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.62.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 28 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
C. A. CHONG

Telephone No. 571-272-1600

Form PCT/IBA/220 (January 2004)

(See notes on accompanying sheet)

2005 DEC 19 12:33
RECEIVED
GLAXOSMITHKLINE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PU60604	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US04/40668	International filing date (day/month/year) 03 December 2004 (03.12.2004)	(Earliest) Priority Date (day/month/year) 03 December 2003 (03.12.2003)
Applicant GLAXO GROUP LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

a. With regard to the language, the international search was carried out on the basis of

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☒ Unity of invention is lacking (See Box No. III)

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/40668

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100

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

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 additional fees, this Authority did not invite payment of any additional fees.
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.: 1-14, n=1 piperidinum compounds

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/40668

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/445, C07D 211/56

US CL : 514/329; 546/223

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/329; 546/223

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 practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/48099 A1 (MERCK PATENT GMBH) 20 June 2002 (20.06.2002), see pages 54-61, piperidinyi species.	1-6

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

Special categories of cited documents:	
* "A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but aimed to understand the principle or theory underlying the invention
"T" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 November 2005 (17.11.2005)

Date of mailing of the international search report

13 DEC 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450Authorized Signature
Gaila Chang

Telephone No. 571-272-1600

Facsimile No. (571) 273-3201

Form PCT/ISA/210 (second sheet) (April 2003)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/40668

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
Group I, claims 1-3, 6-14 in part and 4-5, drawn to piperidinium compounds i.e. $n=1$ and their composition.

Group II, claims 1-3, 6-14 in part when $n=0$, drawn to pyrrolidinyll compounds and their composition.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: prior art indicated that the pyrrolidinium core and the piperidinium core do not share any technical feature as to link the two groups together for the utility. The piperidinium core are evidenced to have chemotactic activity (see CA 138304060) while the pyrrolidinium core have plant growth regulatory activity (see CA 94:121072).

Continuation of B. FIELDS SEARCHED Item 3:
CAS-structure
East/West

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
SOMA G. SIMON
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, UW2220
709 SWDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) 13 DEC 2009

Applicant's or agent's file reference

PU60604

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US04/40668

International filing date (day/month/year)

03 December 2004 (03.12.2004)

Priority date (day/month/year)

03 December 2003 (03.12.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 31/443, C07D 211/56 and US Cl.: 514/329; 546/223

Applicant

GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be "the IPEA" and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Date of completion of this opinion
17 November 2005 (17.11.2005)

Authorized officer
Chia Chang
Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/40668

105
104

Box No. 1 Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
☐ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/LB04/40668

106
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-14, ~~and~~ 1 ~~isopropylidene compounds~~

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/40668

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-14	YES
	Claims NONE	NO
Inventive step (IS)	Claims 1-14	YES
	Claims NONE	NO
Industrial applicability (IA)	Claims 1-14	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-14 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the instantly claimed compounds. Prior art WO 02/48099 differ from the claims in they are not quaternary piperidinium compounds and the substitution is on the 4- position instead of 3-position of the piperidiny ring.

Claims 1-14 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.



Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-053412- -00000-0000
Fac: 2008-08-02 18:45:24 Dep. 2020 NUECREACIONES
Tia: 11 PATENTENYA
Eve: 370 FASENACIONALI
Act 411 PRESENTACION Folio: 107

Delegatura de Propiedad Industrial División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION () MODELO DE UTILIDAD ()	()	()
-Indicación de que se solicita la concesión de una patente.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Descripción de la invención.	()	()
-Dibujos de ser estos pertinentes.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()	()	()

DISEÑO INDUSTRIAL ()

-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que 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 identificación 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:

Fecha:

OLARTE RAISBECK



1101081
Ministerio de Industria y Comercio
Rad. 06-053412-00000-0000
Fec: 2006-06-02 16:45:24 Dep. 2020 NUECREACIONES
T. 1 PATENTE VII
C. 070 FACENACIONAL II
Act. 411 PRESENTACION Folios: 107

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT

ENTRADA EN FASE NACIONAL

03-07-2006

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley
Avenue, Greenford, Middlesex UB6 0NN

Nacionalidad o Domicilio: BRITANICA

Lugar de Constitución: INGLATERRA

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Cual _____

Número _____

3

**REPRESENTANTE
APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Cual _____

Número: 79.782.747 Bta
TP 74.295

4

**INVENTOR (ES)
(72)**

Nombre: (1) JAKOB BUSCH-PETERSEN; (2) JIAN JIN; (3) MICHAEL R. PALOVICH;
(4) WEI FU

Dirección: (1, 2 y 4) 709 Swedeland Road, King of Prussia, PA 19406, E.U.A.; (3)
1250 South Collegeville Road Collegeville, PA 19426, E.U.A.

Nacionalidad o Domicilio: (1) Danes; (2 y 4) Chino; (3) Estadounidense

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PCT (86)

Solicitud Internacional No. PCT/US2004/040668

Fecha Diciembre 3, 2004

Publicación Internacional No. WO 2005/055941

Fecha Junio 23, 2005

6

**Título (54) NUEVOS ANTAGONISTAS DEL RECEPTOR MUSCARÍNICO M, DE
ACETILCOLINA.**

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Clasificación Internacional (51) A61K 31/445, C07D 211/56

8

Prioridad

SI ☒

N ☐

(33) País de Origen

US

(32) Fecha

Diciembre 3, 2003

(31) Número de Solicitud

60/526,766

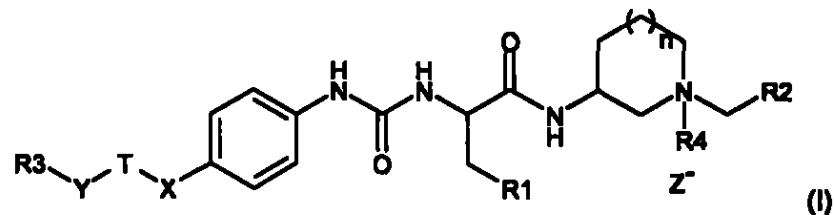
9

Comprobante de pago No. 06 -41,020

Fecha Junio 1, 2006

REIVINDICACIONES

1. Un compuesto de fórmula I como se indica a continuación:



- 5 en la que

n es 0 ó 1;

cuando X es nitrógeno u oxígeno, Y no es nada;

cuando Y es nitrógeno u oxígeno, X no es nada;

T es un grupo sulfonilo (SO₂) o carbonilo (CO);

- 10 cuando T=CO, X es oxígeno o nitrógeno;

Z' se selecciona entre el grupo compuesto por halo, CF₃COO⁻, mesilato, tosilato, o cualquier otro contraión farmacéuticamente aceptable;

- 15 R1 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, alquenilo C₃-C₈, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxil, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo y fenil-alquilo inferior C₁-C₃.

- 20 R2 se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxil, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈ y cicloalquil C₃-C₈-alquilo inferior y anillos heterocíclicos;

- 25 R3 se selecciona entre el grupo compuesto por uno de los siguientes grupos no sustituidos o sustituidos: fenilo, fenil-alquilo inferior C₁-C₈, tiofenilo, tiofenil-alquilo inferior C₁-C₈, furanilo, furanil-alquilo inferior C₁-C₈, piridinilo, piridinil-alquilo inferior C₁-C₈, imidazolilo, imidazolil-alquilo inferior C₁-C₈, naftilo, naftil-alquilo inferior C₁-C₈, quinolinilo, quinolinil-alquilo inferior C₁-C₈, indolilo, indolil-alquilo inferior C₁-C₈, ben-

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- zotiofenilo, benzotiofenil-alquilo inferior C₁-C₈, benzofuranilo, benzofuranil-alquilo inferior C₁-C₈, benzoimidazolilo, benzoimidazolil-alquilo inferior C₁-C₈, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior C₁-C₈, o alquenilo C₃-C₈; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, fenoxi, fenil-alcoxi C₁-C₃, halo, hidroxil, amino, ciano, trifluorometilo, metilenodioxil, etilenodioxil, propilenodioxil, butilenodioxil, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo, fenil-alquilo inferior C₁-C₃, tiofenilo, tiofenil-alquilo inferior C₁-C₃, furanilo, furanil-alquilo inferior C₁-C₃, piridinilo, piridinil-alquilo inferior C₁-C₃, naftilo, naftil-alquilo inferior C₁-C₃, quinolinilo, quinolinil-alquilo inferior C₁-C₃, indolilo, indolil-alquilo inferior C₁-C₃, benzotiofenilo, benzotiofenil-alquilo inferior C₁-C₃, benzofuranilo, benzofuranil-alquilo inferior C₁-C₃, COOH, COR₆, COOR₆, CONHR₆, CON(R₆)₂, COG, NHR₆, N(R₆)₂, G, OCOR₆, OCONHR₆, NHCOR₆, N(R₆)COR₆, NHCOOR₆ y NHCONHR₆;
- 15 R₄ se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈ o cicloalquil C₃-C₈-alquilo inferior.

2. Un compuesto de acuerdo con la reivindicación 1 seleccionado entre el grupo compuesto por:
- 20 n es 0 ó 1;
cuando X es nitrógeno u oxígeno, Y no es nada;
cuando Y es nitrógeno u oxígeno, X no es nada;
T es un grupo sulfonilo (SO₂) o carbonilo (CO);
Z se selecciona entre el grupo compuesto por halo, CF₃COO⁻, mesilato, tosilato, o cualquier otro contraión farmacéuticamente aceptable;
- 25 R₁ se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, alquenilo C₃-C₈, fenilo sustituido o no sustituido o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está sustituido, un grupo está sustituido con uno o más radicales seleccionados entre el grupo compuesto por alcoxi C₁-C₈, halo, hidroxil, amino, ciano, trifluorometilo, alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo y fenil-alquilo inferior C₁-C₃;
- 30 R₂ se selecciona entre el grupo compuesto por alquilo C₁-C₈ ramificado o no ramificado, cicloalquilo C₃-C₈, cicloalquil C₃-C₈-alquilo inferior, fenilo no sustituido o sustituido, o fenil no sustituido o sustituido-alquilo inferior C₁-C₃; donde, cuando está
- 35

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

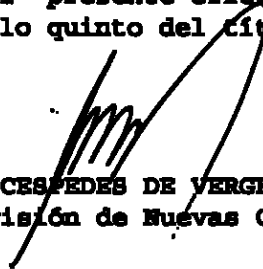
REFERENCIA	Radicación No.	06 53412
	Solicitud internacional	
	Fecha inicio fase nacional	
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	9838

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.
2. Debe aclarar el nombre de los inventores por cuanto difieren en la publicación internacional y el petitorio de la solicitud en fase nacional .

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMONA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 01 SET. 2020 jramos