1444

PETITORIO

1

Industria y Comercio
SUPERINTENDENCIA

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SUPERINTENDENCIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X] Patente de Invención [ ] Patente de Modelo de Utilidad
[ ] Capítulo I. [X] Capítulo II.

(2) SOLICITANTE (71)

Nombre: SMITHKLINE BEECHAM CORPORATION
Dirección: One Franklin Plaza Philadelphia, PA 19103. Estados Unidos de América.
Nacionalidad o Domicilio:
Lugar de Constitución: ESTADOUNIDENSE
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual ____
Número ____

(3) REPRESENTANTE O APODERADO

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Dirección: World Trade Center Torre C, Calle 100 No. 8A-55 Piso 10.
Teléfono: 6386200 Fax: 6386201
E-Mail: filings@phillipsmisbook.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual ____
Número 79.782.747 Bta TP 74.295

(4) INVENTOR (ES) (72)

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Nacionalidad o Domicilio: ESTADOUNIDENSE

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SI [X] NO [ ]	US	Mayo 7, 2001	60/289.327

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

42

2

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] 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.
- [X] Otros: BUSQUEDA INTERNACIONAL

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente.

NOMBRE: CARLOS BOLAÑOS

FIRMA:

C.C. 74.782.747 de Ibagué T.P. 74.295

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

43

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

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JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	53220244	24/06/2003	10,050,000.00

$$$$ C O N C E P T O $$$$

CANT.	IDENTIFICO	CONCEPTO	TOTAL CONCEPTO
1	90905-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	406,000.00
		TOTAL : $	406,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SMITHKLINE BEECHAM CORPORATION

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 certificando que Peter John Giddings es apoderado de Smithkline Beecham Corporation, 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. G229470
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 CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1997

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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 "P. Giddings" 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 corporación denominada **"SMITHKLINE BEECHAM CORPORATION"**, corporación legalmente constituída y existente de acuerdo con las leyes del Estado de Pensilvania, Estados Unidos de América, con domicilio social en 1, Franklin Plaza, Philadelphia, Pensilvania 19101, Estados Unidos de América;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el 11 de julio de 2002, copia del cual he tenido a la vista.

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 trece de agosto del año dos mil tres.

...ESO NOTARIAL ONCE DE ESTE ...CIRCULO HACE CONSTAR QUE ESTA ...FOTOCOPIA COINCIDE CON EL ...ORIGINAL QUE HE TENIDO A LA VISTA.
23 OCT 2003
...BOGOTÁ, D.C. - COLOMBIA
...NOTARIO DE BAUTISTA
...NOTARIA ONCE (11)

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

DE PINNA

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

5. at London/à Londres — 6. the/le — Certified/Attesté 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 — G229470

9. Stamp: timbre:

10. Signature: J. Carlisle

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.

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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Power of Attorney

The undersigned,

SmithKline Beecham Corporation

domiciled in

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

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,

SmithKline Beecham Corporation

domiciliado en

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

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

Date/Fecha: 13 August 2003

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

DILIGENCIA DE RECONOCIMIENTO ONCE DE AGOSTO
EL SUSCRITO NOTARIO HACE CONSTAR QUE ESTA FIRMA COINCIDE CON EL QUE HE TENIDO A LA VISTA.
13 AGO 2003
BOGOTA, D.C. - COLOMBIA
NOTARIA CINCUENTA Y UNO DE BAUTISTA
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(72) Inventors; and
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(74) Agent: HALL, Linda, E.; UW2220, 709 Swedeland Road, King Of Prussia, PA 19406 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, 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, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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

WO 02/089792 A1

(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

8

SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide

- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)

- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* 1980, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* 1996, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* 1999, *401*, 282; Douglas & Ohlstein (2001). Trends Cardiovasc. Med., 10: in press).

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis, dyslipidemia, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: 131; 10-12) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Urotensin antagonists may provide end organ protection in hypertensitive cohorts in addition to lowering blood pressure.

Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* 1999, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 June; 155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, neuromuscular function, parkinsons, movement disorders, sleep-wake cycle, and incentive motivation (Clark *et al.Brain Research* 923 (2001) 120-127.

Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* 1999, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders. Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

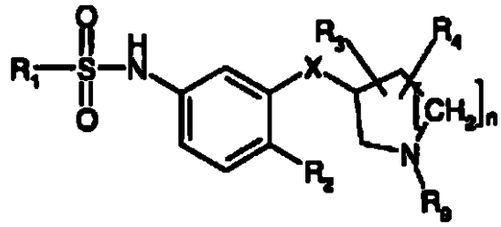
The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):

The present invention provides for compounds of Formula (I):



Formula (I)

wherein:

R_1 is phenyl substituted or unsubstituted by one, two , three, four or five of any of the following: halogen, CF_3, OCF_3, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, NR_5R_6, $CONR_7R_8$, SC_{1-6} alkyl, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl);

R_2 is hydrogen, halogen, CF_3, CN or C_{1-4} alkyl;

R_3, R_4, R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_5, R_6, and R_9, are independently hydrogen or C_{1-6} alkyl;

X is O, S, or CH_2;

n is 1;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine, and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

Preferably R_1 is phenyl substituted or unsubstituted by one, two , three, four, or five of any of the following: halogen, CF_3, OCF_3, CN, C_{1-6} alkyl, C_{1-6} alkoxy, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl), or NO_2.

Preferably R_2 is hydrogen, halogen, CF_3, or C_{1-4} alkyl. More preferably R_2 is halogen or CF_3.

Preferably R_3 is hydrogen.

Preferably R_4 is hydrogen.

Preferably R_9 is hydrogen or C_{1-6} alkyl.

Preferably X is O.

Preferred compounds are:

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,5-trimethoxy-benzenesulfonamide hydrochloride;

(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

(±)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4-trifluoromethylbenzene-sulfonamide;

(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4-trifluoromethylbenzene-sulfonamide;

2-Bromo-N-[4-chloro-3-((S)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide;

4-Bromo-2-chloro-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-5-methoxy-benzenesulfonamide;

2,4-Dibromo-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-5-methoxy-benzenesulfonamide;

(R)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methyl-4,5-dimethoxybenzenesulfonamide;

(±)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(±)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methyl-4-bromobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,5-trichlorobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,4,5,6-pentamethylbenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methoxy-5-bromobenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-(methylpropionate)benzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-4-bromobenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,6-trimethyl-4-methoxybenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,4-trichlorobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,5,6-tetramethylbenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-isopropylbenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-ethylbenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4-cyanobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-dichloro-6-methylbenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-3,6-dibromobenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-trifluoromethoxy-4-bromobenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-fluorobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-butylbenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-difluoro-5-bromobenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-difluoro-5-chlorobenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-fluoro-4-methoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-difluorobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-4-chlorobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-nitro-4-chlorobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dimethyl-4-bromobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dibromobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,6-trichlorobenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-5-fluoro-4-methoxy-2-trifluoromethyl-benzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,5-difluoro-4-methoxy-2-methyl-benzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-6-bromo-2,3-difluoro-4-methoxy-benzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4,5-dimethoxy-2-trifluoromethyl-benzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4,5-dimethoxy-benzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-fluoro-2-trifluoromethyl-benzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,6-trifluoro-benzenesulfonamide;

3,4-Dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

2-Bromo-4,5-dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

2-Chloro-4,5-dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

4,5-Dimethoxy-2-methyl-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

4-Bromo-2-chloro-5-methoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

2-Bromo-4,5-dimethoxy-N-[4-methyl-3-((S)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

N-[4-Chloro-3-((R)-pyrrolidin-3-yloxy)-phenyl]-2-bromo-3,4-dimethoxy-benzenesulfonamide;

(±)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamid
(R)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(±)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;
2-Chloro-4,5-dimethoxy-3-[((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,6-Dichloro-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-benzenesulfonamide;
2-Bromo-4,5-dimethoxy-N-[3-(1-methyl-pyrrolidin-3-yloxy-4-trifluoromethy-phenyl]-benzenesulfonamide;
3,4-Dimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,4,5-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,3,4,5,6-Pentamethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
4-Bromo-2,5-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,3,4-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
4-Isopropyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,4-Dichloro-6-methyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
3,4-Dibromo-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,4,6-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
5-Bromo-2,4-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
5-Chloro-2,4-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
4-Chloro-2,5-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
4-Methoxy-2,3,6-trimethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

3,5-Dimethoxy-2-methyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,4-Dibromo-5-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2-Bromo-5,6-difluoro-4-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

4,5-Dimethoxy-2-trifluoromethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,4,5-Trimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide; and

4-Bromo-2,6-dimethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide.

More preferred compounds are:

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichlorn-4-trifluoromethylbenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,6-trimethyl-4-methoxybenzene-sulfonamide;

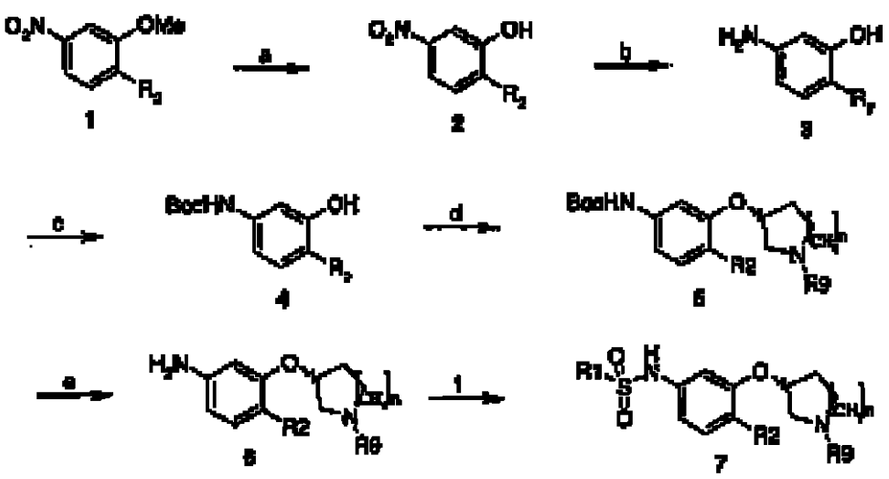
2-Bromo-4,5-dimethoxy-N-[3-((R)-1-methyl-pyrrolindin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2-Chloro-4,5-dimethoxy-N-[3-((R)-1-methyl-pyrrolindin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide; and

2,6-Dichloro-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-benzenesulfonamide.

Compounds of Formula (I) may be prepared as outlined in Scheme 1.

Scheme 1

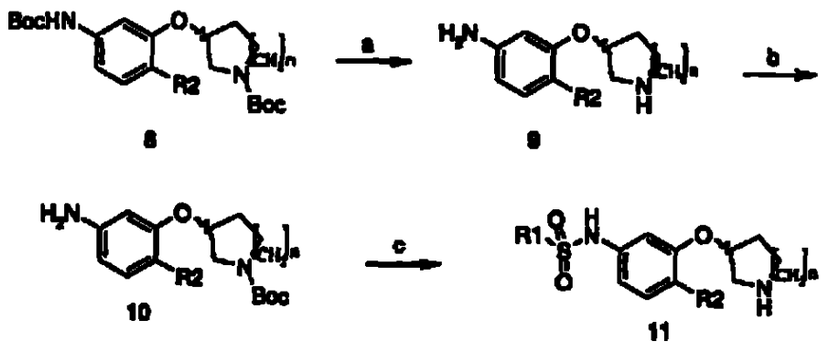


Conditions: a) 48% hydrogen bromide, acetic acid; b) hydrogen (50 psi), platinum on carbon, ethyl acetate; c) di-*tert*-butyldicarbonate, tetrahydrofuran, reflux; d) 1-Rg-pyrrolidin-3-ol, DIAD, triphenylphosphine, tetrahydrofuran, 0 °C to ambient temperature; e) 6 N HCl in dioxane; f) $R1SO_2Cl$, chloroform, ambient temperature.

For example, acid-mediated demethylation of anisoles 1 gave phenols 2. Hydrogenation of the nitro group provided anilines 3, which were subsequently protected as their *tert*-butoxycarbonyl carbamates 4. Alkylation of 4 with various alcohols using standard Mitsunobu conditions, followed by removal of the nitrogen protecting group afforded anilines 6. Subsequent sulfonylation of the anilines furnished the target compounds 7.

Analogs which contain an N-unsubstituted pyrrolidine side chain may be prepared according to scheme 2.

Scheme 2

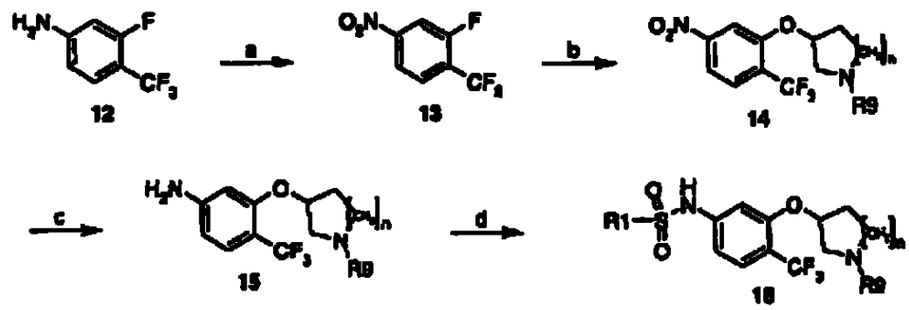


Conditions: a) 6 N hydrogen chloride/dioxane, ambient temperature;
b) di-*tert*-butyl-dicarbonate, tetrahydrofuran, ambient temperature;
c) R1-SO_2Cl, chloroform, ambient temperature; then 6 N hydrogen chloride/dioxane, ambient temperature.

Analogs which contain an N-unsubstituted pyrrolidine side chain were prepared from the corresponding *tert*-butoxycarbonyl derivatives 8. Thus, removal of the protecting groups with 4 N hydrogen chloride in dioxane provided amines 9. The secondary amine was selectively protected as its *tert*-butyl carbamate to furnish aniline 10. Sulfonylation of 10, followed by protecting group removal afforded the target compounds 11.

Compounds wherein R_2 is CF_3 may be prepared as follows:

Scheme 3



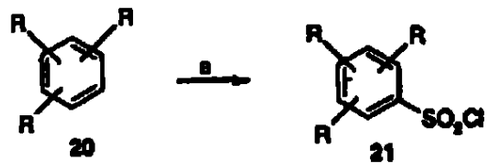
Conditions: a) 50% hydrogen peroxide, trifluoroacetic acetic acid, reflux;
b) 1-R9-pyrrolidin-3-ol, sodium hydride, tetrahydrofuran, 0°C;
c) hydrogen (50 psi), platinum on carbon, ethyl acetate; d) R1-SO_2Cl, chloroform, room temperature.

For example, oxidation of aniline 12 gave nitrobenzene 13. Substitution of the aryl fluoride with various alcohols furnished the ethers 14. Hydrogenation of the nitro group provided anilines 15, which were subsequently sulfonylated with variuos sulfonyl chlorides to furnish the target compounds 16.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

A number of optionally substituted benzenesulfonyl chlorides used in the synthesis of the title compounds were not available commercially and were prepared according to scheme 4. 2,4-Dibromo-5-methoxybenzenesulfonyl chloride was prepared as described in *WO9838182*.

Scheme 4



20 21

Substituted benzenes 20 were treated with chlorosulfonic acid to furnish the desired sulfonyl chlorides 21.

Conditions: a) chlorosulfonic acid, dichloromethane, 0 °C to ambient temperature.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral

administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of

increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ^{125}I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

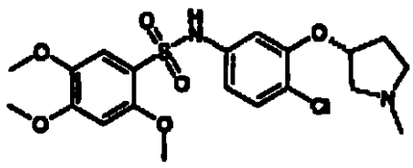
HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^{3}H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1µM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 1 nM – 10000 nM (example 10,Ki = 270 nM).

The following Examples are illustrative but not limiting embodiments of the present invention.

Example 1

(R)-N-(4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,5-trimethoxybenzenesulfonamide hydrochloride.



a) 2-Chloro-5-nitrophenol

2-Chloro-5-nitroanisole (310 g, 1.7 mol) was taken up in a mixture of 48% HBr (1.5 L) and AcOH (1.2 L) and heated at reflux for 3 days. The dark solution was allowed to cool to room temperature, poured into ice water (10 L), and let stand for 3 h. The resultant dull yellow solid was filtered, washed with water, and dried in vacuo (230 g, 79%): mp 115-117 °C.

b) 2-Chloro-5-aminophenol

A solution of 2-chloro-5-nitrophenol (114 g, 0.66 mol) in ethyl acetate (500 mL) was treated with 5% Pt/C (510 mg, 0.5 weight%) and the mixture shaken under a hydrogen atmosphere (30 psi) for 6 h. The mixture was filtered through Celite® and the residue washed well with ethyl acetate. Evaporation of the ethyl acetate gave a solid (95 g, 100% crude yield) which was taken directly into the next step.

c) *4-Chloro-3-hydroxyphenylcarbamic acid tert-butyl ester*

To a solution of 2-chloro-5-aminophenol (95 g, 0.66 mol) in THF (600 mL) was added a solution of di-*tert*-butyl dicarbonate (144 g, 0.66 mol) in THF (600 mL). The reaction was heated at reflux for 6 h, at which time it was allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue diluted with ether (1000 mL) and washed with 1 M citric acid (2 x 1000 mL). The aqueous washings were extracted with ether (500 mL) and the combined organics washed with brine (500 mL), dried ($MgSO_4$), and concentrated. The resultant brown solid was triturated with hexanes and dried in vacuo to give 125 g (78%) of the title compound: mp 103-106 °C.

d) *4-Chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy) aniline*

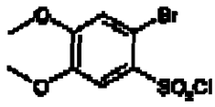
To a cooled (0 °C) solution of 4-chloro-3-hydroxyphenylcarbamic acid *tert*-butyl ester (55 g, 0.23 mol), (S)-1-methyl-pyrrolidin-3-ol (24 g, 0.24 mol), and triphenylphosphine (89 g, 0.34 mol) in THF (1.1 L) was added dropwise via addition funnel a solution of DIAD (67 mL, 0.34 mol) in THF (100 mL) over 1 h. The resultant solution was allowed to slowly warm to ambient temperature and maintained for 16 h. The THF was removed in vacuo and the residue treated with 6 N HCl (650 mL). The resultant mixture was stirred at room temperature for 4 h, at which time it was diluted with water (500 mL) and the filtered to remove the triphenylphosphine oxide. The filtrate was washed with EtOAc (3 x 1 L) and chloroform (5 x 1 L) to remove additional reaction by-products. The aqueous layer was then basified with solid NaOH pellets and extracted with ether (2 x 1 L) and EtOAc (2 x 1 L). The combined organic layers were washed with saturated $NaHCO_3$ (2 x 1 L) and brine (1 L), dried ($MgSO_4$), and concentrated to give 40 g (80%) of the title compound: MS (ES+) m/e $[M+H]^+$ 227.

e) (R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,5-trimethoxybenzenesulfonamide hydrochloride

(R)-3-(1-Methyl-3-pyrrolidinyl)-4-chloroaniline (56 mg, 0.25 mmol) was dissolved in dichloroethane (4 mL). 2,4,5-trimethoxybenzenesulfonyl chloride (66 mg, 0.25 mmol) was added and the mixture was allowed to stir at room temperature for 2 days. The mixture was concentrated and the residue recrystallized from ethanol to furnish the title compound (85 mg, 69%): MS (ES+) m/e $[M+H]^+$ 457.

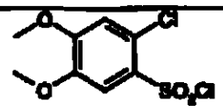
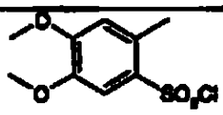
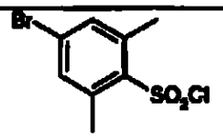
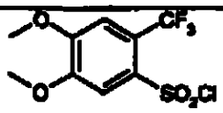
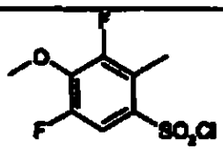
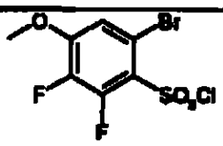
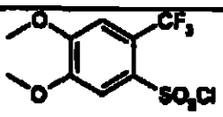
EXAMPLE 2a

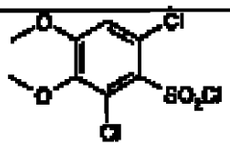
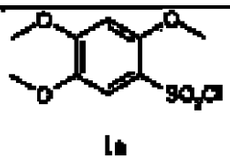
2-Bromo-4,5-dimethoxybenzenesulfonyl chloride



To a cooled (0 °C) solution of 4-bromoveratrole (15 mL, 100 mmol) in dichloromethane (100 mL) was added dropwise chlorosulfonic acid (26 mL, 400 mmol). The reaction was allowed to slowly warm to ambient temperature and maintained for 3 hours, at which time it was concentrated and diluted with ether (300 mL). The resultant solution was then washed with ice cold water (2 x 250 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated to furnish a grayish powder (25 g, 78%).

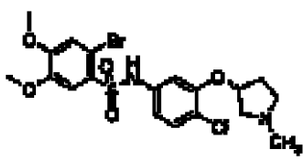
Examples 15a, 16a, 44a, 47a, 48a, 49a, 50a, 51a, and 1a were made as set forth in Example 2a by substituting the appropriate starting materials.

Example	Compound
 15a	2-Chloro-4,5-dimethoxy-benzenesulfonyl chloride
 16a	4,5-Dimethoxy-2-methyl-benzenesulfonyl chloride
 44a	4-bromo-2,6-dimethyl-benzenesulfonyl chloride
 47a	4,5-Dimethoxy-2-trifluoromethyl-benzenesulfonyl chloride
 48a	3,5-Difluoro-4-methoxy-2-methyl-benzenesulfonyl chloride
 49a	6-Bromo-2,3-difluoro-4-methoxy-benzenesulfonyl chloride
 50a	4,5-Dimethoxy-2-trifluoromethyl-benzenesulfonyl chloride

 51a	2,6-Dichloro-4,5-dimethoxy-benzenesulfonyl chloride
 1a	2,4,5-Trimethoxy-benzenesulfonyl chloride

Example 2

(R2-Bromo-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide



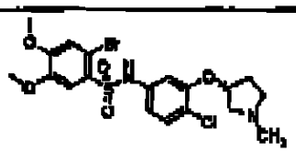
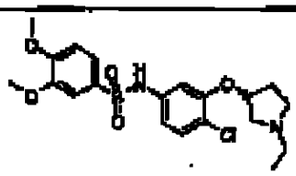
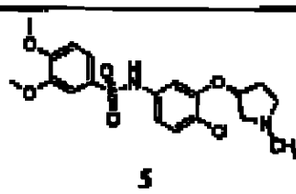
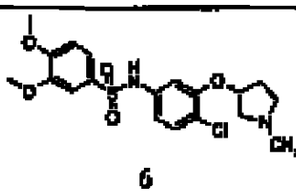
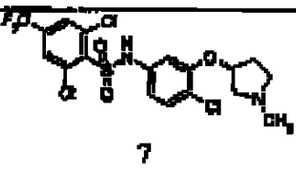
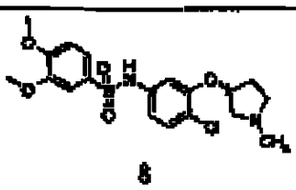
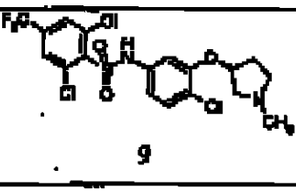
a) 4-Chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy) aniline

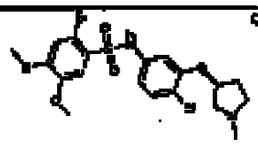
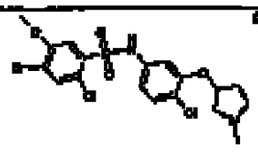
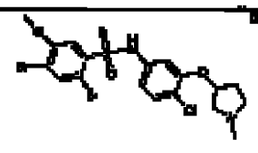
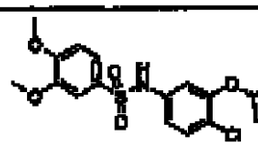
4-Chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy) aniline was prepared according to the procedure in 1(a) - (d).

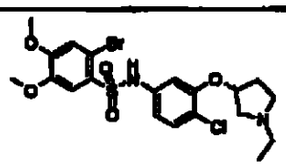
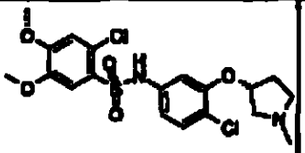
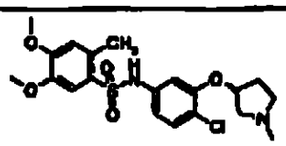
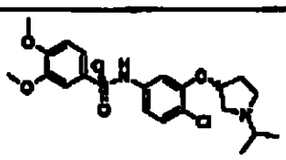
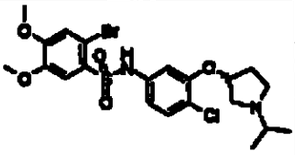
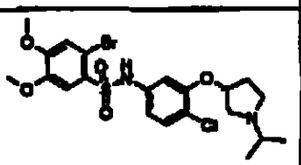
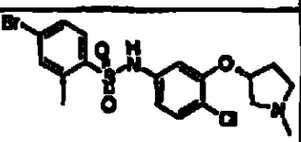
b) 2-Bromo-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide

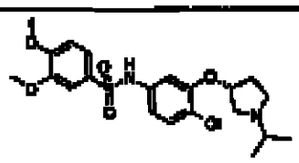
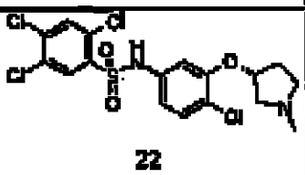
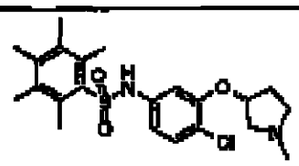
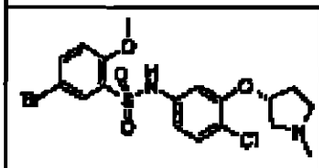
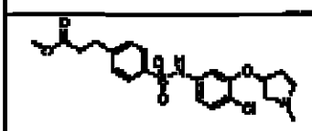
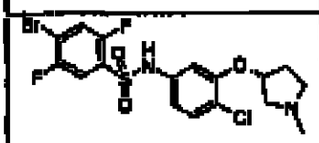
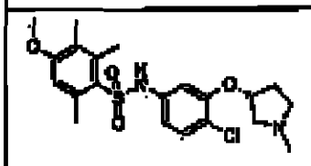
To a solution of 4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy) aniline (30 g, 132 mmol) in 1,2-dichloroethane (500 mL) was added a solution of 2-bromo-4,5-dimethoxybenzenesulfonyl chloride (42 g, 135 mmol) in 1,2-dichloroethane (300 mL). The resultant solution was maintained at ambient temperature for 14 h, at which time the solids that had formed were filtered, washed with dichloromethane and ether, and dried in vacuo (50 °C) to afford 58 g (81 %) of the title compound: mp 214 °C (dec); MS (ES+) m/e $[M+H]^+$ 505.

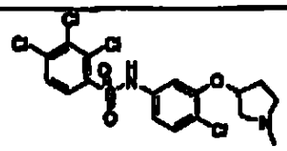
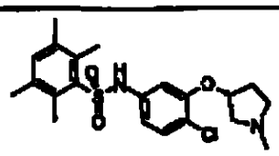
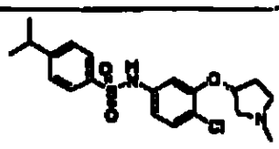
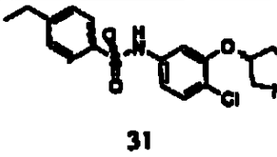
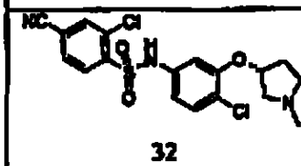
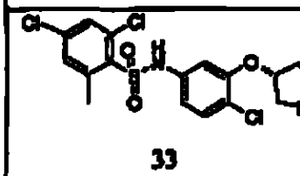
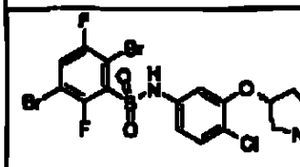
Examples 3-53 were made as set forth in Example 1 by substituting the appropriate starting materials.

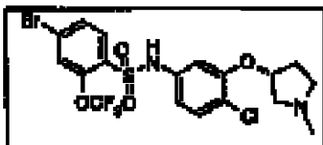
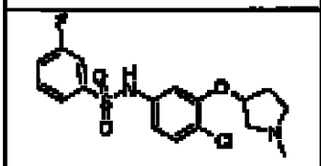
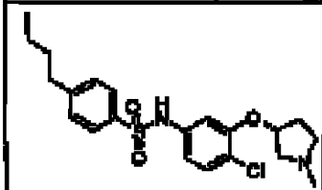
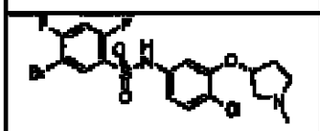
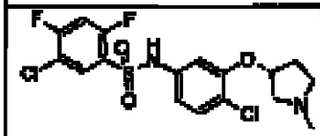
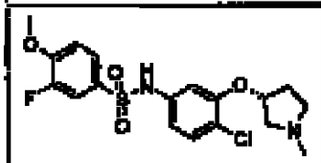
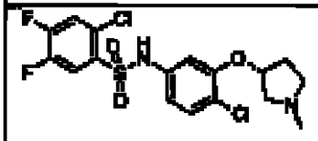
Example	Compound	MS (ES+) m/e [M+H]+
 3	(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide	506
 4	(±)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	441
 5	(S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	427
 6	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	427
 7	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4-trifluoromethylbenzene-sulfonamide	503
 8	(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	427
 9	(S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4-trifluoromethylbenzene-sulfonamide	503

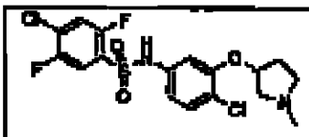
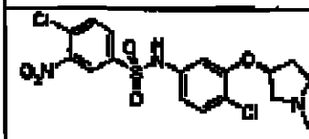
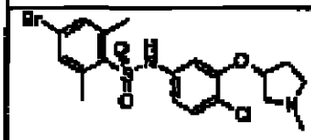
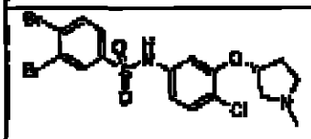
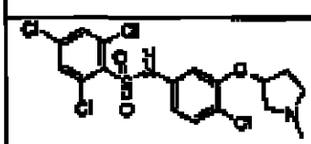
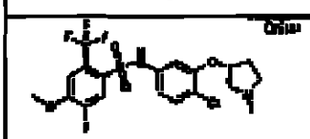
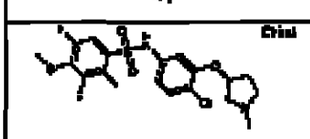
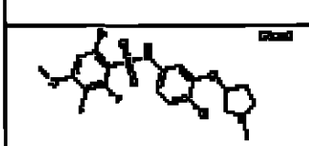
 10	2-Bromo-N-[4-chloro-3-((S)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide	506
 11	4-Bromo-2-chloro-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-5-methoxy-benzenesulfonamide	510
 12	2,4-Dibromo-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-5-methoxy-benzenesulfonamide	553
 13	(R)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	441

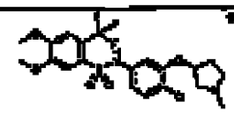
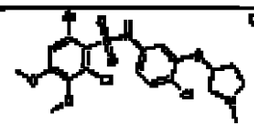
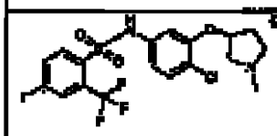
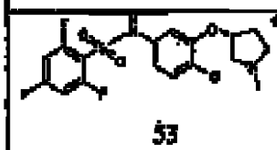
 14	(R)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide	520
 15	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-dimethoxybenzenesulfonamide	461
 16	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methyl-4,5-dimethoxybenzenesulfonamide	441
 17	(±)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	455
 18	(±)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide	534
 19	(R)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide	534
 20	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methyl-4-bromobenzenesulfonamide	460

 21	(R)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	455
 22	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,5-trichlorobenzenesulfonamide	469
 23	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,4,5,6-pentamethylbenzenesulfonamide	437
 24	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methoxy-5-bromobenzene-sulfonamide	476
 25	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-(methylpropionate)benzene-sulfonamide	453
 26	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3-difluoro-4-bromobenzene-sulfonamide	482
 27	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,6-trimethyl-4-methoxybenzene-sulfonamide	439

 28	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,4-trichlorobenzenesulfonamide	469
 29	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,5,6-tetramethylbenzenesulfonamide	423
 30	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-isopropylbenzenesulfonamide	409
 31	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-ethylbenzenesulfonamide	395
 32	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4-cyanobenzenesulfonamide	426
 33	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-dichloro-6-methylbenzene-sulfonamide	449
 34	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-3,6-dibromobenzene-sulfonamide	561

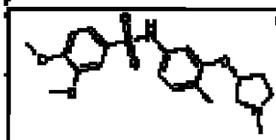
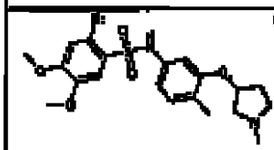
 35	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-difluoromethoxy-4-bromobenzene-sulfonamide	460
 36	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-fluorobenzenesulfonamide	385
 37	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-butylbenzenesulfonamide	423
 38	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-difluoro-5-bromobenzene-sulfonamide	482
 39	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-difluoro-5-chlorobenzene-sulfonamide	437
 40	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-fluoro-4-methoxybenzenesulfonamide	415
 41	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-difluorobenzenesulfonamide	437

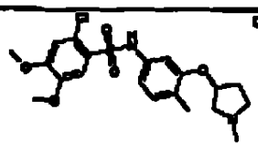
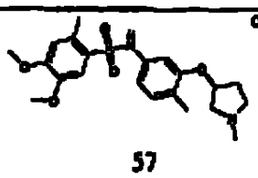
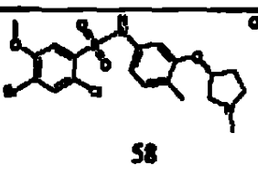
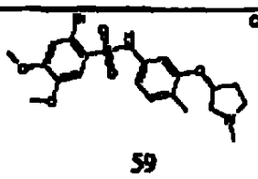
 42	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-4-chlorobenzene-sulfonamide	437
 43	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-5-nitro-4-chlorobenzenesulfonamide	446
 44	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dimethyl-4-bromobenzene-sulfonamide	474
 45	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dibromobenzenesulfonamide	525
 46	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,6-trichlorobenzenesulfonamide	469
 47	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-5-fluoro-4-methoxy-2-trifluoromethyl-benzenesulfonamide	483
 48	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,5-difluoro-4-methoxy-2-methyl-benzenesulfonamide	447
 49	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-6-bromo-2,3-difluoro-4-methoxy-benzenesulfonamide	512

 50	(R)-N-(4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4,5-dimethoxy-2-trifluoromethyl-benzenesulfonamide	495
 51	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4,5-dimethoxy-benzenesulfonamide	495
 52	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-fluoro-2-trifluoromethyl-benzenesulfonamide	453
 53	(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,6-trifluoro-benzenesulfonamide	421

EXAMPLES 54-59

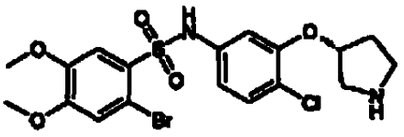
Substituting 5-amino-o-cresol for 2-chloro-5-aminophenol and substituting various sulfonyl chlorides for 2,4,5-trimethoxybenzenesulfonyl chloride, examples 54-59 were prepared following the procedures described in 1e-1e:

Example	Compound	MS (ES+) m/e $[M+H]^+$
 54	3,4-Dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide	407
 55	2-Bromo-4,5-dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide	486

 56	2-Chloro-4,5-dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide	441
 57	4,5-Dimethoxy-2-methyl-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide	421
 58	4-Bromo-2-chloro-5-methoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide	490
 59	2-Bromo-4,5-dimethoxy-N-[4-methyl-3-((S)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide	486

EXAMPLE 60

N-(4-Chloro-3-((R)-pyrrolidin-3-yloxy)-phenyl]-2-bromo-3,4-dimethoxy-benzenesulfonamide



a) (R)-3-(5-amino-2-chlorophenoxy)-pyrrolidine

To a solution of (R)-3-(5-*tert*-butoxycarbonylamino-2-chlorophenoxy)-pyrrolidine-1-carboxylic acid-*tert*-butyl ester (2 g, 4.9 mmol) in dioxane (30 mL) was added 6 N hydrogen chloride (20 mL). The reaction mixture was stirred for 2 hours, at which time it was concentrated. The resultant residue was triturated with ethyl acetate and dichloromethane, then diluted with 2.5 M potassium hydroxide (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organics were washed with brine (50 mL), dried over magnesium sulfate, and concentrated to give (R)-3-(5-amino-2-chlorophenoxy)-pyrrolidine (810 mg, 75%).

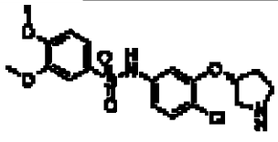
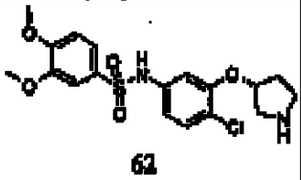
b) (R)-3-(5-amino-2-chlorophenoxy)-pyrrolidine-1-carboxylic acid-tert-butyl ester

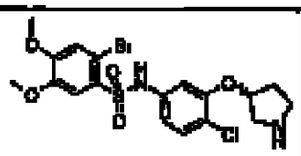
To a solution of (R)-3-(5-amino-2-chlorophenoxy)-pyrrolidine (810 mg, 3.9 mmol) in tetrahydrofuran (40 mL) was added di-*tert*-butyl-dicarbonate (830 mg, 3.9 mmol). The resultant solution was maintained at ambient temperature for 20 hours, at which time it was diluted with ether (100 mL), washed with 5% aqueous citric acid (100 mL), water (100 mL), and brine (50 mL), and dried over magnesium sulfate. Concentration of the solution gave (R)-3-(5-amino-2-chlorophenoxy)-pyrrolidine-1-carboxylic acid-tert-butyl ester (1.2 g, 99%).

c) N-[4-Chloro-3-((R)-pyrrolidin-3-yloxy)-phenyl]-2-bromo-3,4-dimethoxy-benzenesulfonamide

To a solution of (R)-3-(5-amino-2-chlorophenoxy)-pyrrolidine-1-carboxylic acid-tert-butyl ester (100 mg, 0.33 mmol) in chloroform (5 mL) was added 2-bromo-4,5-dimethoxybenzenesulfonyl chloride (120 mg, 0.33 mmol). The resultant solution was maintained at ambient temperature for 24 hours, at which time it was concentrated. The residue was diluted with dioxane (4 mL) and 6 N hydrogen chloride (2 mL) and stirred for 5 hours, at which time it was concentrated. Crystallization from ethanol furnished the title compound (22 mg, 11%). MS (ES+) m/e 492 $[M+H]^+$

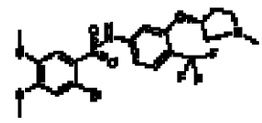
Using the appropriate starting materials, the following compounds were made according to example 60.

Example	Compound	MS (ES+) m/e $[M+H]^+$
 61	(±)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	413
 62	(R)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide	413

 63	(±)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide	492

EXAMPLE 64

2-Bromo-4,5-dimethoxy-N-[3-(1-methyl-pyrrolidin-3-yloxy-4-trifluormethy-phenyl]-benzenesulfonamide



a) 2-Fluoro-4-nitrobenzotrifluoride

A solution of 4-amino-2-fluorobenzotrifluoride (25.0g, 0.14mol, 1.0eq) in trifluoroacetic acid (140ml) was heated to reflux then was treated with the dropwise addition of 50% hydrogen peroxide (66.7ml, 1.18mol, 8.4eq) over 35min. The reaction was heated at reflux for 1.5hrs further then cooled to ambient temperature. Poured into ice-water (1L) then stirred overnight. The oil that separated was collected (decanting the water phase) then diluted with diethyl ether (150ml). The ether solution was washed with aqueous 10% HCl (100ml), saturated aqueous sodium bicarbonate (2x100ml), and brine (100ml) then dried over anhydrous magnesium sulphate. Evaporation under reduced pressure gave an orange-brown oil. Distillation (14torr, 88-90°C) gave the product as a yellow liquid (15.0g, 51%)

b) 2-((R)-1-Methyl-pyrrolidin-3-yloxy)-4-nitrobenzotrifluoride

A solution of 2-fluoro-4-nitrobenzotrifluoride (12.4g, 59.3mmol, 1.0eq) and (R)-1-methyl-pyrrolidin-3-ol (6.0g, 59.3mmol, 1.0eq) in anhydrous tetrahydrofuran (150ml) was cooled to 0°C then slowly treated with portions of 60% sodium hydride (4.7g, 0.12mol, 2eq) over 5min. Without removing the ice bath, the reaction was allowed to come to room temperature and stir for 48hrs. Quenched with water (50ml) and brine (100ml) then extracted into diethyl ether (5x100ml). Extracts dried over anhydrous magnesium sulfate and decolorizing charcoal for 1hr. Filtered through Celite. The filtrate was treated with silica (35g) then evaporated to give the crude product suspended on silica. Column chromatography on silica (1% MeOH/EtOAc→5%MeOH/EtOAc) gave the product (Rf=0.3 in 5%MeOH/EtOAc) as an orange oil (7.85g, 46%).

c) 3-((R)-1-Methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenylamine

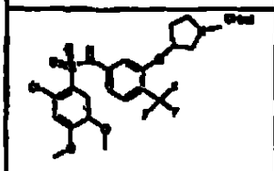
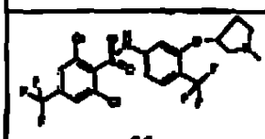
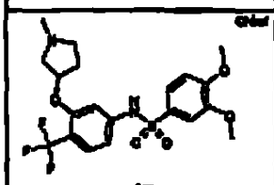
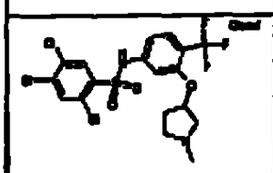
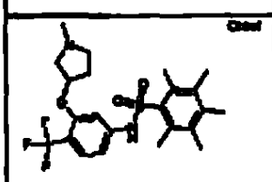
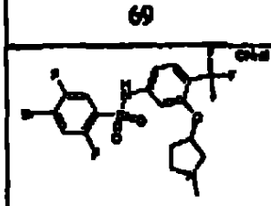
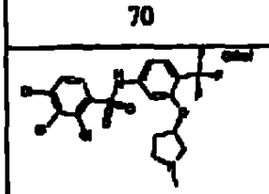
A solution of 2-((R)-1-Methyl-pyrrolidin-3-yloxy)-4-nitrobenzotrifluoride (7.8 g, 26.9 mmol) in ethyl acetate (50 ml) was treated with 10% platinum on carbon (200mg) then subjected to 40psi hydrogen pressure for 3hrs. The slurry was treated with anhydrous magnesium sulfate (5 g) then filtered through a pad of Celite. The filter cake was rinsed with ethyl acetate (2x25 ml) then the filtrate was evaporated under reduced pressure to an oil. This oil was evaporated twice for dichloromethane (50 ml) to remove trapped ethyl acetate. This gave the product as a clear light brown oil that solidified on standing (6.9 g, 99%): LCMS 249 ($M^+ + H$).

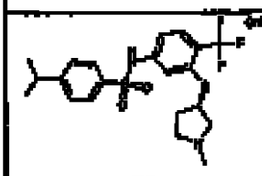
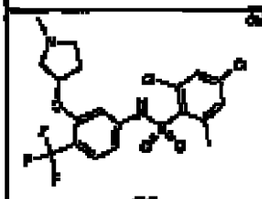
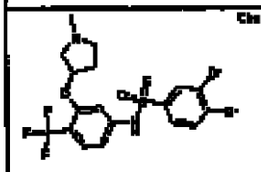
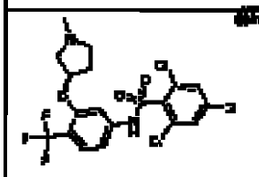
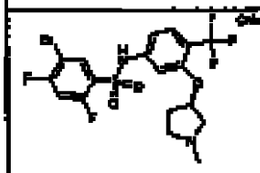
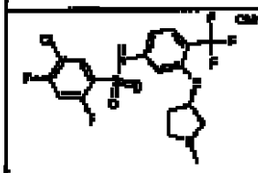
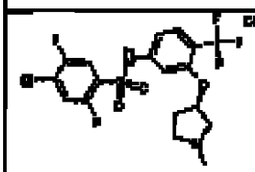
d) 2-Bromo-4,5-dimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide

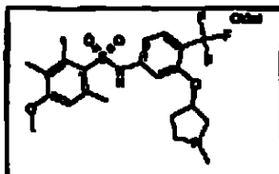
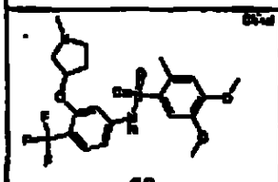
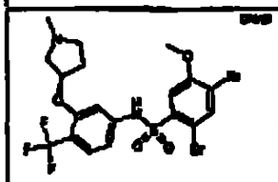
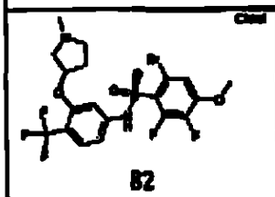
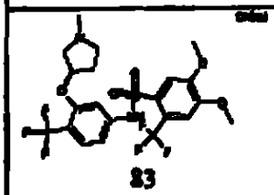
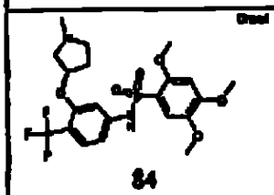
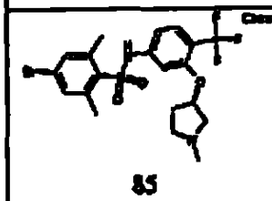
A solution of 3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenylamine (250 mg, 0.96 mmol) and 2-bromo-4,5-dimethoxybenzenesulfonyl chloride (303 mg, 0.96 mmol) in anhydrous 1,2-dichloroethane (5 ml) was stirred at ambient temperature for 3 days. The reaction mixture was evaporated under reduced pressure to a gum, then taken into dimethylsulfoxide (3 ml) and purified by preparative HPLC. The combined fractions were evaporated under reduced pressure to give the product as the TFA salt. This was treated with aqueous 10% NaOH (50 ml) and methylene chloride (50 ml). The resulting suspension was stirred vigorously for 20 min, then filtered to collect the insoluble product free base. The dried free base was dissolved into methanol (5 ml) then treated with concentrated hydrochloric acid (0.1 ml). Evaporation under reduced pressure gave the product hydrochloride salt as a pale yellow solid (347 mg, 63%): MS (ES+) m/e $[M+H]^+$ 539.

EXAMPLES 65-85

Substituting 3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenylamine for (R)-3-(1-methyl-3-pyrrolidinyl)-4-chloroaniline and substituting various sulfonyl chlorides for 2,4,5-trimethoxybenzenesulfonyl chloride, examples 65-85 were prepared following the procedure described in 1e:

Example	Compound	MS (ES+) m/e [M+H]+
 65	2-Chloro-4,5-dimethoxy-3-[((R)-1-methyl-pyrrolindin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	495
 66	2,6-Dichloro-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-benzenesulfonamide	537
 67	3,4-Dimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	461
 68	2,4,5-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	503
 69	2,3,4,5,6-Pentamethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	471
 70	4-Bromo-2,5-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	516
	2,3,4-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	503

71		
 72	4-Isopropyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	443
 73	2,4-Dichloro-6-methyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	483
 74	3,4-Dibromo-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	559
 75	2,4,6-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	503
 76	5-Bromo-2,4-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	516
 77	5-Chloro-2,4-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	471
 78	4-Chloro-2,5-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	471

 79	4-Methoxy-2,3,6-trimethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	473
 80	3,5-Dimethoxy-2-methyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	475
 81	2,4-Dibromo-5-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	589
 82	2-Bromo-5,6-difluoro-4-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	546
 83	4,5-Dimethoxy-2-trifluoromethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	529
 84	2,4,5-Trimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	491
 85	4-Bromo-2,6-dimethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide	508

EXAMPLE 86

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Parenteral Formulation

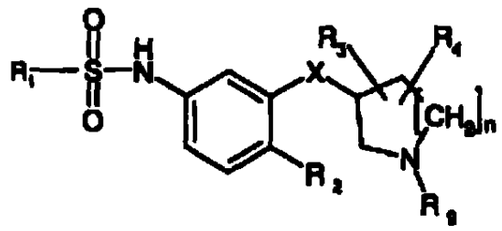
A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within

the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

R^1 is phenyl substituted or unsubstituted by one, two , three, four or five of any of the following: halogen, CF_3, OCF_3, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, NR_5R_6, $CONR_7R_8$, SC_{1-6} alkyl, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl);

R_2 is hydrogen, halogen, CF_3, CN or C_{1-4} alkyl;

R_3, R_4, R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_5, R_6, and R_9, are independently hydrogen or C_{1-6} alkyl;

X is O, S, or CH_2;

n is 1;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is phenyl substituted or unsubstituted by one, two, three, four, or five of any of the following: halogen, CF_3, OCF_3, CN, C_{1-6} alkyl, C_{1-6} alkoxy, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl), or NO_2; R_2 is hydrogen, halogen, CF_3, or C_{1-4} alkyl; R_3 is hydrogen; R_4 is hydrogen; R_9 is hydrogen or C_{1-6} alkyl; and X is O.

3. A compound according to claim 1 wherein R_1 is phenyl substituted or unsubstituted by one, two, three or four of the following: halogen, CF_3, CN, methyl, methoxy; R_2 is halogen or CF_3, R_3 is hydrogen; R_4 is hydrogen; R_9 is hydrogen or C_{1-6} alkyl; and X is O.

4. A compound according to claim 1 chosen from the group consisting of:
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,5-triimethoxy-benzenesulfonamide hydrochloride;
(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;
(±)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4-trifluoromethylbenzene-sulfonamide;
(±)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(S)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4-trifluoromethylbenzene-sulfonamide;
2-Bromo-N-[4-chloro-3-((S)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide;
4-Bromo-2-chloro-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-5-methoxy-benzenesulfonamide;
2,4-Dibromo-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-5-methoxy-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-ethyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methyl-4,5-dimethoxybenzenesulfonamide;
(±)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(±)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methyl-4-bromobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-isopropyl-3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,5-trichlorobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,4,5,6-pentamethylbenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-methoxy-5-bromobenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-(methylpropionate)benzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-4-bromobenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,6-trimethyl-4-methoxybenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,4-trichlorobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,5,6-tetramethylbenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-isopropylbenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-ethylbenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4-cyanobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-dichloro-6-methylbenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-3,6-dibromobenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-trifluoromethoxy-4-bromobenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-fluorobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-butylbenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-difluoro-5-bromobenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4-difluoro-5-chlorobenzene-sulfonamide;

(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-fluoro-4-methoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-difluorobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,5-difluoro-4-chlorobenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3-nitro-4-chlorobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dimethyl-4-bromobenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,4-dibromobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,6-trichlorobenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-5-fluoro-4-methoxy-2-trifluoromethyl-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-3,5-difluoro-4-methoxy-2-methyl-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-6-bromo-2,3-difluoro-4-methoxy-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4,5-dimethoxy-2-trifluoromethyl-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4,5-dimethoxy-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-4-fluoro-2-trifluoromethyl-benzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,4,6-trifluoro-benzenesulfonamide;
3,4-Dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;
2-Bromo-4,5-dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;
2-Chloro-4,5-dimethoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;
4,5-Dimethoxy-2-methyl-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;
4-Bromo-2-chloro-5-methoxy-N-[4-methyl-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

2-Bromo-4,5-dimethoxy-N-[4-methyl-3-((S)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-benzenesulfonamide;

N-[4-Chloro-3-((R)-pyrrolidin-3-yloxy)-phenyl]-2-bromo-3,4-dimethoxy-benzenesulfonamide;

(±)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(R)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-3,4-dimethoxybenzenesulfonamide;

(±)-N-[4-Chloro-3-(3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;

2-Chloro-4,5-dimethoxy-3-[((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,6-Dichloro-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-benzenesulfonamide;

2-Bromo-4,5-dimethoxy-N-[3-(1-methyl-pyrrolidin-3-yloxy-4-trifluormethy-phenyl]-benzenesulfonamide;

3,4-Dimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,4,5-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,3,4,5,6-Pentamethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

4-Bromo-2,5-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,3,4-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

4-Isopropyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,4-Dichloro-6-methyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

3,4-Dibromo-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

2,4,6-Trichloro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

5-Bromo-2,4-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluormethyl-phenyl]-benzenesulfonamide;

5-Chloro-2,4-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;

4-Chloro-2,5-difluoro-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
4-Methoxy-2,3,6-trimethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
3,5-Dimethoxy-2-methyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,4-Dibromo-5-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2-Bromo-5,6-difluoro-4-methoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
4,5-Dimethoxy-2-trifluoromethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2,4,5-Trimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide; or
4-Bromo-2,6-dimethyl-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide.

5. A compound according to claim 1 chosen from the group consisting of:
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-bromo-4,5-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,6-dichloro-4-trifluoromethylbenzene-sulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2-chloro-4,5-dimethoxybenzenesulfonamide;
(R)-N-[4-Chloro-3-(1-methyl-3-pyrrolidinyloxy)-phenyl]-2,3,6-trimethyl-4-methoxybenzene-sulfonamide;
2-Bromo-4,5-dimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide;
2-Chloro-4,5-dimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide; or
2,6-Dichloro-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-4-trifluoromethyl-benzenesulfonamide.

6. A compound of Claim 1 chosen from:

2-Bromo-4,5-dimethoxy-N-[3-((R)-1-methyl-pyrrolidin-3-yloxy)-4-trifluoromethyl-phenyl]-benzenesulfonamide; or
2-Bromo-N-[4-chloro-3-((R)-1-methyl-pyrrolidin-3-yloxy)-phenyl]-4,5-dimethoxy-benzenesulfonamide.

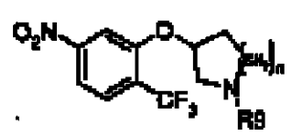
7. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

8. A pharmaceutical composition comprising a compound of formula (I) of claim 5 and a pharmaceutically acceptable carrier or excipient.

9. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

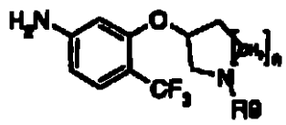
10. A method according to Claim 9 wherein the disease is congestive heart failure, stroke, ischemic heart disease , angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease, peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

11. A process for the preparation of a compound of Formula (I) of claim 1 or a pharmaceutically acceptable salt thereof, which process comprises hydrogenation of a compound of Formula (II)



(II)

wherein R_9 and n are as described in claim 1, or a group convertible thereto, to give a compound of Formula (III)



(III)

which is reacted with a compound of Formula (IV)

$$R_1 - SO_2Cl$$

(IV)

wherein R_1 is as described in claim 1, or a group convertible thereto,

and when desired or necessary, conversion of R_1 and/or R_9;

to afford a compound of Formula (I).

SULFONAMIDAS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a sulfonamidas, a composiciones farmacéuticas que las contienen y a su uso como antagonistas de la urotensina II

ANTECEDENTES DE LA INVENCIÓN

El control integral de la homeostasis cardiovascular se consigue a través de una combinación de ambos el control neuronal directo y la activación neurohormonal sistémica. Aunque la liberación resultante tanto de los factores contráctiles como de los factores relajantes está normalmente bajo una regulación restrictiva, una desviación en este *statu quo* puede dar como resultado una disfunción cardiohemodinámica con consecuencias patológicas.

Los principales factores vasoactivos en los mamíferos que comprendan este eje neurohumoral, principalmente angiotensina-II, endotelina-1, norepinefrina, funcionan todos por medio de una interacción con receptores específicos acoplados a la G-proteína (GPCR). La urotensina-II, representa un nuevo miembro de este eje neurohumoral.

En los peces, este péptido tiene importantes acciones hemodinámicas y endocrinas en diversos sistemas orgánicos y en los tejidos:

- contracción del músculo liso

  tanto de origen vascular como no vascular que incluye las preparaciones del músculo liso del tracto gastrointestinal y del tracto genitourinario. Después de la administración sistémica de un péptido exógeno se han descrito tanto actividad presora como depresora

- osmorregulación:

  efectos que incluyen la modulación del transporte transepitelial de iones (Na^+, Cl^-). Aunque se ha descrito un efecto diurético, se plantea que tal efecto es secundario para dirigir los efectos renovasculares (GFR elevados)

- metabolismo:

  la urotensina-II influye en la secreción de prolactina y presenta un efecto lipolítico en los peces (activación de la triacilglicerol-lipasa que da como resultado la movilización de ácidos grasos libres no esterificados)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* 1980, 77, 5021; Conlon, *et. al. J. Exp. Zool.* 1996, 275, 226)

  En estudios con humanos se ha encontrado que la urotensina-II:

- era un vasoconstrictor extremadamente potente y eficaz
- presentaba una actividad contráctil sostenida que era extremadamente resistente al lavado
- tenía efectos perjudiciales sobre el comportamiento cardíaco (contractilidad del miocardio)

La urotensina-II humana se evaluó en cuanto a su actividad contráctil en la aorta aislada de la rata y se demostró que era el agonista contráctil más potente identificado hasta la fecha. Basándose en la farmacología *in vitro* y en el perfil hemodinámico *in vivo* de la urotensina-II humana, ésta desempeña un papel patológico en las enfermedades cardiovasculares caracterizado por una vasoconstricción excesiva o anormal y una disfunción miocárdica. (Ames *et. al. Nature* 1999, *401*, 282; Douglas & Ohlstein (2001). Trends Cardiovasc. Med., 10: en imprenta).

Los compuestos que antagonizan el receptor de la urotensina-II pueden ser útiles en el tratamiento de la insuficiencia cardíaca congestiva, ictus, cardiopatía isquémica (angina, isquemia miocárdica), arritmia cardíaca, hipertensión (esencial y pulmonar), COPD, fibrosis (por ejemplo, fibrosis pulmonar), restenosis, aterosclerosis, dislipidemia, asma, (Hai DWP, Lutmann MA, Douglas SA: 2000, Br J Pharmacol: 131; 10-12) inflamación neurógena y vasculopatías metabólicas todas las cuales se caracterizan por una vasoconstricción anormal y/o disfunción miocárdica. Los antagonistas de la urotensina pueden proporcionar una protección a los órganos en cohortes hipersensibles además de reducir la tensión arterial.

Puesto que la U-II y GPR14 se expresan ambas dentro del CNS de los mamíferos (Ames *et. al. Nature* 1999, *401*, 282), también pueden ser útiles en el tratamiento de la adicción, esquizofrenia, trastornos cognitivos/enfermedad de Alzheimer, (Garrion J. Psichopharmacology (Berl) 2001 June; 155(4):426-33), impulsividad, ansiedad, estrés, depresión, dolor, migraña, función neuromuscular, enfermedad de Parkinson, trastornos del movimiento, ciclo sueño-vigilia, y motivación por estímulos (Clark *et al. Brain Research* 923 (2001) 120-127.

Los receptores funcionales de la U-II se expresan en las líneas celulares de los rabdomiosarcomas y pueden tener por tanto indicaciones oncológicas. La urotensina puede estar también implicada en diferentes enfermedades metabólicas tales como la diabetes (Ames *et. al. Nature* 1999, *401*, 282. Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) y en diferentes trastornos gastrointestinales, trastornos de los huesos, cartílagos, y articulaciones (por ejemplo, artritis y osteoporosis); y trastornos genitourinarios. Por tanto, estos compuestos pueden ser útiles para la prevención (tratamien-

to) del reflujo gástrico, motilidad gástrica y úlceras, artritis, osteoporosis e incontinencia urinaria.

SUMARIO DE LA INVENCIÓN

En un aspecto, esta invención proporciona sulfonamidas y composiciones farmacéuticas que las contienen.

En un segundo aspecto, esta invención proporciona el uso de sulfonamidas como antagonistas de la urotensina II, y como inhibidores de la urotensina II.

En otro aspecto, esta invención proporciona el uso de sulfonamidas para tratar enfermedades asociadas con el equilibrio de la urotensina II.

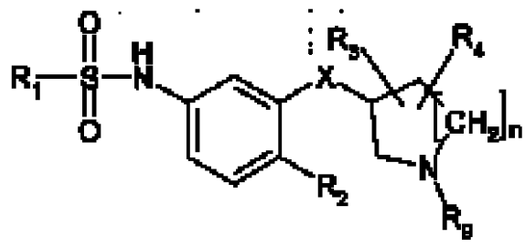
En otro aspecto más, esta invención proporciona el uso de sulfonamidas para el tratamiento de la insuficiencia cardiaca congestiva, ictus, cardiopatía isquémica (angina, isquemia miocárdica), arritmia cardiaca, hipertensión (esencial y pulmonar), enfermedad renal (insuficiencia renal aguda y crónica/enfermedad renal en etapa terminal) junto con enfermedad vascular periférica (disfunción eréctil del varón, retinopatía diabética, claudicación intermitente/enfermedad isquémica de los miembros) e ictus isquémico/hemorrágico, COPD, restenosis, asma, inflamación neurógena, migraña, vasculopatías metabólicas, enfermedades de los huesos/cartílagos/articulaciones, artritis y otras enfermedades inflamatorias, fibrosis (por ejemplo, fibrosis pulmonar), sepsis, aterosclerosis, dislipidemia, adicción, esquizofrenia, trastornos cognitivos/enfermedad de Alzheimer, impulsividad, ansiedad, estrés, depresión, enfermedad de Parkinson, trastornos del movimiento, ciclo sueño-vigilia, motivación por estímulos, dolor, función neuromuscular, diabetes, reflujo gástrico, trastornos de la motilidad gástrica, úlceras y enfermedades genitourinarias.

El antagonista de la urotensina se puede administrar solo o conjuntamente con uno o más de otros agentes terapéuticos, siendo seleccionados dichos agentes del grupo constituido por los antagonistas del receptor de la endotelina, inhibidores de la enzima conversora de la angiotensina (ACE), antagonistas del receptor de la A-II, inhibidores de la vasopeptidasa, diuréticos, digoxina, y antagonistas duales no selectivos del receptor adrenérgico β y del receptor adrenérgico α_1.

Otros aspectos y ventajas de la presente invención se describen además en la siguiente descripción detallada de sus realizaciones preferidas.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención proporciona compuestos de la fórmula (I):



Fórmula (I)

en la que:

R_1 es fenilo sin sustituir o sustituido con uno, dos, tres, cuatro o cinco de cualquiera de los siguientes: halógeno, CF_3, OCF_3, SCF_3, NO_2, CN, alquilo C_{1-6}, alcoxi C_{1-6}, NR_5R_6, $CONR_7R_8$, S-alquilo C_{1-6}, CO_2(alquilo C_{1-6}), (alquil C_{1-6})-CO_2(alquilo C_{1-6});

R_2 es hidrógeno, halógeno, CF_3, CN o alquilo C_{1-4};

R_3, R_4, R_7, y R_8 son independientemente hidrógeno, alquilo C_{1-6}, o bencilo;

R_5, R_6, y R_9, son independientemente hidrógeno o alquilo C_{1-6};

X es O, S, o CH_2;

n es 1;

o una de sus sales farmacéuticamente aceptables.

Cuando se usa aquí, el término "alquilo" incluye todos los isómeros de cadena lineal y ramificada. Ejemplos representativos de los mismos incluyen metilo, etilo, *n*-propilo, *iso*-propilo, *n*-butilo, *sec*-butilo, *iso*-butilo, *t*-butilo, *n*-pentilo y *n*-hexilo.

Cuando se usan aquí, los términos 'halógeno' y 'halo' incluyen flúor, cloro, bromo y yodo, y radicales fluoro, cloro, bromo y yodo, respectivamente.

Los compuestos de la presente invención pueden contener uno o más átomos de carbono asimétricos y pueden existir en forma racémica y en forma ópticamente activa. Todos estos compuestos y sus diastereoisómeros se considera que están dentro del alcance de la presente invención.

Preferiblemente R_1 es fenilo sin sustituir o sustituido con uno, dos, tres, cuatro o cinco de cualquiera de los siguientes: halógeno, CF_3, OCF_3, CN, alquilo C_{1-6}, alcoxi C_{1-6}, CO_2(alquilo C_{1-6}), (alquil C_{1-6})-CO_2(alquilo C_{1-6}), o NO_2.

Preferiblemente R_2 es hidrógeno, halógeno, CF_3, o alquilo C_{1-4}. Más preferiblemente R_2 es halógeno o CF_3.

Preferiblemente R_3 es hidrógeno.

Preferiblemente R_4 es hidrógeno.

Preferiblemente R_9 es hidrógeno o alquilo C_{1-6}.

Preferiblemente X es O.

Los compuestos preferidos son:

hidrocloruro de (R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,5-trimetoxi-bencenosulfonamida;

(±)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

(±)-N-[4-cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(S)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluorometilbenceno-sulfonamida;

(±)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(S)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluorometilbenceno-sulfonamida;

2-bromo-N-[4-cloro-3-((S)-1-metil-pirrolidin-3-iloxi)-fenil]-4,5-dimetoxi-bencenosulfonamida;

4-bromo-2-cloro-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-5-metoxi-bencenosulfonamida;

2,4-dibromo-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-5-metoxi-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metil-4,5-dimetoxibencenosulfonamida;

(+)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(+)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metil-4-bromobencenosulfonamida;

(R)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,5-triclorobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,4,5,6-pentametilbencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metoxi-5-bromobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-(metilpropionato)benceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-4-bromobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,6-trimetil-4-metoxibenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,4-triclorobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,5,6-tetrametilbencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-isopropilbencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-etilbencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4-cianobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-dicloro-6-metilbenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-3,6-dibromobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-trifluorometoxi-4-bromobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-fluorobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-butilbencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-difluoro-5-bromobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-difluoro-5-clorobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-fluoro-4-metoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-difluorobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-4-clorobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-nitro-4-clorobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dimetil-4-bromobenceno-sulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dibromobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,6-triclorobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-5-fluoro-4-metoxi-2-trifluorometil-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,5-difluoro-4-metoxi-2-metil-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-6-bromo-2,3-difluoro-4-metoxi-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4,5-dimetoxi-2-trifluorometil-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4,5-dimetoxi-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-fluoro-2-trifluorometil-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,6-trifluoro-bencenosulfonamida;

3,4-dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;

2-bromo-4,5-dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;

2-cloro-4,5-dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;

4,5-dimetoxi-2-metil-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;

4-bromo-2-cloro-5-metoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;

2-bromo-4,5-dimetoxi-N-[4-metil-3-((S)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;

N-[4-cloro-3-((R)-pirrolidin-3-iloxi)-fenil]-2-bromo-3,4-dimetoxi-bencenosulfonamida;

(±)-N-[4-cloro-3-(3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;

(±)-N-[4-cloro-3-(3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

2-cloro-4,5-dimetoxi-3-[((R)-1-metil-pirrolindin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,6-dicloro-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-4-trifluorometil-bencenosulfonamida;

2-bromo-4,5-dimetoxi-N-[3-(1-metil-pirrolidin-3-iloxi-4-trifluorometil-fenil]-bencenosulfonamida;

3,4-dimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4,5-tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,3,4,5,6-pentametil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-bromo-2,5-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,3,4-tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-isopropil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4-dicloro-6-metil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

3,4-dibromo-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4,6-tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

5-bromo-2,4-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

5-cloro-2,4-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-cloro-2,5-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-metoxi-2,3,6-trimetil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

3,5-dimetoxi-2-metil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4-dibromo-5-metoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2-bromo-5,6-difluoro-4-metoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4,5-dimetoxi-2-trifluorometil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4,5-trimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida; y

4-bromo-2,6-dimetil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida.

Los compuestos más preferidos son:

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluorometilbenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,6-trimetil-4-metoxibenceno-sulfonamida;

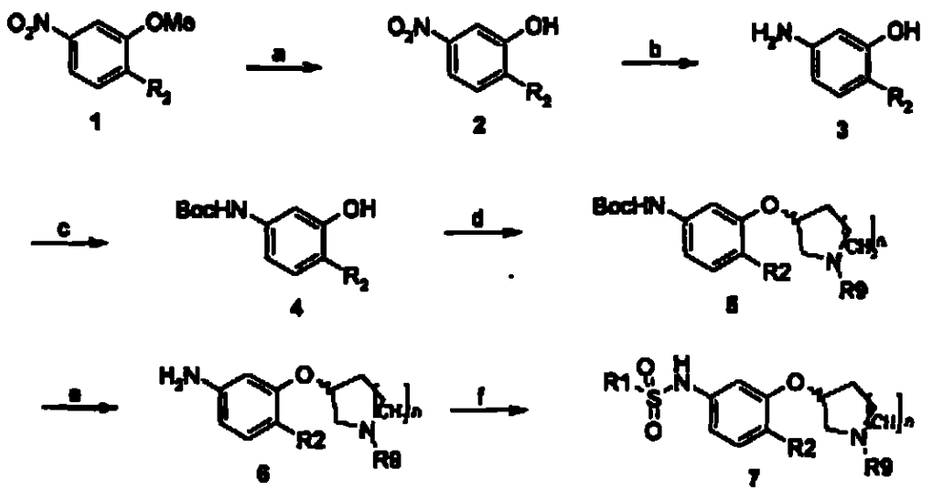
2-bromo-4,5-dimetoxi-N-[3-((R)-1-metil-pirrolindin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2-cloro-4,5-dimetoxi-N-[3-((R)-1-metil-pirrolindin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida; y

2,6-dicloro-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-4-trifluorometil-bencenosulfonamida.

Los compuestos de la fórmula (I) se pueden preparar como se indica en el esquema 1.

Esquema 1



Condiciones: a) bromuro de hidrógeno al 48 %, ácido acético; b) hidrógeno (344,8 kPa), platino sobre carbón, acetato de etilo; c) dicarbonato de di-*terc*-butilo, tetrahidrofurano, a reflujo;

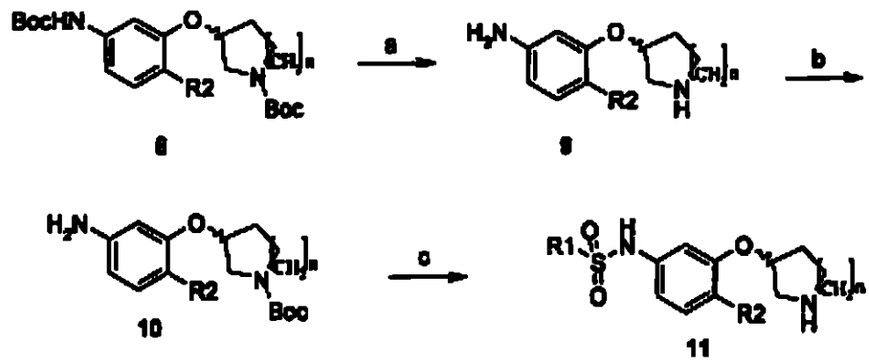
d) 1-Rg-pirrolidin-3-ol, DIAD, trifenilfosfina, tetrahidrofurano, 0 °C a temperatura ambiente; e) HCl 6 N en dioxano; f) $R1SO_2Cl$, cloroformo, temperatura ambiente.

Por ejemplo, la desmetilación de los anisoles 1 mediada por un ácido dio los fenoles 2. La hidrogenación del grupo nitro proporcionó las anilinas 3, que fueron posteriormente protegidas como sus carbamatos de *terc*-butoxicarbonilo 4. Por alquilación

de 4 con diferentes alcoholes usando las condiciones estándar de Mitsunobu, seguida por la separación del grupo protector del nitrógeno se obtuvieron las anilinas 6. Por subsiguiente sulfonilación de las anilinas se obtuvieron los compuestos 7 deseados.

Los análogos que contienen una cadena lateral de pirrolidina sin sustituir en el N se pueden preparar según el esquema 2.

Esquema 2



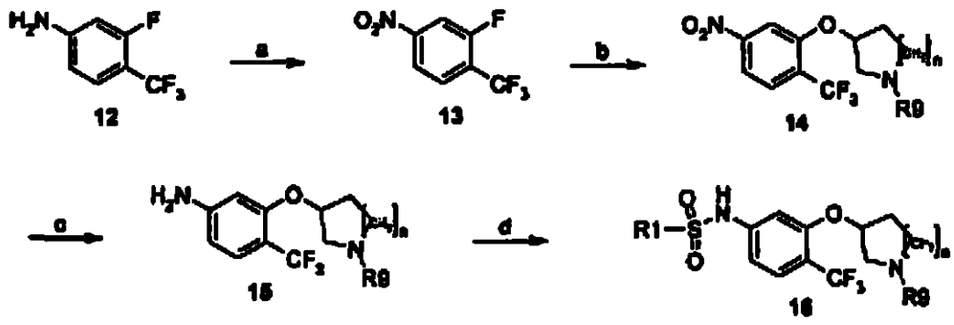
6 9 11

Condiciones: a) cloruro de hidrógeno 6 N/dioxano, temperatura ambiente;
b) dicarbonato de di-*terc*-butilo, tetrahidrofurano, temperatura ambiente;
c) R1-SO_2Cl, cloroformo, temperatura ambiente; después cloruro de hidrógeno 6 N/dioxano, temperatura ambiente.

Los análogos que contienen una cadena lateral de pirrolidina sin sustituir en N se prepararon a partir de los correspondientes derivados 8 de *terc*-butoxicarbonilo. Así, la separación de los grupos protectores con cloruro de hidrógeno 4 N en dioxano proporcionó las aminas 9. La amina secundaria se protegió selectivamente como su carbamato de *terc*-butilo para dar la anilina 10. Por sulfonilación de 10, seguida por la separación del grupo protector se obtuvieron los compuestos 11 deseados.

Los compuestos en los que R_2 es CF_3 se pueden preparar como sigue:

Esquema 3



12 13 14 15 16

Condiciones: a) peróxido de hidrógeno al 50 %, ácido trifluoroacético, a reflujo;
b) 1-R9-pirrolidin-3-ol, hidruro de sodio, tetrahidrofurano, 0 °C;

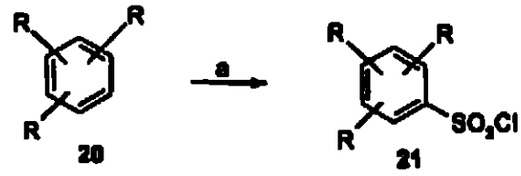
c) hidrógeno (344,8 kPa), platino sobre carbón, acetato de etilo; d) R1-SO_2Cl, cloroformo, temperatura ambiente.

Por ejemplo, la oxidación de la anilina 12 dio el nitrobenceno 13. La sustitución del fluoruro de arilo con diferentes alcoholes dio los éteres 14. La hidrogenación del grupo nitro proporcionó las anilinas 15, que fueron posteriormente sulfoniladas con diferentes cloruros de sulfonilo para dar los compuestos 16 deseados.

Con manipulación apropiada, que incluye el uso de un grupo o grupos alternativos protectores del nitrógeno, se realizó la síntesis de los restantes compuestos de la fórmula (I) por métodos análogos a los anteriores y a los descritos en la sección experimental.

Algunos de los cloruros de bencenosulfonilo opcionalmente sustituidos usados en la síntesis de los compuestos del epígrafe no estaban comercialmente disponibles y se prepararon según el esquema 4. El cloruro de 2,4-dibromo-5-metoxibencenosulfonilo se preparó como se describe en el documento *WO9838182*.

Esquema 4



20 21

Los bencenos sustituidos 20 se trataron con ácido clorosulfónico para obtener los deseados cloruros de sulfonilo 21.

Condiciones: a) ácido clorosulfónico, diclorometano, de 0 °C a temperatura ambiente.

Para usar un compuesto de la fórmula (I) o una de sus sales farmacéuticamente aceptables para el tratamiento de los humanos y otros mamíferos normalmente se formula de acuerdo con la práctica farmacéutica estándar como una composición farmacéutica.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables se pueden administrar de una manera estándar para el tratamiento de las enfermedades indicadas, por ejemplo oralmente, parenteralmente, sub-lingualmente, transdérmicamente, rectalmente, por inhalación o por administración bucal.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables que son activos cuando se administran oralmente se pueden formular como jarabes, comprimidos, cápsulas y comprimidos para chupar. Una formulación en jarabe consistirá generalmente en una suspensión o solución del compuesto o sal en un vehículo líquido por ejemplo, etanol, aceite de cacahuete, aceite de oliva, glicerina o agua con un agente aromatizante o colorante. Cuando la composición está en la forma de com-

primidos, se puede usar cualquier vehículo farmacéutico usado rutinariamente para preparar formulaciones sólidas. Ejemplos de tales vehículos incluyen estearato de magnesio, *terra alba*, talco, gelatina, agar, pectina, goma arábiga, ácido esteárico, almidón, lactosa y sacarosa. Cuando la composición está en la forma de una cápsula, es adecuada cualquier encapsulación rutinaria, por ejemplo usando los vehículos mencionados en una cápsula de gelatina dura. Cuando la composición está en la forma de una cápsula de gelatina blanda se puede considerar cualquier vehículo farmacéutico usado rutinariamente para preparar dispersiones o suspensiones, por ejemplo gomas acuosas, celulosas, silicatos o aceites y se incorporan en una cápsula de gelatina blanda.

Las composiciones parenterales típicas consisten en una solución o suspensión del compuesto o sal en vehículo estéril acuoso o no acuoso que contiene opcionalmente un aceite parenteralmente aceptable, por ejemplo polietilenglicol, polivinilpirrolidona, lecitina, aceite de cacahuete, o aceite de sésamo.

Las composiciones típicas para inhalación están en la forma de una solución, suspensión o emulsión que se pueden administrar como polvo seco o en la forma de un aerosol usando un propelente convencional tal como diclorodifluorometano o triclorofluorometano.

Una formulación típica de supositorios comprende un compuesto de la fórmula (1) o una de sus sales farmacéuticamente aceptables que es activo cuando se administra de este modo, con un agente aglutinante y/o lubrificante, por ejemplo glicoles poliméricos, gelatinas, manteca de cacao u otras ceras o grasas vegetales de baja punto de fusión o sus análogos sintéticos.

Las formulaciones transdérmicas típicas comprenden un vehículo convencional acuoso o no acuoso, por ejemplo una crema, pomada, loción o pasta o están en la forma de un emplasto, parche o membrana medicados.

Preferiblemente la composición está en una forma farmacéutica unitaria, por ejemplo un comprimido, cápsula o una dosis en aerosol medida, de forma que los pacientes puedan administrarse a si mismos una dosis individual.

Cada dosis unitaria para administración oral contiene de forma adecuada de 0,1 mg a 500 mg/Kg, y preferiblemente de 1 mg a 100 mg/Kg, y cada dosis unitaria para administración parenteral contiene de forma adecuada de 0,1 mg a 100 mg, de un compuesto de la fórmula (I) o de una de sus sales farmacéuticamente aceptables calculado como el ácido libre. Cada dosis unitaria para administración intranasal contiene de forma adecuada 1-400 mg y preferiblemente de 10 a 200 mg por persona.

1/1464

Una formulación tópica contiene de forma adecuada de 0,01 a 1,0 % de un compuesto de la fórmula (I).

El régimen de dosificación diario para administración oral es de forma adecuada de aproximadamente 0,01 mg/Kg a 40 mg/Kg, de un compuesto de la fórmula (I) o de una de sus sales *farmacéuticamente aceptables calculado como el ácido libre*. El régimen de dosificación diario para administración parenteral es de forma adecuada de aproximadamente 0,001 mg/Kg a 40 mg/Kg, de un compuesto de la fórmula (I) o de una de sus sales farmacéuticamente aceptables calculado como el ácido libre. El régimen de dosificación diario para administración intranasal e inhalación oral es de forma adecuada de aproximadamente 10 a aproximadamente 500 mg/persona. El ingrediente activo se puede administrar de 1 a 6 veces al día, suficiente para presentar la actividad deseada.

Estos análogos de sulfonamida se pueden usar para el tratamiento de la insuficiencia cardiaca congestiva, ictus, cardiopatía isquémica (angina, isquemia miocárdica), arritmia cardiaca, hipertensión (esencial y pulmonar), enfermedad renal (insuficiencia renal aguda y crónica/enfermedad renal en etapa terminal) junto con enfermedad vascular periférica (disfunción eréctil del varón, retinopatía diabética, claudicación intermitente/enfermedad isquémica de los miembros) e ictus isquémico/hemorrágico, COPD, restenosis, asma, inflamación neurógena, migraña, vasculopatías metabólicas, enfermedades de los huesos/cartílagos/articulaciones, artritis y otras enfermedades inflamatorias, fibrosis (por ejemplo, fibrosis pulmonar), sepsis, aterosclerosis, dislipidemia, adicción, esquizofrenia, trastornos cognitivos/enfermedad de Alzheimer, impulsividad, ansiedad, estrés, depresión, dolor, función neuromuscular, diabetes, reflujo gástrico, trastornos de la motilidad gástrica, úlceras y enfermedades genitourinarias.

El antagonista de la urotensina se puede administrar solo o conjuntamente con uno o más de otros agentes terapéuticos, siendo seleccionados dichos agentes del grupo constituido por antagonistas del receptor de la endotelina, inhibidores de la enzima conversora de la angiotensina (ACE), antagonistas del receptor de la A-II, inhibidores de la vasopeptidasa, diuréticos, digoxina, y antagonistas duales no selectivos del receptor adrenérgico β y del receptor adrenérgico α_1.

No se esperan efectos toxicológicos inaceptables cuando se administran los compuestos de la invención de acuerdo con la presente invención.

La actividad biológica de los compuestos de la fórmula (I) se demuestra por los siguientes ensayos:

Unión al radioligando:

Se incubaron membranas celulares HEK-293 que contienen GPR-14 humano y de rata clonado estable (20 µg/ensayo) con [^{125}I] h-U-II 200 pM (200 Ci/mmol^{-1}) en presencia de concentraciones crecientes de los compuestos del ensayo en DMSO (0,1 nM a 10 µM), en un volumen final de incubación de 200 µl (Tris-HCl 20 mM, $MgCl_2$ 5 mM). Se llevó a cabo la incubación durante 30 minutos a temperatura ambiente seguida por filtración por filtros GF/B con un recolector de células Brandel. La unión de la U-II marcada con ^{125}I se cuantificó por conteo de radiaciones gamma. La unión no específica se definió por la unión de la ^{125}I U-II en presencia de U-II 100 nM humana sin marcar. El análisis de los datos se realizó por ajuste no lineal de los mínimos cuadrados.

Movilización del Ca^{2+}:

Se utilizó el ensayo de FLIPR de movilización del Ca^{2+} basado en una placa de microtitulación (Molecular Devices, Sunnivale, CA) para la identificación funcional de las células HEK-293 activadoras del ligando que expresan GPR-14 recombinante (estable). Al día siguiente de la transfección, se extendieron las células en unas placas negras/transparentes de 96 pocillos recubiertas con poli-D-lisina. Después de 18-24 horas se aspiró el medio y las células recubiertas con Fluo 3AM se expusieron a diferentes concentraciones (10 nM a 30 µM) de los compuestos de ensayo seguido por h-U-II. Una vez comenzado el ensayo, se leyó la fluorescencia cada segundo durante un minuto y después cada 3 segundos durante el siguiente minuto. Se calculó la concentración inhibidora del 50 % (IC_{50}) para los diferentes compuestos de ensayo.

Ensayos de fosfatos de inositol:

Las células HEK-293-GPR14 en un matraz T150 se premarcaron durante la noche con 1 µCi de mio-[^{3}H] inositol por cada ml de medio de Eagel modificado por Dulbecco libre de inositol. Después del marcado, se lavaron las células dos veces con solución salina de Dulbecco tamponada con fosfato (DPBS) y después se incubaron en DPBS que contiene LiCl 10 mM durante 10 min a 37 °C. Se inició el experimento por la adición de concentraciones crecientes de h-U-II (1 pM a 1µM) en ausencia y presencia de tres concentraciones diferentes (0,3, 1 y 10 µM) de los compuestos de ensayo y se continuó la incubación durante 5 min más a 37 °C, tras lo cual se terminó la reacción por la adición de ácido tricloroacético al 10 % (concentración final) y centrifugación. Se neutralizaron los sobrenadantes con 100 µl de base Trizma 1M y se separaron los fosfatos de inositol sobre columnas AG 1-X8 (0,8 ml de empaquetado, mallas 100-200) en fase de formiato. Se eluyó el monofosfato de inositol con 8 ml de for-

mieto de amonio 200 mM. Se eluyeron el di y tris fosfato de inositol reunidos con 4 ml de formiato de amonio 1 *M*/ácido fórmico 0,1 M. Se contaron las fracciones eluidas en un contador de beta-centelleo. Se calculó K_B basándose en el desplazamiento de la curva de control.

La actividad de los compuestos de esta invención (ensayo de unión del radioligando) varía de: Ki = 1 nM – 10000 nM (ejemplo 10, Ki = 270 nM).

Los siguientes ejemplos son ilustrativos pero no limitantes de las realizaciones de la presente invención.

Ejemplo 1

Hidrocloruro de (R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,5-trimetoxibenceno-sulfonamida.

a) 2-Cloro-5-nitrofenol

Se recogió 2-cloro-5-nitroanisol (310 g, 1,7 mol) en una mezcla de HBr al 48 % (1,5 l) y AcOH (1,2 l) y se calentó a reflujo durante 3 días. Se dejó que la solución oscura se enfriara a temperatura ambiente, se vertió sobre hielo-agua (10 l), y se dejó en reposo durante 3 h. Se filtró el sólido amarillo oscuro resultante, se lavó con agua, y se secó en vacío (230 g, 79 %); punto de fusión 115-117 °C.

b) 2-Cloro-5-aminofenol

Se trató una solución de 2-cloro-5-nitrofenol (114 g, 0,66 mol) en acetato de etilo (500 ml) con Pt al 5 %/C (510 mg, 0,5 % en peso) y la mezcla se agitó en una atmósfera de hidrógeno (206,8 kPa) durante 6 h. Se filtró la mezcla a través de Celite® y se lavó bien el residuo con acetato de etilo. La evaporación del acetato de etilo dio un sólido (95 g, 100 % de rendimiento crudo) que se utilizó directamente en la siguiente etapa.

c) Éster terc-butílico del ácido 4-cloro-3-hidroxifenilcarbámico

A una solución de 2-cloro-5-aminofenol (95 g, 0,66 mol) en THF (600 ml) se añadió a solución de dicarbonato de di-*terc*-butilo (144 g, 0,68 mol) en THF (600 ml). Se calentó la reacción a reflujo durante 6 h, a cuyo tiempo se dejó que se enfriara a temperatura ambiente. Se separó el disolvente en vacío y se diluyó el residuo con éter (1000 ml) y se lavó con ácido cítrico 1 M (2 x 1000 ml). Los lavados acuosos se extrajeron con éter (500 ml) y los extractos orgánicos reunidos se lavaron con salmuera (500 ml), se secaron ($MgSO_4$), y se concentraron. El sólido pardo resultante se trituró

con hexano y se secó en vacío para dar 125 g (78 %) del compuesto del epígrafe: punto de fusión 103-106 °C.

d) 4-Cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-anilina

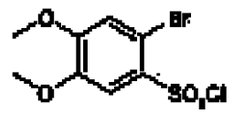
A una solución enfriada (0 °C) de éster *terc*-butílico del ácido 4-cloro-3-hidroxifenilcarbámico (55 g, 0,23 mol), (S)-1-metil-pirrolidin-3-ol (24 g, 0,24 mol), y trifenilfosfina (89 g, 0,34 mol) en THF (1,1 l) se añadió gota a gota por medio de un embudo de adición una solución de DIAD (67 ml, 0,34 mol) en THF (100 ml) a lo largo de 1 h. La solución resultante se dejó que se calentara lentamente a temperatura ambiente y se mantuvo durante 16 h. Se separó el THF en vacío y se trató el residuo con HCl 6 N (650 ml). La mezcla resultante se agitó a temperatura ambiente durante 4 h, a cuyo tiempo se diluyó con agua (500 ml) y se filtró para separar el óxido de trifenilfosfina. Se lavó el filtrado con EtOAc (3 x 1 l) y cloroformo (5 x 1 l) para separar los subproductos adicionales de la reacción. Se alcalinizó entonces la capa acuosa con NaOH sólido en lentejas y se extrajo con éter (2 x 1 l) y EtOAc (2 x 1 l). Las capas orgánicas reunidas se lavaron con $NaHCO_3$ saturado (2 x 1 l) y salmuera (1 l), se secaron ($MgSO_4$), y se concentraron para dar 40 g (80 %) del compuesto del epígrafe: MS (ES+) m/e $[M+H]^+$ 227.

e) Hidrocloruro de (R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,5-trimetoxibencenosulfonamida

Se disolvió (R)-3-(1-metil-3-pirrolidinil)-4-cloroanilina (58 mg, 0,25 mmol) en dicloroetano (4 ml). Se añadió cloruro de 2,4,5-trimetoxibencenosulfonilo (66 mg, 0,25 mmol) y se dejó que se agitara la mezcla a temperatura ambiente durante 2 días. Se concentró la mezcla y se recristalizó el residuo en etanol para obtener el compuesto del epígrafe (85 mg, 69 %): MS (ES+) m/e $[M+H]^+$ 467.

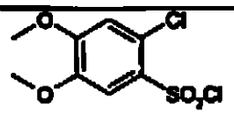
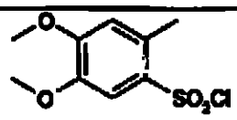
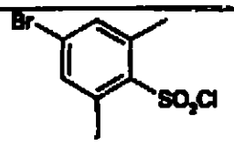
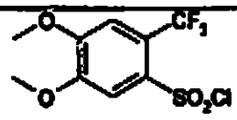
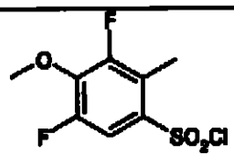
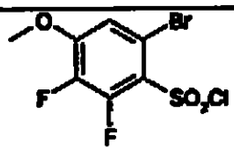
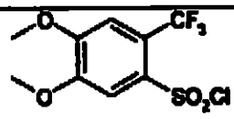
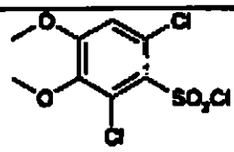
Ejemplo 2a

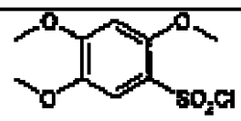
Cloruro de 2-bromo-4,5-dimetoxibencenosulfonilo



A una solución enfriada (0 °C) de 4-bromoveratrol (15 ml, 100 mmol) en diclorometano (100 ml) se añadió gota a gota ácido clorosulfónico (26 ml, 400 mmol). Se dejó que la reacción se calentara lentamente a temperatura ambiente y se mantuvo durante 3 horas, a cuyo tiempo se concentró y se diluyó con éter (300 ml). La solución resultante se lavó entonces con agua enfriada con hielo (2 x 250 ml) y salmuera (100 ml), se secó sobre sulfato de magnesio, y se concentró para obtener un polvo grisáceo (25 g, 78 %).

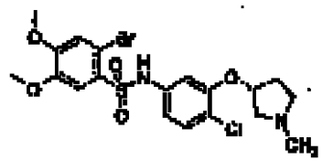
Los ejemplos 15a, 16a, 44a, 47a, 48a, 49a, 50a, 51a, y 1a se prepararon como se indica en el ejemplo 2a sustituyendo los materiales de partida apropiados.

Ejemplo	Compuesto
 15a	Cloruro de 2-cloro-4,5-dimetoxi-bencenosulfonilo
 16a	Cloruro de 4,5-dimetoxi-2-metil-bencenosulfonilo
 44a	Cloruro de 4-bromo-2,6-dimetil-bencenosulfonilo
 47a	Cloruro de 4,5-dimetoxi-2-trifluoro-metil-bencenosulfonilo
 48a	Cloruro de 3,5-difluoro-4-metoxi-2-metil-bencenosulfonilo
 49a	Cloruro de 6-bromo-2,3-difluoro-4-metoxi-bencenosulfonilo
 50a	Cloruro de 4,5-dimetoxi-2-trifluoro-metil-bencenosulfonilo
 51a	Cloruro de 2,6-dicloro-4,5-dimetoxi-bencenosulfonilo

 1a	Cloruro de 2,4,5-trimetoxi-bencenosulfonilo

Ejemplo 2

(R)2-Bromo-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-4,5-dimetoxi-bencenosulfonamida



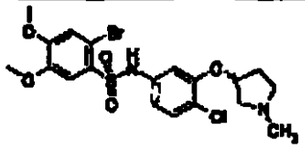
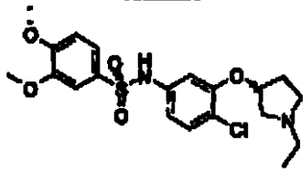
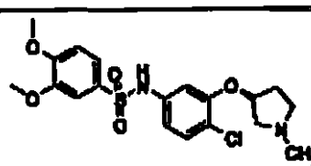
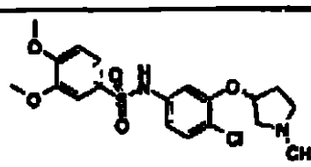
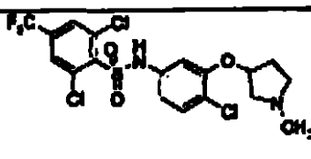
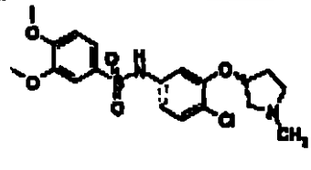
a) 4-Cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-anilina

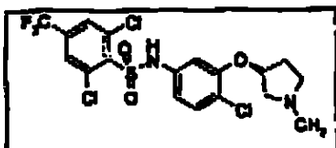
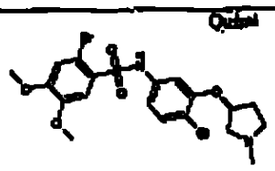
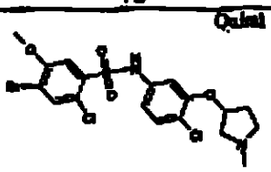
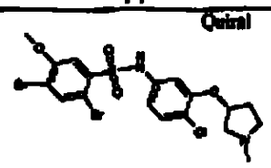
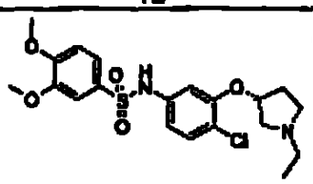
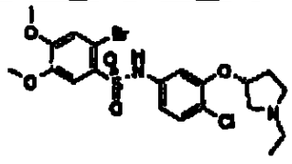
Se preparó 4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-anilina según el procedimiento de 1(a) - (d).

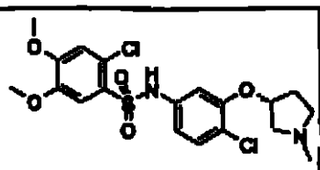
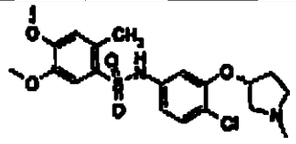
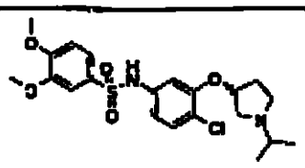
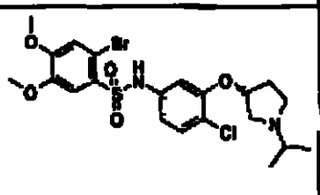
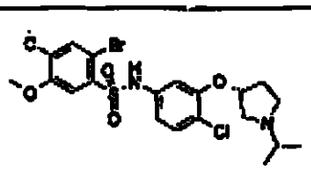
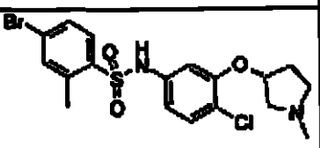
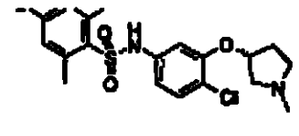
b) 2-Bromo-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-4,5-dimetoxi-bencenosulfonamida

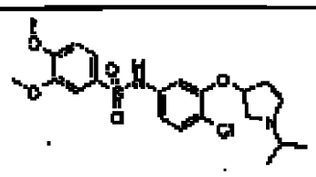
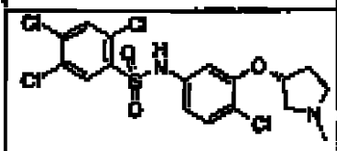
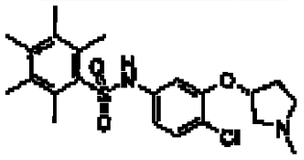
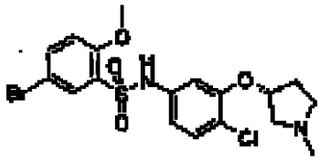
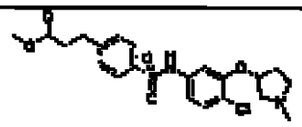
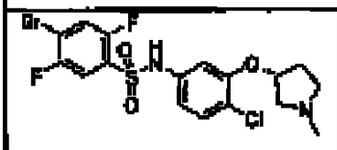
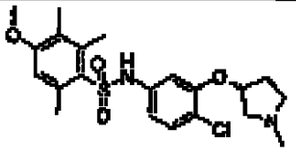
A una solución de 4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-anilina (30 g, 132 mmol) en 1,2-dicloroetano (500 ml) se añadió una solución de cloruro de 2-bromo-4,5-dimetoxibencenosulfonilo (42 g, 135 mmol) en 1,2-dicloroetano (300 ml). La solución resultante se mantuvo a temperatura ambiente durante 14 h, a cuyo tiempo los sólidos que se habían formado se filtraron, se lavaron con diclorometano y éter, y se secaron en vacío (50 °C) para obtener 58 g (81 %) del compuesto del epígrafe: punto de fusión 214 °C (con descomposición); MS (ES+) m/e $[M+H]^+$ 505.

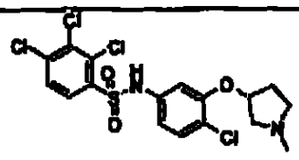
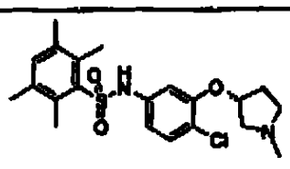
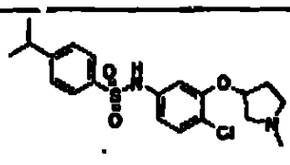
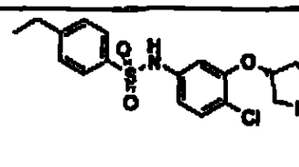
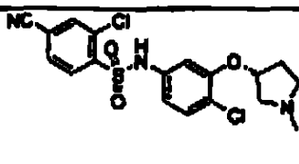
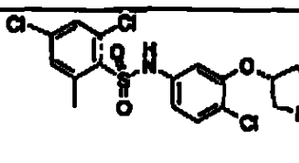
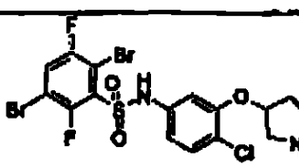
Los ejemplos 3-53 se prepararon como se indica en el ejemplo 1 sustituyendo los materiales de partida apropiados.

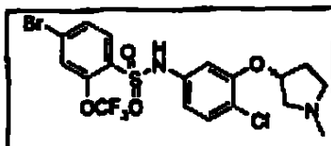
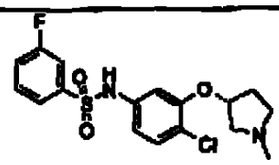
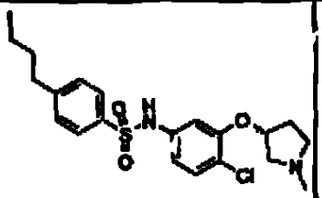
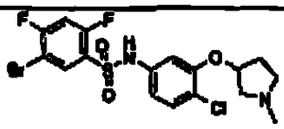
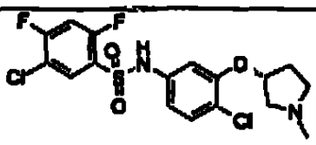
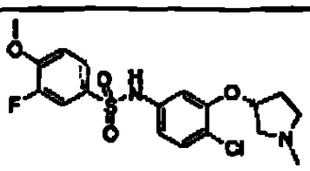
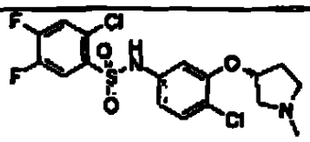
Ejemplo	Compuesto	MS (ES+) m/e $[M+H]^+$
 3	(+)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida	506
 4	(+)-N-[4-Cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida	441
 5	(S)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibenceno-sulfonamida	427
 6	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibenceno-sulfonamida	427
 7	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluoro-metilbenceno-sulfonamida	503
 8	(+)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibenceno-sulfonamida	427

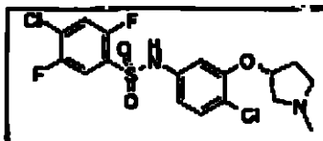
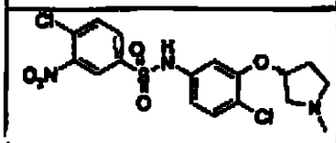
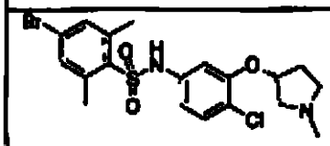
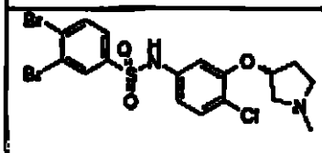
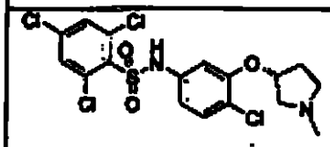
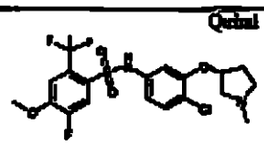
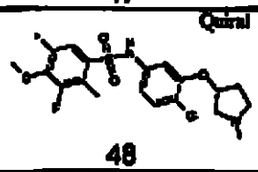
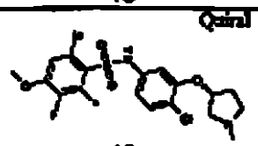
 9	(S)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluorometilbenceno-sulfonamida	503
 10	2-Bromo-N-[4-cloro-3-((S)-1-metil-pirrolidin-3-iloxi)-fenil]-4,5-dimetoxi-bencenosulfonamida	508
 11	4-Bromo-2-cloro-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-5-metoxi-bencenosulfonamida	510
 12	2,4-Dibromo-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-5-metoxi-bencenosulfonamida	555
 13	(R)-N-[4-Cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibenceno-sulfonamida	441
 14	(R)-N-[4-Cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxi-bencenosulfonamida	520

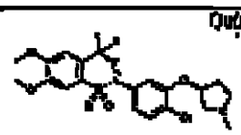
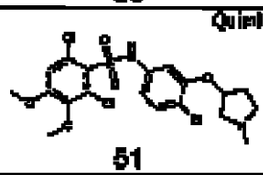
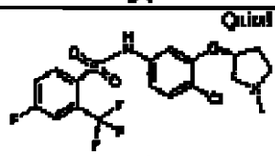
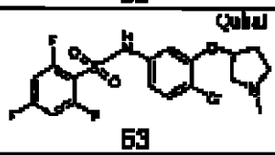
 15	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-dimetoxi-bencenosulfonamida	461
 16	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metil-4,5-dimetoxi-bencenosulfonamida	441
 17	(±)-N-[4-Cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxiben-cenosulfonamida	455
 18	(±)-N-[4-Cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-di-metoxibencenosulfonamida	534
 19	(R)-N-[4-Cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida	534
 20	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metil-4-bromobence-nosulfonamida	460
 27	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,6-trimetil-4-metoxi-benceno-sulfonamida	439

 21	(R)-N-[4-Cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida	455
 22	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,5-triclorobenceno-sulfonamida	469
 23	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,4,5,6-pentametil-bencenosulfonamida	437
 24	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metoxi-5-bromobenceno-sulfonamida	476
 25	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-(metilpropionato)benceno-sulfonamida	453
 26	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-4-bromo-benceno-sulfonamida	482
 27	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,6-trimetil-4-metoxi-benceno-sulfonamida	439

 28	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,4-triclorobenceno-sulfonamida	469
 29	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,5,6-tetrametilbencenosulfonamida	423
 30	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-isopropilbencenosulfonamida	409
 31	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-etilbencenosulfonamida	395
 32	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4-cianobencenosulfonamida	426
 33	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-dicloro-6-metil-benceno-sulfonamida	449
 34	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-3,6-dibromobenceno-sulfonamida	561

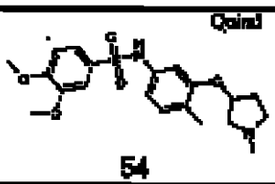
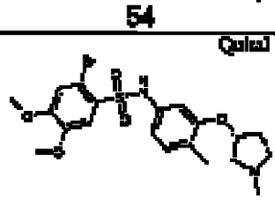
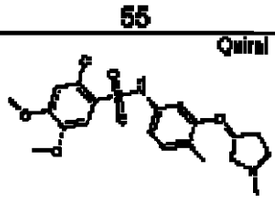
 35	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-trifluorometoxi-4-bromobenceno-sulfonamida	460
 36	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-fluorobencenosulfonamida	385
 37	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-butilbencenosulfonamida	423
 38	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-difluoro-5-bromobenceno-sulfonamida	482
 39	(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-difluoro-5-clorobenceno-sulfonamida	437
 40	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-fluoro-4-metoxibencenosulfonamida	415
 41	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-difluorobencenosulfonamida	437

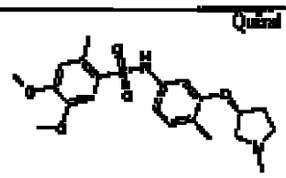
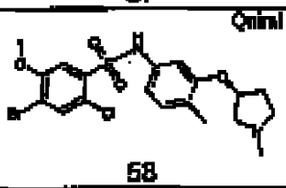
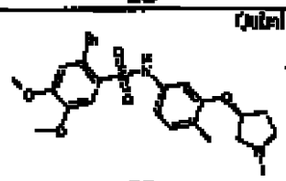
 42	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-4-clorobenceno-sulfonamida	437
 43	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-nitro-4-clorobencenosulfonamida	446
 44	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dimetil-4-bromo-benceno-sulfonamida	474
 45	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dibromobenceno-sulfonamida	525
 46	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,6-triclorobenceno-sulfonamida	469
 47	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-5-fluoro-4-metoxi-2-trifluorometil-bencenosulfonamida	483
 48	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,5-difluoro-4-metoxi-2-metil-bencenosulfonamida	447
 49	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-6-bromo-2,3-difluoro-4-metoxi-bencenosulfonamida	512

 50	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4,5-dimetoxi-2-trifluorometil-bencenosulfonamida	495
 51	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4,5-dimetoxi-bencenosulfonamida	495
 52	(R)-N-[4-Cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-fluoro-2-trifluorometil-bencenosulfonamida	453
 53	(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,6-trifluoro-bencenosulfonamida	421

Ejemplos 54-59

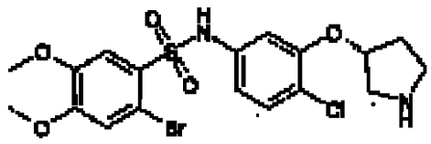
Sustituyendo el 2-cloro-5-aminofenol por 5-amino-o-cresol y sustituyendo el cloruro de 2,4,5-trimetoxibencenosulfonilo por diferentes cloruros de sulfonilo, se prepararon los ejemplos 54-59 siguiendo los procedimientos descritos en 1c-1e:

Ejemplo	Compuesto	MS (ES+) m/e [M+H]+
 54	3,4-Dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida	407
 55	2-Bromo-4,5-dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida	486
 56	2-Cloro-4,5-dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida	441

 57	4,5-Dimetoxi-2-metil-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida	421
 58	4-Bromo-2-cloro-5-metoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida	490
 59	2-Bromo-4,5-dimetoxi-N-[4-metil-3-((S)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida	486

Ejemplo 60

N-[4-cloro-3-((R)-pirrolidin-3-iloxi)-fenil]-2-bromo-3,4-dimetoxi-bencenosulfonamida



a) (R)-3-(5-Amino-2-clorofenoxi)-pirrolidina

A una solución de éster *terc*-butílico del ácido (R)-3-(5-*terc*-butoxicarbonilamino-2-clorofenoxi)-pirrolidin-1-carboxílico (2 g, 4,9 mmol) en dioxano (30 ml) se añadió cloruro de hidrógeno 6 N (20 ml). Se agitó la mezcla de reacción durante 2 horas, a cuyo tiempo se concentró. El residuo resultante se trituró con acetato de etilo y diclorometano, después se diluyó con hidróxido de potasio 2,5 M (50 ml) y se extrajo con diclorometano (3 x 50 ml). Los extractos orgánicos reunidos se lavaron con salmuera (50 ml), se secaron sobre sulfato de magnesio, y se concentraron para dar (R)-3-(5-amino-2-clorofenoxi)-pirrolidina (810 mg, 75 %).

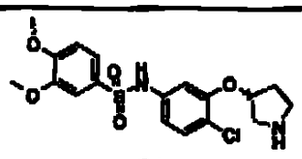
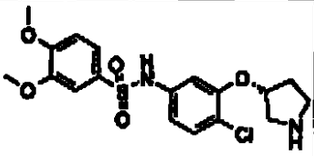
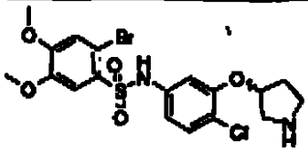
b) Éster terc-butílico del ácido (R)-3-(5-amino-2-clorofenoxi)-pirrolidin-1-carboxílico

A una solución de (R)-3-(5-amino-2-clorofenoxi)-pirrolidina (810 mg, 3,9 mmol) en tetrahidrofurano (40 ml) se añadió dicarbonato de di-terc-butilo (830 mg, 3,9 mmol). La solución resultante se mantuvo a temperatura ambiente durante 20 horas, a cuyo tiempo se diluyó con éter (100 ml), se lavó con ácido cítrico acuoso al 5 % (100 ml), agua (100 ml), y salmuera (50 ml), y se secó sobre sulfato de magnesio. La concentración de la solución dio el éster terc-butílico del ácido (R)-3-(5-amino-2-clorofenoxi)-pirrolidin-1-carboxílico (1,2 g, 99 %).

c) N-[4-Cloro-3-((R)-pirrolidin-3-iloxi)-fenil]-2-bromo-3,4-dimetoxi-bencenosulfonamida

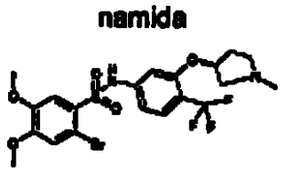
A una solución de éster terc-butílico del ácido (R)-3-(5-amino-2-clorofenoxi)-pirrolidin-1-carboxílico (100 mg, 0,33 mmol) en cloroformo (5 ml) se añadió cloruro de 2-bromo-4,5-dimetoxibencenosulfonilo (120 mg, 0,33 mmol). La solución resultante se mantuvo a temperatura ambiente durante 24 horas, a cuyo tiempo se concentró. Se diluyó el residuo con dioxano (4 ml) y cloruro de hidrógeno 6 N (2 ml) y se agitó durante 5 horas, a cuyo tiempo se concentró. Por cristalización en etanol se obtuvo el compuesto del epígrafe (22 mg, 11 %). MS (ES+) m/e 492 $[M+H]^+$

Usando los materiales de partida apropiados, se prepararon los siguientes compuestos según el ejemplo 60.

Ejemplo	Compuesto	MS (ES+) m/e $[M+H]^+$
 61	(±)-N-[4-Cloro-3-(3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida	413
 62	(R)-N-[4-Cloro-3-(3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida	413
 63	(±)-N-[4-Cloro-3-(3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida	492

Ejemplo 64

2-bromo-4,5-dimetoxi-N-[3-(1-metil-pirrolidin-3-iloxi-4-trifluorometil-fenil]-bencenosulfonamida



a) 2-Fluoro-4-nitrobenzotrifluoruro

Se calentó a reflujo una solución de 4-amino-2-fluorobenzotrifluoruro (25,0 g, 0,14 mol, 1,0 equivalente) en ácido trifluoroacético (140 ml) y después se trató con la adición gota a gota de peróxido de hidrógeno al 50 % (68,7 ml, 1,18 mol, 8,4 equivalentes) a lo largo de 35 min. La reacción se calentó a reflujo durante 1,5 h y después se enfrió a temperatura ambiente. Se vertió sobre hielo-agua (1 l) y a continuación se agitó durante toda la noche. Se recogió el aceite que se había separado (decantando la fase acuosa) y después se diluyó con éter dietílico (150 ml). La solución etérea se lavó con HCl acuoso al 10 % (100 ml), bicarbonato de sodio acuoso saturado (2 x 100 ml), y salmuera (100 ml) y después se secó sobre sulfato de magnesio anhidro. La evaporación a presión reducida dio un aceite pardo anaranjado. Por destilación (1666 Pa, 88-90 °C) se obtuvo el producto como un líquido amarillo (15,0 g, 51 %).

b) 2-((R)-1-Metil-pirrolidin-3-iloxi)-4-nitrobenzotrifluoruro

Una solución de 2-fluoro-4-nitrobenzotrifluoruro (12,4 g, 59,3 mmol, 1,0 equivalentes) y (R)-1-metil-pirrolidin-3-ol (6,0 g, 59,3 mmol, 1,0 equivalentes) en tetrahidrofurano anhidro (150 ml) se enfrió a 0 °C y después se trató lentamente con porciones de hidruro de sodio al 60 % (4,7 g, 0,12 mol, 2 equivalentes) a lo largo de 5 min. Sin separar el baño de hielo, se dejó que la reacción llegara a temperatura ambiente y se agitó durante 48 h. Sofocada con agua (50 ml) y salmuera (100 ml) se extrajo después con éter dietílico (5 x 100 ml). Los extractos se secaron sobre sulfato de magnesio anhidro y carbón decolorante durante 1 h. Se filtró a través de Celite. Se trató el filtrado con sílice (35 g) y después se evaporó para dar el producto crudo suspendido en sílice. La cromatografía en columna sobre sílice (MeOH 1 %/EtOAc→ MeOH 5 % /EtOAc) dio el producto (Rf=0,3 en MeOH 1 % /EtOAc) como un aceite naranja (7,85 g, 48 %).

c) 3-((R)-1-Metil-pirrolidin-3-iloxi)-4-trifluorometil-fenilamina

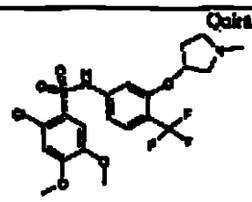
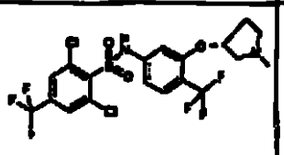
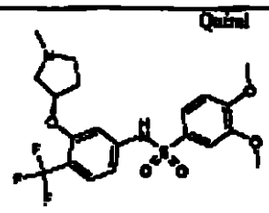
Una solución de 2-((R)-1-metil-pirrolidin-3-iloxi)-4-nitrobenzotrifluoruro (7,8 g, 26,8 mmol) en acetato de etilo (50 ml) se trató con platino al 10 % sobre carbón (200 mg) después se sometió a 275,8 kPa de presión de hidrógeno durante 3 h. Se trató la suspensión con sulfato de magnesio anhidro (5 g) y después se filtró a través de un lecho de Celite. La torta del filtro se lavó con acetato de etilo (2 x 25 ml) y después se evaporó el filtrado a presión reducida hasta un aceite. Se evaporó este aceite dos veces para que el diclorometano (50 ml) separe el acetato de etilo atrapado. Esto dio el producto como un aceite pardo claro límpido que se solidificó en reposo (6,9 g, 99 %): LCMS 249 ($M^+ + H$).

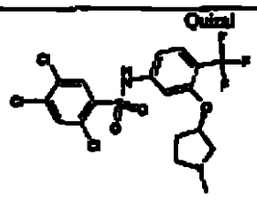
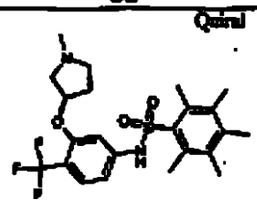
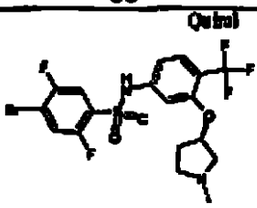
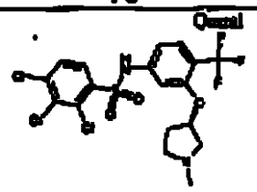
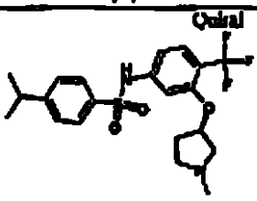
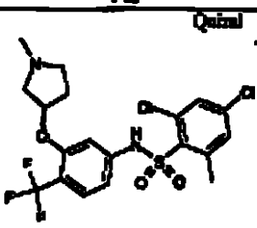
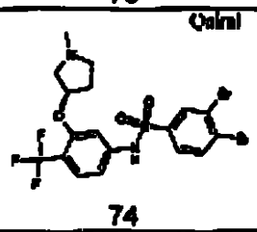
d) 2-Bromo-4,5-dimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida

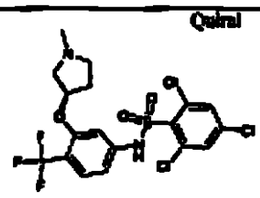
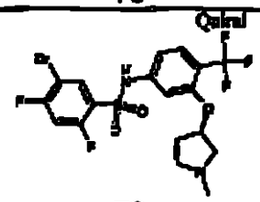
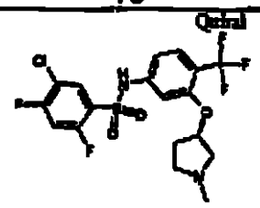
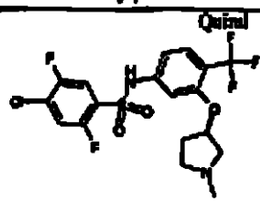
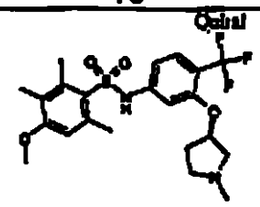
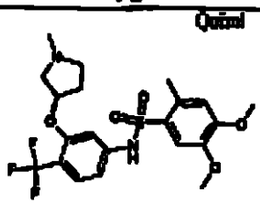
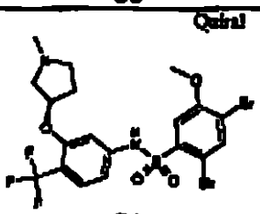
Una solución de 3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenilamina (250 mg, 0,96 mmol) y cloruro de 2-bromo-4,5-dimetoxibencenosulfonilo (303 mg, 0,96 mmol) en 1,2-dicloroetano anhidro (5 ml), se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se evaporó a presión reducida hasta una goma, después se recogió en dimetilsulfóxido (3 ml) y se purificó por HPLC preparativa. Las fracciones reunidas se evaporaron a presión reducida para dar el producto como la sal de TFA. Ésta se trató con NaOH acuoso al 10 % (50 ml) y cloruro de metileno (50 ml). La suspensión resultante se agitó vigorosamente durante 20 min, después se filtró para recoger la base libre del producto insoluble. La base libre seca se disolvió en metanol (5 ml) después se trató con ácido clorhídrico concentrado (0,1 ml). Por evaporación a presión reducida se obtuvo la sal hidrocloruro del producto como un sólido amarillo pálido (347 mg, 63 %): MS (ES+) m/e $[M+H]^+$ 539.

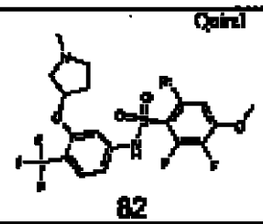
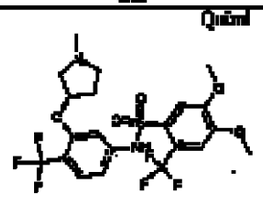
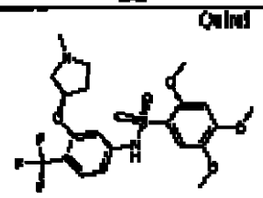
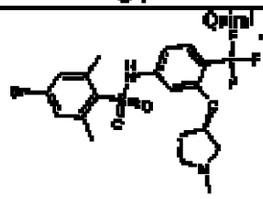
Ejemplos 65-85

Sustituyendo la (R)-3-(1-metil-3-pirrolidinil)-4-cloroanilina por 3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenilamina y sustituyendo el cloruro de 2,4,5-trimetoxi-bencenosulfonilo por diferentes cloruros de sulfonilo, se prepararon los ejemplos 65-85 siguiendo el procedimiento descrito en 1e:

Ejemplo	Compuesto	MS (ES+) m/e $[M+H]^+$
 65	2-Cloro-4,5-dimetoxi-3-[((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	495
 66	2,6-Dicloro-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-4-trifluoro-metil-bencenosulfonamida	537
 67	3,4-Dimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bence-nosulfonamida	461

 68	2,4,5-Tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	503
 69	2,3,4,5,6-Pentametil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	471
 70	4-Bromo-2,5-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	516
 71	2,3,4-Tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	503
 72	4-Isopropil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	443
 73	2,4-Dicloro-6-metil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	483
 74	3,4-Dibromo-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	559

 75	2,4,6-Tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	503
 76	5-Bromo-2,4-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	516
 77	5-Cloro-2,4-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	471
 78	4-Cloro-2,5-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	471
 79	4-Metoxi-2,3,6-trimetil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	473
 80	3,5-Dimetoxi-2-metil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	475
 81	2,4-Dibromo-5-metoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	589

 82	2-Bromo-5,6-difluoro-4-metoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	546
 83	4,5-Dimetoxi-2-trifluorometil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	529
 84	2,4,5-Trimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	491
 85	4-Bromo-2,6-dimetil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida	508

Ejemplo 86

Las formulaciones para uso farmacéutico que incorporan los compuestos de la presente invención se pueden preparar en diferentes formas y con numerosos excipientes. Ejemplos de tales formulaciones se dan a continuación.

Comprimidos/Ingredientes	Por comprimido
1. Ingrediente activo (Compuesto de la fórmula I)	40 mg
2. Almidón de maíz	20 mg
3. Ácido algínico	20 mg
4. Alginato de sodio	20 mg
5. Estearato de magnesio	1,3 mg
	2,3 mg

Procedimiento para comprimidos:

Etapa 1: Mezclar los ingredientes No. 1, No. 2, No. 3 y No. 4 en un mezclador adecuado.

Etapa 2: Añadir suficiente agua en porciones a la mezcla de la Etapa 1 mezclando cuidadosamente después de cada adición. Seguir con tales adiciones de agua y mezclados hasta que la masa sea de una consistencia que permita su conversión en gránulos húmedos.

Etapa 3: La masa húmeda se convierte en gránulos al pasarla a través de un granulador oscilante usando un tamiz de malla No. 8 (2,38 mm).

Etapa 4: Los gránulos húmedos se introducen después en una estufa a 60 °C hasta que estén secos.

Etapa 5: Los gránulos secos se lubrifican con el ingrediente No. 5.

Etapa 6: Los gránulos lubrificados se comprimen en una máquina de comprimir adecuada.

Formulación inhalante

Un compuesto de la fórmula I, (de 1 mg a 100 mg) se convierte en aerosol desde un inhalador con dosis medidas para administrar la cantidad deseada de fármaco para uso.

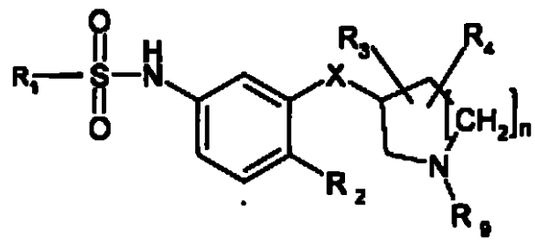
Formulación parenteral

Una composición farmacéutica para administración parenteral se prepara disolviendo una cantidad apropiada de un compuesto de la fórmula I en polietilenglicol con calentamiento. Se diluye después esta solución con agua para inyección de la Ph. Eur. (hasta 100 ml). Se esteriliza después la solución por filtración a través de una membrana filtrante de 0,22 micras y se sella en envase estériles.

La anterior memoria descriptiva y ejemplos describen completamente cómo preparar y usar los compuestos de la presente invención. Sin embargo, la presente invención no se limita a las particulares realizaciones descritas anteriormente, sino que incluye todas sus modificaciones dentro del alcance de las siguientes reivindicaciones. Las diferentes referencias a revistas, patentes y otras publicaciones que se citan aquí comprenden los últimos adelantos de la técnica y se incorporan aquí como referencia como totalmente publicadas.

REIVINDICACIONES

1. Un compuesto de la fórmula (I):



Fórmula (I)

en la que:

R^1 es fenilo sin sustituir o sustituido con uno, dos, tres, cuatro o cinco de cualquiera de los siguientes: halógeno, CF_3, OCF_3, SCF_3, NO_2, CN, alquilo C_{1-6}, alcoxi C_{1-6}, NR_5R_6, $CONR_7R_8$, S-alquilo C_{1-6}, CO_2(alquilo C_{1-6}), (alquil C_{1-6})-CO_2-(alquilo C_{1-6});

R_2 es hidrógeno, halógeno, CF_3, CN o alquilo C_{1-4};

R_3, R_4, R_7, y R_8 son independientemente hidrógeno, alquilo C_{1-6}, o bencilo;

R_5, R_6, y R_9, son independientemente hidrógeno o alquilo C_{1-6};

X es O, S, o CH_2;

n es 1;

o una de sus sales farmacéuticamente aceptables.

2. Un compuesto según la reivindicación 1, en el que R^1 es fenilo sin sustituir o sustituido con uno, dos, tres, cuatro o cinco de cualquiera de los siguientes: halógeno, CF_3, OCF_3, CN, alquilo C_{1-6}, alcoxi C_{1-6}, CO_2(alquilo C_{1-6}), (alquil C_{1-6})-CO_2(alquilo C_{1-6}), o NO_2; R_2 es hidrógeno, halógeno, CF_3, o alquilo C_{1-4}; R_3 es hidrógeno; R_4 es hidrógeno; R_9 es hidrógeno o alquilo C_{1-6}; y X es O.

3. Un compuesto según la reivindicación 1, en el que R_1 es fenilo sin sustituir o sustituido con uno, dos, tres, o cuatro de los siguientes: halógeno, CF_3, CN, metilo, metoxi; R_2 es halógeno o CF_3, R_3 es hidrógeno; R_4 es hidrógeno; R_9 es hidrógeno o alquilo C_{1-6}; y X es O.

4. Un compuesto según la reivindicación 1, elegido del grupo constituido por: hidrocloruro de (R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,5-trimetoxi-benceno-sulfonamida;

(+)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;
(+)-N-[4-cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(S)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluorometilbenceno-sulfonamida;
(+)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(S)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluorometilbenceno-sulfonamida;
2-bromo-N-[4-cloro-3-((S)-1-metil-pirrolidin-3-iloxi)-fenil]-4,5-dimetoxi-bencenosulfonamida;
4-bromo-2-cloro-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-5-metoxi-bencenosulfonamida;
2,4-Dibromo-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-5-metoxi-bencenosulfonamida;
(R)-N-[4-cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-etil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metil-4,5-dimetoxibencenosulfonamida;
(+)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(+)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metil-4-bromobencenosulfonamida;
(R)-N-[4-cloro-3-(1-isopropil-3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,5-triclorobencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,4,5,6-pentametilbencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-metoxi-5-bromobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-(metilpropionato)benceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-4-bromobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,6-trimetil-4-metoxibenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,4-triclorobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,5,6-tetrametilbencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-isopropilbencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-etilbencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4-cianobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-dicloro-6-metilbenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-3,6-dibromobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-trifluorometoxi-4-bromobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-fluorobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-butilbencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-difluoro-5-bromobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4-difluoro-5-clorobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-fluoro-4-metoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-difluorobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,5-difluoro-4-clorobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3-nitro-4-clorobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dimetil-4-bromobenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,4-dibromobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,6-triclorobencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-5-fluoro-4-metoxi-2-trifluorometil-bencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-3,5-difluoro-4-metoxi-2-metil-benceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-6-bromo-2,3-difluoro-4-metoxi-bencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4,5-dimetoxi-2-trifluorometil-bencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4,5-dimetoxi-bencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-4-fluoro-2-trifluorometil-bencenosulfonamida;
(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,4,6-trifluoro-bencenosulfonamida;
3,4-Dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;
2-bromo-4,5-dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;
2-cloro-4,5-dimetoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;
4,5-Dimetoxi-2-metil-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;
4-bromo-2-cloro-5-metoxi-N-[4-metil-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;
2-bromo-4,5-dimetoxi-N-[4-metil-3-((S)-1-metil-pirrolidin-3-iloxi)-fenil]-bencenosulfonamida;
N-[4-cloro-3-((R)-pirrolidin-3-iloxi)-fenil]-2-bromo-3,4-dimetoxi-bencenosulfonamida;
(±)-N-[4-cloro-3-(3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(R)-N-[4-cloro-3-(3-pirrolidiniloxi)-fenil]-3,4-dimetoxibencenosulfonamida;
(±)-N-[4-cloro-3-(3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;
2-cloro-4,5-dimetoxi-3-[((R)-1-metil-pirrolindin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;
2,6-Dicloro-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-4-trifluorometil-bencenosulfonamida;
2-bromo-4,5-dimetoxi-N-[3-(1-metil-pirrolidin-3-iloxi-4-trifluorometil-fenil]-bencenosulfonamida;
3,4-Dimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;
2,4,5-tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;
2,3,4,5,6-pentametil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-bromo-2,5-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,3,4-tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-isopropil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4-Dicloro-6-metil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

3,4-Dibromo-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4,6-tricloro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

5-bromo-2,4-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

5-cloro-2,4-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-cloro-2,5-difluoro-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4-Metoxi-2,3,6-trimetil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

3,5-Dimetoxi-2-metil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4-Dibromo-5-metoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2-bromo-5,6-difluoro-4-metoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

4,5-Dimetoxi-2-trifluorometil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2,4,5-trimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida; o

4-bromo-2,6-dimetil-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida.

5. Un compuesto según la reivindicación 1, elegido del grupo constituido por:

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-bromo-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,6-dicloro-4-trifluorometilbenceno-sulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2-cloro-4,5-dimetoxibencenosulfonamida;

(R)-N-[4-cloro-3-(1-metil-3-pirrolidiniloxi)-fenil]-2,3,6-trimetil-4-metoxibenceno-sulfonamida;

2-bromo-4,5-dimetoxi-N-[3-((R)-1-metil-pirrolindin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida;

2-cloro-4,5-dimetoxi-N-[3-((R)-1-metil-pirrolindin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida; o

2,6-dicloro-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-4-trifluorometil-bencenosulfonamida.

6. Un compuesto de la reivindicación 1, elegido entre:

2-bromo-4,5-dimetoxi-N-[3-((R)-1-metil-pirrolidin-3-iloxi)-4-trifluorometil-fenil]-bencenosulfonamida; o

2-bromo-N-[4-cloro-3-((R)-1-metil-pirrolidin-3-iloxi)-fenil]-4,5-dimetoxi-bencenosulfonamida.

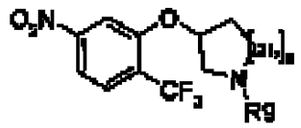
7. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de la reivindicación 1 y un vehículo o excipiente farmacéuticamente aceptable.

8. Una composición farmacéutica que comprende un compuesto de la fórmula (I) de la reivindicación 5 y un vehículo o excipiente farmacéuticamente aceptable.

9. Un método para tratar enfermedades asociadas con el equilibrio de la urotensina II por medio de antagonizar el receptor de la urotensina-II, que comprende administrar a un paciente que lo necesite, un compuesto de la fórmula I de la reivindicación 1.

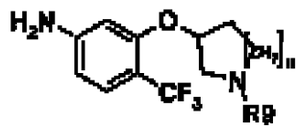
10. Un método según la reivindicación 9, en el que la enfermedad es insuficiencia cardiaca congestiva, ictus, cardiopatía isquémica, angina, isquemia miocárdica, arritmia cardiaca, hipertensión esencial y pulmonar, enfermedad renal, insuficiencia renal aguda y crónica, enfermedad renal en etapa terminal, enfermedad vascular periférica, disfunción eréctil del varón, retinopatía diabética, claudicación intermitente/enfermedad isquémica de los miembros, ictus isquémico/hemorrágico, COPD, restenosis, asma, inflamación neurógena, migraña, vasculopatías metabólicas, enfermedades de los huesos/cartílagos/articulaciones, artritis y otras enfermedades inflamatorias, fibrosis, fibrosis pulmonar, sepsis, aterosclerosis, dislipidemia, adicción, esquizofrenia, trastornos cognitivos, enfermedad de Alzheimer, impulsividad, ansiedad, estrés, depresión, enfermedad de Parkinson, trastornos del movimiento, ciclo sueño-vigilia, motivación por estímulos, dolor, función neuromuscular, diabetes, reflujo gástrico, trastornos de la motilidad gástrica, úlceras y enfermedades genitourinarias.

11. Un procedimiento para la preparación de un compuesto de la fórmula (I) de la reivindicación 1 o una de sus sales farmacéuticamente aceptables, cuyo procedimiento comprende la hidrogenación de un compuesto de la fórmula (II)



(II)

en la que R_9 y n son como se describe en la reivindicación 1, o un grupo convertible en los mismos, para dar un compuesto de la fórmula (III)



(III)

que se hace reaccionar con un compuesto de la fórmula (IV)

$$R_1 - SO_2Cl$$

(IV)

en la que R_1 es como se describe en la reivindicación 1, o un grupo convertible en el mismo,

y cuando se desee o sea necesario, conversión de R_1 y/o R_9;

para obtener un compuesto de la fórmula (I).

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RESUMEN DE LA DESCRIPCIÓN

La presente invención se refiere a sulfonamidas, a composiciones farmacéuticas que las contienen, y a su uso como antagonistas de la urotensina II.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P51877A	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/16548	International filing date (day/month/year) 07 MAY 2000	Priority date (day/month/year) 07 MAY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/40; C07D 207/10 and US Cl.: 514/414; 548/546		
Applicant SMITHKLINE BEECHAM CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04 OCTOBER 2000	04 FEBRUARY 2002
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LAURA L. STOCKTON Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998)o

95 1/05

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/14943

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-36 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the claims:
pages 37-44 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/fig NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/14048

A. CLASSIFICATION OF SUBJECT MATTER

. IPC(7) :A61K 31/00; C07D 307/18
US Cl. :514/464; 549/360

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. : 514/464; 549/360

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)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-329626 A (HOSHIKO ET AL) 29 November 1994 (29/11/94), see entire document, especially columns 29-31.	1-11

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

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 01 JULY 2000	Date of mailing of the international search report 30 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LAURA L. STOCKTON Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/14545

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7): A61K 31/40; C07D 207/18
US Cl.: 514/424; 548/556
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. : 514/424; 548/556

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)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-329626 A (HOSHIKO ET AL) 29 November 1994 (29/11/94), see entire document, especially columns 29-31.	1-11

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

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 01 JULY 2000	Date of mailing of the international search report 30 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Felicia D. Robert for LAURA L. STOCKTON Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19444

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7): A61K 31/40; C07D 207/12
US CL: 514/409; 548/559
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. : 514/409; 548/559

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)
STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-329626 A (HOSHIKO ET AL) 29 November 1994 (29/11/94), see entire document, especially columns 29-31.	1-11

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

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 01 JULY 2002	Date of mailing of the international search report 30 JUL 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LAURA L. STOCKTON Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/10540

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/40; C07D 207/16
US CL. :514/424; 548/550
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. : 514/424; 548/550

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)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-329626 A (HOSHIKO ET AL) 29 November 1994 (29/11/94), see entire document, especially columns 29-31.	1-11

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

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier document published on or after the international filing date	"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
"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	"&"	document member of the same patent family

Date of the actual completion of the international search 01 JULY 2002	Date of mailing of the international search report 30 JUL 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Felicia D. Robertson LAURA L. STOCKTON Telephone No. (703) 308-1235

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109/400

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/16848

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/48; C07D 207/10
US CL :514/424; 548/566

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. : 514/424; 548/566

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)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-329626 A (HOSHIKO ET AL) 29 November 1994 (29/11/94), see entire document, especially columns 29-31.	1-11

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Felicia D. Robertson LAURA L. STOCKTON Telephone No. (703) 308-1235

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101 Hist

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19549

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/40; C07D 207/18
US CL. :514/424; 548/558

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. : 514/424; 548/558

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)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-329626 A (HOSHIKO ET AL) 29 November 1994 (29/11/94), see entire document, especially columns 29-31.	1-11

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

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer LAURA L. STOCKTON Telephone No. (703) 308-1234

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102 1102

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/14648

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/00; C07D 207/10
US CL :514/424; 548/558

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. : 514/424; 548/558

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)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 06-329626 A (HOSHIKO ET AL) 29 November 1994 (29/11/94), see entire document, especially columns 29-31.	1-11

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Felicia D. Robertson LAURA L. STOCKTON Telephone No. (703) 308-1235

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103/105

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/10568

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/40; C07D 207/16
US CL. :514/424; 548/558
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. : 514/424; 548/558

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)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Felicia D. Roberts LAURA L. STOCKTON Telephone No. (703) 308-1235

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SUPERINDUSTRIA Y COMERCIO
Radicación : 03098576 00000000
Fecha (GMT): 2003-11-07 16:27:31 Folios: 102
Trámite : 911 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOS
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de pago de las tasas establecidas.		
COMPLETA ( ) **INCOMPLETA**	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica 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 solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable:

Fecha:

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
CARLOS R. OLARTE
Apoderado
SMITHKLINE BEECHAM CORPORATION

Oficio N° 11430

ASUNTO:		
	Radicación N°	03-88576
	Solicitud internacional	PCT/US02/14543
	Fecha inicio fase nacional	07/12/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el 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:

- 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).
- El solicitante debe presentar un nuevo título que permita identificar la materia de la cual trata la solicitud, ya que el título relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular unica 5.2.9).

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 N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 26 DIC. 2003.

202080