Industria y Comercio

SUPERINTENDENCIA

QF 03-65410

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

03-65410

21 **EXPEDIENTE No.**

54 **TÍTULO** Derivados de eteres utiles como agentes Inhibidores de las isozimas PDE4

51 **CLASIFICACIÓN INTERNACIONAL** A61K 31/44, C07D 405/12

71 **SOLICITANTE** Pfizer Products INC

DOMICILIO Eastern Point Road, Estado de Connecticut, Estados Unidos de América

74 **APODERADO** Carlos R. Olarte

22 **BOGOTÁ, D. C.,** Julio 31, 2003

(FORMA P-10)

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO 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: PFIZER PRODUCTS INC.

Dirección: Eastern Poitn Road Estado de Connecticut Estados Unidos de America.

Nacionalidad o Domicilio

Lugar de Constitución: Connecticut; Estados Unidos de América.

Teléfono: Fax:

E-Mail:

IDENTIFICACION

C C [ ] NIT [ ]

C E [ ] Otro [ ]

Cual: _____

Número: _____

(3) REPRESENTANTE O APODERADO

Nombre: CARLOS R OLARTE

Dirección: World Trade Center Torre C, Calle 100 No 8A-55 Piso 10

Teléfono: 6386200 Fax: 6386201

E-Mail: filings@olarteraisbeck.com

IDENTIFICACION

C C [X] NIT [ ]

C E [ ] Otro [ ]

Cual: _____

Número: 79 782 747 Bta TP 74 295

(4) INVENTOR (ES) (72)

Nombre: ROBERT JAMES CHAMBERS, THOMAS VICTOR MAGEE, ANTHONY MARFAT

Dirección: Eastern Point Road, Groton Connecticut 06340, Estados Unidos de América.

Nacionalidad o Domicilio: ESTADOUNIDENSE

(5) PCT (85)

Solicitud Internacional No: PCT/IB01/02726 Fecha: Diciembre 24, 2001

Publicación Internacional No: WO 02/060896 Fecha: Agosto 8, 2002

(6) Titulo (54): DERIVADOS DE ETERES UTILES COMO AGENTES INHIBIDORES DE LAS ISOZIMAS PDE4

(7) Clasificación Internacional (51): A61K 31/44 C07D 405/12

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	Enero 31, 2001	60/265,304

(9) Comprobante de pago No 52673 **Fecha** 28-07-03

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

(10) **ANEXOS**

00002

2

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [X] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional (Resumen descripción reivindicaciones dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen descripción reivindicaciones dibujos)
- [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 R OLARTE

FIRMA

C C 79 782 747 de Bta T P 74.295

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

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2	PODER
3	DOCUMENTO DE CESION
4	SOLICITUD INTERNACIONAL
5	TRADUCCION DE SOLICITUD INTERNACIONAL
6	EXAMEN PRELIMINAR
7	BUSQUEDA INTERNACIONAL
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Dependencia 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 52,673
FECHA : JULIO 28 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	Vr PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00110-6	13594221	28/07/2003	1,700,000 00

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

CANT	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL DE PATENTE DE IN	400,000 00
		TOTAL : $	400 000 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 5

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER PRODUCTS INC

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J Trevor Lumb, Vicepresidente de Pfizer Products Inc

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J Trevor Lumb ejercía funciones de Vicepresidente de la Compañía Pfizer Products Inc , con sede en Groton, Connecticut, Estados Unidos

Firma del notario

Sello notarial certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1 País Reino Unido de Gran Bretaña e Irlanda del Norte
Este documento Publico
2 ha sido firmado por K Greenwood
3 ejerce funciones de Notario Publico
4 Lleva el sello de dicho Notario Publico

CERTIFICADO

5 En Londres 6 El 17 de julio de 2003
7 Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8 No G210435
9 Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10 Firma de R Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país

Es traducción fiel del inglés, con copia archivo para confrontación Bogotá 25 de julio-2003

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés Español Inglés
Resolución No 2117 del 7 Oct 1987

6

00009

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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BOGOTA COLOMBIA
TELEPHONE. +57 1 638-6200
FAX. +57 1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

Pfizer Products Inc

domiciled in

Eastern Point Road, Groton, Connecticut 06340 USA

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,

Pfizer Products Inc

domiciliado en

Eastern Point Road, Groton, Connecticut 06340 USA

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. _____

Date/Fecha. July 14, 2003

City,Country/Ciudad,País New York, USA

NOTARIO ... DE ESTE ... COTEJAR QUE ESTA ... COINCIDE CON EL ... 28 JUL ... BOGOTA, D.C. ... NAVARRETE ... NOTARIA ...

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TELEPHONE +57 1 638-6200
FAX. +57 1 638-6201

www olarteraisbeck.com

Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies

1 That J Trevor Lumb
of legal age and domiciled in
New York, USA
signed the foregoing document.

2 That the grantor has executed the foregoing document as Vice President of Pfizer Products Inc

3 That Pfizer Products Inc ,
having its principal place of business located in
Groton, Connecticut, U S A.
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes

4 That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal

5 The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s)

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica.

1 Que
J Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

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

4 Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social

4 Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima

5 El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s)

NOTARIO ONCE DE ESTE CIRCULO PUEDO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
21 JUL 2003
BOGOTA, D.C. COLOMBIA
NOTARIA ONCE (11)

NOTARY PUBLIC (Signature)

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14 Day Of July
2003
KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND GREEMAN

0001 87

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: K Greenwood
a été signé par:

3 Acting in the capacity of: Notary Public
agissant en qualité de:

4. Bears the seal/stamp of: The Said Notary Public
est revêtu du sceau/timbre de:

Certified/Attesté
5 at London/à Londres 6. the/le 17 July 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 **G210435**

9 Stamp
timbre:

10. Signature: R. Bawden

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

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HAGO CONSTAR QUE ESTA
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QUE HE TENIDO A LA VISTA.
28 JUL 2003
BOGOTA, D.C. - COLOMBIA
NAVARRO DE RAMISTA
NOTARIA ONCE (11)

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia PC11896ARMS

CESION A PFIZER PRODUCTS INC **CO-1**

Por una contraprestación valiosa pagada a nosotros, por PFIZER PRODUCTS INC ,una compañía organizada bajo las leyes del Estado de Connecticut, Estados Unidos de América, cuya dirección postal completa es Eastern Point Road, Groton, Connecticut 06340, Estados Unidos de America, por el presente yo (nosotros) vendemos y cedemos a la mencionada PFIZER PRODUCTS INC , todos mis (nuestros) derechos, titulo e interés en y referente a mi (nuestra) invencion para una mejora nueva y util en DERIVADOS ETER UTILES COMO INHIBIDORES DE ISOZIMAS PDE4 en cuanto a la Republica de Colombia, tan totalmente como se describe en la especificación, y por el presente yo (nosotros) autorizamos y solicitamos al Comisionado de patentes de Colombia que expida tal patente a la mencionada PFIZER PRODUCTS INC , de acuerdo con esta cesión

En testimonio de lo anterior, firmamos en estas fechas

Firma	Lugar y fecha
Robert James Chambers	Groton, Connecticut, 9 noviembre, 2001
Thomas Victor Magee	Groton, Connecticut, 2 noviembre, 2001
Anthony Marfat	Groton, Connecticut, 2 noviembre, 2001

Sello notarial Certificado, verificado y autenticado en la Localidad de Egham en Surrey, 26 ilegible, 2001 por el Notario Kenneth Greenwood- Horne Engall & Freeman Sello Notario Publico en alto relieve rojo

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

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Este documento Público 2 ha sido firmado por K Greenwood
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CERTIFICADO 5 En Londres 6 El 27 de noviembre de 2001
7 Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad 8 No G961668
9 Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10 Firma de M Monaghan - Por Secretario de Estado

Es traducción fiel del inglés, con copia archivo para confrontación Bogotá 25 de julio-2003

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés Español Inglés
Resolución No 2117 del 7 Oct 1987

PC11896ARMS

CO-1

ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER PRODUCTS INC** a corporation organized under the laws of the State of Connecticut, United States of America whose full post office address is Eastern Point Road, Groton, Connecticut 06340, United States of America, I (we) do hereby sell and assign to the said **PFIZER PRODUCTS INC.**, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in **ETHER DERIVATIVES USEFUL AS INHIBITORS OF PDE4 ISOZYMES** so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER PRODUCTS INC** in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

Place, date and signature - Robert James CHAMBERS	09 November 2001 Groton, Connecticut, USA
Place, date and signature - Thomas Victor MAGEE	02 November 2001 Groton, Connecticut, USA
Place, date and signature - Anthony MARFAT	02 November 2001 Groton, Connecticut, USA

Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 2 Day Of November

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

11

APOSTILLE

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

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: K Greenwood
a été signé par

3 Acting in the capacity of: Notary Public
agissant en qualité de

4 Bears the seal/stamp of: The Said Notary Public
est revêtu du sceau/timbre de

Certified/Attesté

5 at London/à Londres

6. the/le 27 November 2001

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: G961668

9 Stamp
timbre:

FOREIGN AND COMMONWEALTH OFFICE
LONDON

10. Signature: M. Monaghan

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

(19) World Intellectual Property Organization
International Bureau

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8 August 2002 (08.08.2002)

PCT

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WO 02/060896 A1

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(21) International Application Number: PCT/IB01/02726

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24 December 2001 (24.12.2001)

(25) Filing Language English

(26) Publication Language: English

(30) Priority Data:
60/265,304 31 January 2001 (31.01.2001) US

(71) Applicant *(for all designated States except US)* PFIZER PRODUCTS INC [US/US] Eastern Point Road Groton, CT 06340 (US).

(72) Inventors, and
(75) Inventors/Applicants *(for US only)* CHAMBERS, Robert, James [US/US] Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). MAGEE, Thomas, Victor [US/US] Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). MARFAT, Anthony [US/US] Pfizer Global Research and Development, Eastern Point Road, Groton CT 06340 (US).

(74) Agents: LUMB, J., Trevor et al Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (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, ZW

(84) Designated States *(regional)* ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM AZ, BY, KG KZ, MD, RU, TJ TM), European patent (AT BE, CH, CY DE, DK, ES, FI, FR, GB GR, IE, IT LU MC, NL, PT SE, TR), OAPI patent (BF BJ CF, CG CI, CM GA, GN GQ, GW ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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 02/060896 A1

(54) Title: ETHER DERIVATIVES USEFUL AS INHIBITORS OF PDE4 ISOZYMES

(57) Abstract: Compounds useful as inhibitors of PDE4 in the treatment of diseases regulated by the activation and degranulation of eosinophils, especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease, of the formula (I) wherein j is 0 or 1 provided that when j is 0, n must be 2 k is 0 or 1, m is 1 2, or 3 n is 1 or 2, W^1 and W^2 are -O-, -S(=O)$_t$-, where t is 0, 1, or 2, or -N(R^2)-, Y is =C(R^1)-, or -[N⇒(O)$_k$] where k is 0 or 1 R^1 is -H -F, -Cl -CN -NO_2, -(C_1-C_4) alkyl, -(C_2-C_4) alkynyl fluorinated-(C_1-C_3) alkyl, fluorinated-(C_1-C_2) alkoxy, -OR^{16}, or -C(=O)$NR^{22a}R^{22b}$, R^A and R^B are -H, -F -CF_3, -(C_1-C_4) alkyl, -(C_3-C_7) cycloalkyl, phenyl or benzyl substituted by 0-3 R^{16}; or R^A and R^B are taken together to form a spiro moiety of the formula (Ia) where r and s are 0-4 provided r + s is ≥1 but not > 5 and X^A is -CH_2-, -CHF, -CF_2, -NR^{15}-, -O-, or -S(=O)$_t$-, where t is 0, 1 R^C and R^D are the same as R^A and R^B except that one of them must be -H, R^1 and R^2 are -H -F -Cl, -CN -NO_2, -(C_1-C_4) alkyl, -(C_2-C_4) alkynyl, fluorinated-(C_1-C_3) alkyl, -OR^{16}, or -C(=O)$NR^{22a}R^{22b}$, R^3 is -H, -(C_1-C_3) alkyl, phenyl, benzyl, or -OR^{16}; R^4 R^5 and R^6 D, J_1 and J_2 are defined in the application.

ETHER DERIVATIVES USEFUL AS INHIBITORS OF PDE4 ISOZYMES

1.0 REFERENCE TO RELATED APPLICATIONS

Reference is made to co-pending International application and US application based thereon, Serial No. PCT/IB98/00315, both filed March 10, 1998 (Attorney Docket No. PC9762A), and published as WO 98/45268 on October 15, 1998, claiming priority from application Serial No 60/043403 filed April 4, 1997 (Attorney Docket No PC9762), now abandoned, which discloses nicotinamide derivatives having biological activity as inhibitors of PDE4 isozymes, and thus being useful in the treatment of inflammatory, respiratory and allergic diseases and conditions Nothing that is disclosed in the above-mentioned applications would teach the person of ordinary skill in the pertinent art the novel compounds of the present invention or their unexpectedly high level of inhibitory selectivity for PDE 4 isozymes

Reference is also made to copending application Serial No 09/345,185 filed June 30, 1999 (Attorney Docket No. PC10096A); claiming priority from application Serial No. 60/105,120 filed October 21, 1998 (Attorney Docket No. PC10096), which discloses compounds and processes for preparing N-substituted nicotinamide derivatives. However, the disclosed compounds and processes are not the same as those of the present invention

Reference is further made to copending applications filed of even date with the instant application, Attorney Docket Nos PC11712; PC11848, PC11893, PC11894, PC11895, and PC11897, which involve other classes of nicotinamide derivatives useful as inhibitors of PDE4 isozymes The disclosures of all of said copending applications are incorporated herein by reference in their entireties.

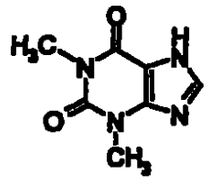
2.0 BACKGROUND OF THE INVENTION

The 3',5'-cyclic nucleotide phosphodiesterases (PDEs) comprise a large class of enzymes divided into at least eleven different families which are structurally, biochemically and pharmacologically distinct from one another The enzymes within each family are commonly referred to as isoenzymes, or isozymes A total of more than fifteen gene products is included within this class, and further diversity results from differential splicing and post-translational processing of those gene products The present invention relates to the four gene products of the fourth family of PDEs, *i.e.*, PDE4A, PDE4B, PDE4C, and PDE4D, and their inhibition, including selective inhibition of PDE4D These enzymes are collectively referred to as being isoforms or subtypes of the PDE4 isozyme family Further below will be found a more detailed discussion of the genomic organization, molecular structure and

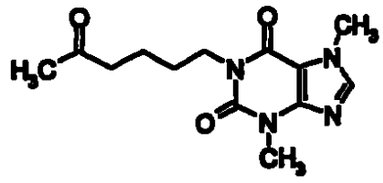
enzymatic activity, differential splicing, transcriptional regulation and phosphorylation, distribution and expression, and selective inhibition of the PDE4 isozyme subtypes

The PDE4s are characterized by selective, high affinity hydrolytic degradation of the second messenger cyclic nucleotide, adenosine 3',5'-cyclic monophosphate (cAMP), and by sensitivity to inhibition by rolipram A number of selective inhibitors of the PDE4s have been discovered in recent years, and beneficial pharmacological effects resulting from that inhibition have been shown in a variety of disease models See, *e.g.*, Torphy *et al.*, *Environ. Health Perspect.* 102 Suppl 10, 79-84, 1994, Duplantier *et al.*, *J Med. Chem.* 39 120-125, 1996, Schneider *et al.*, *Pharmacol. Biochem. Behav* 50 211-217, 1995, Banner and Page, *Br J. Pharmacol.* 114 93-98, 1995, Barnette *et al.*, *J Pharmacol. Exp. Ther* 273 674-679, 1995; Wright *et al* "Differential *in vivo* and *in vitro* bronchorelaxant activities of CP-80633, a selective phosphodiesterase 4 inhibitor," *Can. J. Physiol. Pharmacol.* 75 1001-1008, 1997; Manabe *et al.* "Anti-inflammatory and bronchodilator properties of KF19514, a phosphodiesterase 4 and 1 inhibitor," *Eur J Pharmacol.* 332 97-107, 1997, and Ukita *et al.* "Novel, potent, and selective phosphodiesterase-4 inhibitors as antiasthmatic agents. synthesis and biological activities of a series of 1-pyridylnaphthalene derivatives," *J Med. Chem.* 42 1088-1099, 1999 Accordingly, there continues to be considerable interest in the art with regard to the discovery of further selective inhibitors of PDE4s

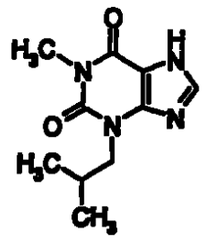
The present invention is also concerned with the use of selective PDE4 inhibitors for the improved therapeutic treatment of a number of inflammatory, respiratory and allergic diseases and conditions, but especially for the treatment of asthma; chronic obstructive pulmonary disease (COPD) including chronic bronchitis, emphysema, and bronchiectasis; chronic rhinitis, and chronic sinusitis. Heretofore in the art, however, the first-line therapy for treatment of asthma and other obstructive airway diseases has been the nonselective PDE inhibitor theophylline, as well as pentoxifylline and IBMX, which may be represented by Formulas (0.0 1), (0.0.2), and (0 0.3), respectively



Theophylline
(0.0.1)



Pentoxifylline
(0.0.2)

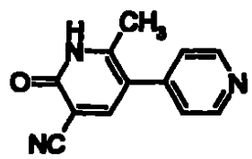


IBMX

(0.0.3)

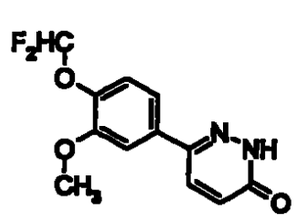
Theophylline, which has the PDEs as one of its biochemical targets, in addition to its well characterized bronchodilatory activity, affects the vasculature of patients with increased pulmonary artery pressure, suppresses inflammatory cell responses, and induces apoptosis of eosinophils. Theophylline's adverse events, most commonly cardiac dysrhythmias and nausea, are also mediated by PDE inhibition, however, leading to the search for more selective inhibitors of PDEs that are able to suppress both immune cell functions *in vitro* and allergic pulmonary inflammation *in vivo*, while at the same time having improved side-effect profiles. Within the airways of patients suffering from asthma and other obstructive airway diseases, PDE4 is the most important of the PDE isozymes as a target for drug discovery because of its distribution in airway smooth muscle and inflammatory cells. Several PDE4 inhibitors introduced to the art thus far have been designed to have an improved therapeutic index concerning the cardiovascular, gastrointestinal, and central nervous system side effects of the above-mentioned nonselective xanthines.

Airflow obstruction and airway inflammation are features of asthma as well as COPD While bronchial asthma is predominantly characterized by an eosinophilic inflammation, neutrophils appear to play a major role in the pathogenesis of COPD Thus, PDEs that are involved in smooth muscle relaxation and are also found in eosinophils as well as neutrophils probably constitute an essential element of the progress of both diseases. The PDEs involved include PDE3s as well as PDE4s, and bronchodilating inhibitors have been discovered which are selective PDE3 inhibitors and dual PDE3/4 selective inhibitors Examples of these are milrinone, a selective PDE3 inhibitor, as well as zardaverine and benafentrine, both dual PDE3/4 selective inhibitors, which may be represented by Formulas (0.0.4), (0.0.5), and (0.0.6), respectively



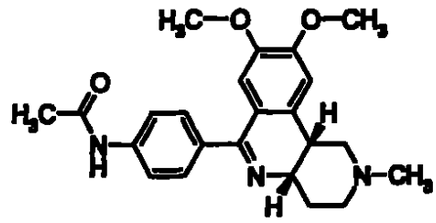
Milrinone

(0.0.4)



Zardaverine

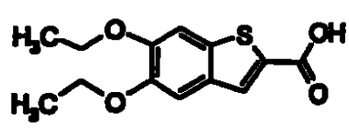
(0.0.5)



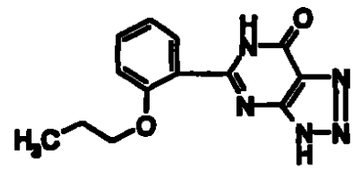
Benafentrine

(0.0.6)

However, benafentrine results in bronchodilation only when administered by inhalation, and zardaverine produces only a modest and short-lived bronchodilation Milrinone, a cardiotonic agent, induces short-lived bronchodilation and a slight degree of protection against induced bronchoconstriction, but has marked adverse events, e.g., tachycardia and hypotension. Unsatisfactory results have also been obtained with a weakly selective PDE4 inhibitor, tibenelast, and a selective PDE5 inhibitor, zaprinast, which may be represented by Formulas (0.0 7) and (0.0.8)·



Tibenelast
(0.0 7)



Zaprinast

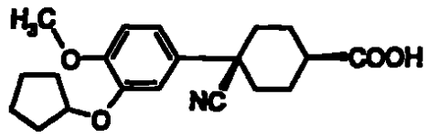
(0.0.8)

More relative success has been obtained in the art with the discovery and development of selective PDE4 inhibitors.

In vivo, PDE4 inhibitors reduce the influx of eosinophils to the lungs of allergen-challenged animals while also reducing the bronchoconstriction and elevated bronchial responsiveness occurring after allergen challenge. PDE4 inhibitors also suppress the activity of immune cells, including $CD4^+$ T-lymphocytes, monocytes, mast cells, and basophils, reduce pulmonary edema, inhibit excitatory nonadrenergic noncholinergic neurotransmission (eNANC); potentiate inhibitory nonadrenergic noncholinergic neurotransmission (iNANC); reduce airway smooth muscle mitogenesis, and induce bronchodilation PDE4 inhibitors also suppress the activity of a number of inflammatory cells associated with the pathophysiology of COPD, including monocytes/macrophages, $CD8^+$ T-lymphocytes, and neutrophils PDE4 inhibitors also reduce vascular smooth muscle mitogenesis and, and potentially interfere with the ability of airway epithelial cells to generate pro-inflammatory mediators. Through the release of neutral proteases and acid hydrolases from their granules, and the generation of reactive oxygen species, neutrophils contribute to the tissue destruction associated with

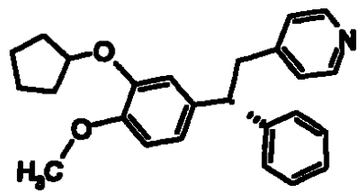
chronic inflammation, and are further implicated in the pathology of conditions such as emphysema.

Selective PDE4 inhibitors which have been discovered thus far that provide therapeutic advantages include SB-207,499, identified as ARIFLO®, which may be represented by Formula (0 1.9):



SB-207,499 (0 1.9)

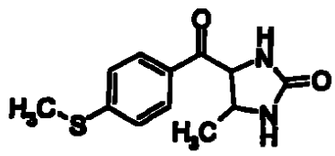
SB-207,499, administered orally at dosages of 5, 10, and 15 mg *b.i.d.*, has produced significant increases in trough FEV_1 (forced expiratory volume in 1 second) from placebo at week 2 of a study involving a large number of patients Another potent, selective PDE4 inhibitor, CDP840, has shown suppression of late reactions to inhaled allergen after 9.5 days of oral administration at doses of 15 and 30 mg in a group of patients with bronchial asthma. CDP840 may be represented by Formula (0.0 9)



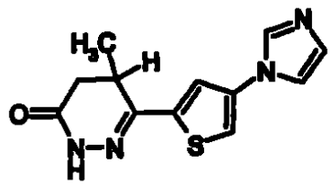
CDP840 (0.0.9)

PDEs have also been investigated as potential therapy for obstructive lung disease, including COPD In a large study of SB-207,499 in patients with COPD, the group of patients receiving 15 mg *b.i.d.* has experienced a progressive improvement in trough FEV_1, reaching a maximum mean difference compared with placebo of 160 mL at week 6, which represents an 11% improvement. See Compton *et al.*, "The efficacy of Ariflo (SB207499), a second generation, oral PDE4 inhibitor, in patients with COPD," *Am. J Respir Crit. Care Med.* 159, 1999 Patients with severe COPD have been observed to have pulmonary hypertension, and decreases in mean pulmonary artery pressure under clinical conditions have been achieved by oral administration of the selective PDE3 inhibitors milrinone and enoximone. Enoximone has also been shown to reduce airway resistance in patients hospitalized with decompensated COPD See Leeman *et al.*, *Chest* 91 662-6, 1987 Using selective PDE3 inhibition by motapizone and selective PDE5 inhibition by zaprinast, it has been shown that combined inhibition of PDE 3 and 5 exerts a relaxation of pulmonary artery rings which corresponds broadly to the pattern of PDE isozymes found in the pulmonary artery smooth muscle See Rabe *et al.*, *Am. J Physiol.* 266 (LCMP 10). L536-L543, 1994. The structures of milrinone and zaprinast are shown above as Formulas (0 0.4) and (0 0.8), respectively

The structures of enoximone and motapizone may be represented by Formulas (0.0 10) and (0 0 11), respectively

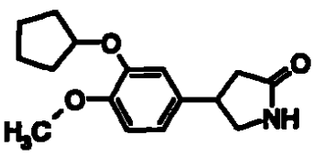


Enoximone
(0.0 10)

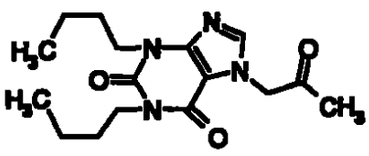


Motapizone
(0.0 11)

The effects of PDE4 inhibitors on various inflammatory cell responses can be used as a basis for profiling and selecting inhibitors for further study These effects include elevation of cAMP and inhibition of superoxide production, degranulation, chemotaxis, and tumor necrosis factor alpha (TNFα) release in eosinophils, neutrophils and monocytes. PDE4 inhibitors may induce emesis, *i.e.*, nausea and vomiting, which, as expected, is an adverse effect. The emesis adverse effect became apparent when PDE4 inhibitors were first investigated for CNS indications such as depression, when rolipram and denbufylline were used in clinical trials Rolipram and denbufylline may be represented by Formulas (0 0 12) and (0.0 13), respectively

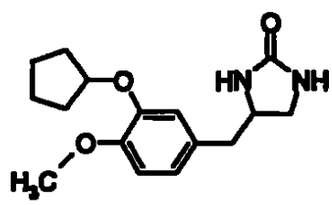


Rolipram
(0.0.12)



Denbufylline
(0.0.13)

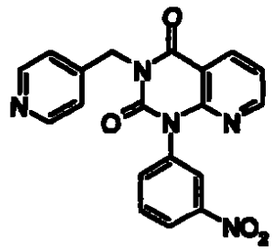
The mechanism(s) by which PDE4 inhibitors may potentially induce emesis is/are uncertain, but a study of the PDE4 inhibitor Ro-20-1724 suggests that nausea and vomiting are at least partially mediated by the emesis centers in the brain Gastrointestinal adverse events may be caused by local effects, *e.g.*, rolipram is a very potent stimulator of acid secretion from gastric parietal cells, and the resulting excess acid, by producing local irritation, may exacerbate gastrointestinal disturbances Ro-20-1724 may be represented by Formula (0.0 14):



Ro-20-1724
(0.0 14)

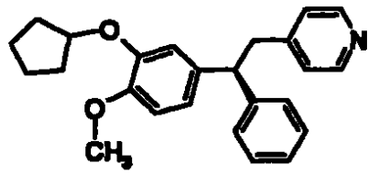
Efforts to minimize or eliminate the above-mentioned adverse events sometimes associated with PDE4 inhibitors have included creating inhibitors which do not penetrate the central nervous system, and administering PDE4 inhibitors by inhalation rather than orally

With regard to the PDE4 subtypes, A, B, C, and D, it has been found that PDE4C is usually less sensitive to all inhibitors, whereas, with respect to the subtypes A, B, and D, there is as yet no clear evidence of inhibitor specificity, which is defined as a 10-fold difference in IC_{50} values While most inhibitors, especially RS-25,344, are more potent against PDE4D, this does not amount to selectivity RS-25,344 may be represented by Formula (0.0 15):



RS-25,344 (0.0.15)

On the other hand, there is a stereoselective effect on the elevation of cAMP in a range of cell types, which has been demonstrated with the results of an investigation of CDP840, shown above as Formula (0 0 9), and its less active enantiomer CT-1731, which is represented by Formula (0 0 16):

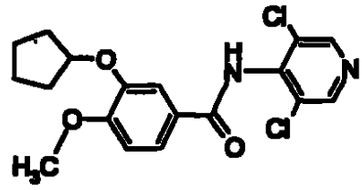


CT-1731 (0.0 16)

It has been known for some time that rolipram had the ability to interact with a high-affinity binding site on brain membranes, and it was later established in the art that this high-affinity rolipram binding site (S_r), which is distinct from the catalytic site (S_c), exists in a truncated recombinant PDE4A and a full-length recombinant PDE4B. More recently, S_r has been identified on all four PDE4 subtypes See Hughes *et al.*, *Drug Discovery Today* 2(3) 89-101, 1997 The presence of S_r appears to have a profound effect on the ability of certain inhibitors such as rolipram and RS-25,344 to inhibit the catalytic activity of PDE4 isozymes

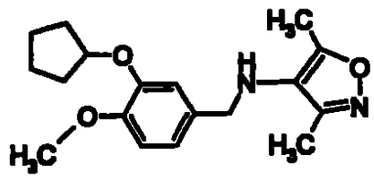
The impact of residues on inhibitor binding is also significant. A single amino acid substitution (alanine for aspartate) in the catalytic region of PDE4B has been shown to be critical for inhibition by rolipram, and this appears to be a class effect because related inhibitors RP-73,401 and Ro-20-1724 also lose potency on the mutant enzyme. However, the role of binding of inhibitors to the S_c or to the S_r, in terms of elevation of cAMP and inhibition of cell responses, is not fully understood at the present time.

RP-73,401, in guinea-pig studies, has been found to be active in (1) the inhibition of antigen-induced lung eosinophilia and eosinophil peroxidase (EPO), Banner, K.H , "The effect of selective phosphodiesterase inhibitors in comparison with other anti-asthma drugs on allergen-induced eosinophilia in guinea-pig airways," *Pulm Pharmacol.* 8 37-42, 1995; (2) antigen-induced bronchoalveolar lavage (BAL) eosinophilia, Raeburn *et al.*, "Anti-inflammatory and bronchodilator properties of RP73401, a novel and selective phosphodiesterase Type IV inhibitor," *Br J Pharmacol.* 113 1423-1431, 1994, (3) antigen-induced airway eosinophilia and platelet activating factor- (PAF)- and ozone-induced airway hyper-responsiveness (AHR), Karlsson *et al.*, "Anti-inflammatory effects of the novel phosphodiesterase IV inhibitor RP73401," *Int. Arch. Allergy Immunol.* 107 425-426, 1995, and (4) IL-5 induced pleural eosinophilia. Development of RP-73,401, piclamilast, has been discontinued Piclamilast may be represented by Formula (0 0.17)



Piclamilast (RP-73,401) (0.0 17)

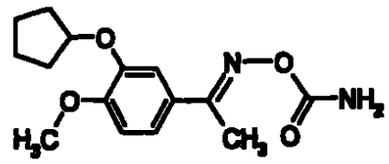
A related series of compounds is represented by RPR-132294 and RPR-132703, which have been demonstrated in rat studies to have activity in the inhibition of antigen-induced bronchospasm, Escott *et al.*, "Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic ratio in rats and dogs," *Br J Pharmacol.* 123(Proc. Suppl) 40P, 1998, and Thuraisingham *et al.*, "Biological activity and side effect profile of RPR-132294 and RPR-132703 – novel PDE4 inhibitors," *XVth EFMC Int. Symp. Med. Chem.*, 1998. The structure of RPR-132294 may be represented by Formula (0.0 18)



RPR-132294

(0.0 18)

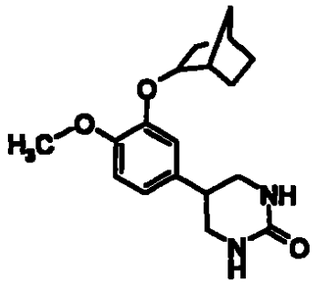
Another compound whose development has been discontinued is WAY-PDA-641, filaminast, which in studies in the dog, has been found to be active in the inhibition of serotonin-induced bronchoconstriction Filaminast may be represented by Formula (0.0 19)



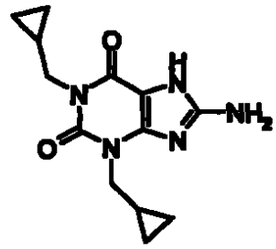
Filaminast (WAY-PDA-641)

(0 0 19)

It has been suggested in the art that PDE4 inhibitors that have a high affinity at the S_r can be correlated with emesis and increased gastric acid secretion RS-23,544, RP-73,401, and CP-80,633 elicit emesis and have a high affinity at the S_r. CDP840 and SB-207,499 have a comparatively low affinity at the S_r, but CDP840 has a significantly higher potency at the S_r than does SB-207,499 CDP840 has been demonstrated to provide significant inhibition of late-phase response in the treatment of asthma without any adverse events of nausea or headache Another PDE4 inhibitor that has been shown to have adverse events of nausea and vomiting is BRL-61,063, also referred to as cipamfylline, which is described further below The development of CDP840 has been discontinued, while CP-80,633, atizoram, has been advanced into clinical studies CP-80,633 and BRL-61,063 may be represented by Formulas (0.0.20) and (0 1 12), respectively

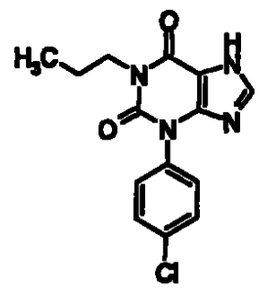


Atizoram (CP-80,633)
(0.0.20)



Cipamfylline (BRL-61,063)
(0 1 12)

Another compound which is in development is LAS-31025, arofylline, which in guinea-pig studies, has been found to be active in the inhibition of antigen-induced bronchoconstriction, Belete, B J , "Characterization of LAS31025 a new selective PDE IV inhibitor for bronchial asthma," *Third Int. Conf On Cyclic Nucleotide Phosphodiesterase. From Genes to Therapies*, Glasgow, UK, 1996, Abstract 73 LAS-31025, arofylline, may be represented by Formula (0 0.21):



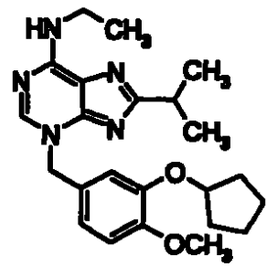
Arofylline (LAS-31025)

(0 0.21)

A number of PDE4 inhibitors have been advanced in development. For example, the effects of V-11294A on LPS-stimulated *ex vivo* TNF release and PHA induced lymphocyte proliferation have been determined in a randomized, double-blind placebo-controlled study which has found that an oral dose of 300 mg is effective in reducing TNF levels and lymphocyte proliferation, Landells *et al.*, "Oral administration of the phosphodiesterase (PDE) 4 inhibitor, V11294A inhibits ex-vivo agonist-induced cell activation," *Eur Resp. J* 12(Suppl. 28) 382s, 1998, and Gale *et al.*, "Pharmacodynamic-pharmacokinetic (PD/PK) profile of the phosphodiesterase (PDE) 4 inhibitor, V11294A, in human volunteers," *Am. J Respir Crit. Care Med.* 159 A811, 1999.

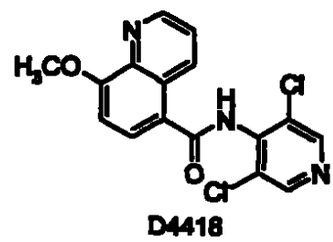
The compound D4418 has been administered to healthy volunteers in a single escalating dose, randomized, placebo-controlled Phase I study; Montana *et al.*, "Activity of D4418, a novel phosphodiesterase 4 (PDE4) inhibitor, effects in cellular and animal models of asthma and early clinical studies," *Am. J Respir Crit. Care Med.* 159 A106, 1999 D4418 is a moderately potent PDE4 inhibitor with an IC_{50} of 200 nM It has good oral absorption; a 200 mg dose provides a plasma C_{max} of 1.4 µg/ml D4418 has been discontinued from development due to its moderate potency, and has been replaced by the preclinical development candidate D4396.

V-11294A and D4418 may be represented by Formulas (0 0.22) and (0.0.23), respectively



V-11294A

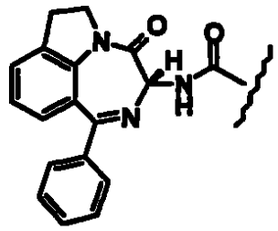
(0.0.22)



D4418

(0 0.23)

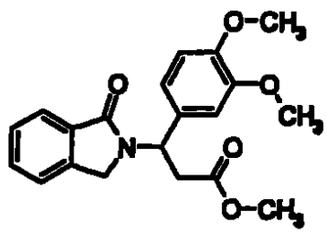
Another compound, CI-1018, has been evaluated in 54 subjects and no adverse events were reported at doses up to 400 mg, Pruniaux *et al.*, "The novel phosphodiesterase inhibitor *CI-1018 inhibits* antigen-induced lung eosinophilia in sensitized brown-norway *rats* - comparison with rolipram," *Inflammation* S-04-6, 1999 CI-1018 has been demonstrated to have good oral bioavailability (57% in the rat) and good oral potency of with an ED_{50} of 5mg/kg in that same species. CI-1018 is a relatively weak PDE4 inhibitor with an IC_{50} of 1 1μM in U937 cells CI-1018 has also been identified as, or associated with as closely related in structure to, PD-168787, which in rat studies has been demonstrated to have activity in the inhibition of antigen-induced eosinophilia, Pascal *et al.*, "Synthesis and structure-activity relationships of 4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]-diazepino[6,7,1-hi] indolines. novel PDE4 inhibitors," *215th ACS*, Dallas, USA, MEDI 50, 1998. Inferred structures for CI-1018 and PD-168787 belong to a diazephone class whose nucleus may be represented by Formula (0.0.24):



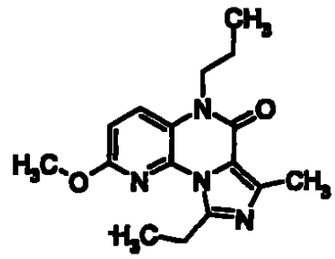
(0.0.24)

The above-mentioned compounds have also been evaluated in animal models which demonstrate their PDE4 inhibition activity For example, V-11294A, in guinea-pig studies, has been found to be active in the inhibition of antigen-induced bronchoconstriction; Cavalla *et al.*, "Activity of V11294A, a novel phosphodiesterase 4 (PDE4) inhibitor, in cellular and animal models of asthma," *Amer J Respir Crit. Care Med*, 155 A660, 1997 D4418, in guinea-pig studies, has been found to be active in the inhibition of antigen-induced early and late phase bronchoconstriction and BAL eosinophilia; Montana, *et al., Ibid* CI-1018, in rat studies, has been found to be active in the inhibition of antigen-induced eosinophilia, Burnouf, *et al.*, "Pharmacology of the novel phosphodiesterase Type 4 inhibitor, CI-1018," *215th ACS Nat. Meeting*, MEDI 008, 1998

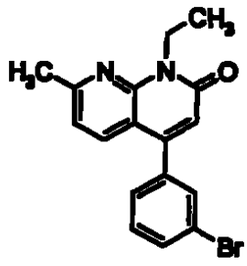
Other compounds which have been advanced in development include CDC-3052, D-22888, YM-58997, and roflumilast, which may be represented by Formulas (0.0.27), (0 0.28), (0.0.29), and (0.0.30), respectively



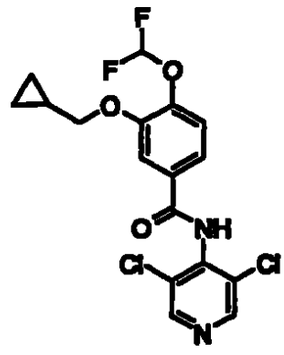
CDC-3052
(0.0.27)



D-22888
(0.0.28)

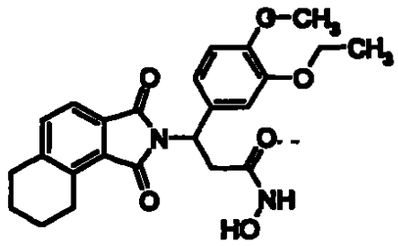


YM-58977
(0.0.29)

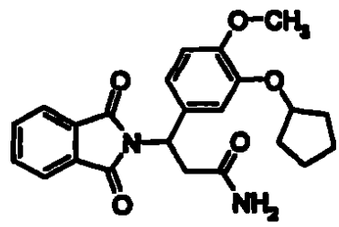


Roflumilast
(0.0.30)

CDC-3052 has been discontinued from development, but has been succeeded by very potent inhibitors of PDE4 such as the compound represented by Formula (0.0.31), and by the anti-inflammatory compound CDC-801 represented by Formula (0.0.32), respectively



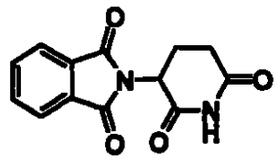
CDC-801
(0.0.31)



(0.0.32)

The compound of Formula (0.0 32) is reported to have IC_{50} values of 42 pM and 130 nM as an inhibitor of PDE4 and TNFproduction, respectively; Muller *et al.*, "N-Phthaloyl beta-aryl-beta-amino derivatives. Potent TNF-alpha and PDE4 inhibitors," *217th American Chemical* Society, Annheim, Germany, MEDI 200, 1999; and Muller et al, "Thalidomide analogs and PDE4 inhibition," Bioorg Med Chem Letts 8 2669-2674, 1998.

CDC-801 is from a series of compounds based on thalidomide and has been developed primarily to improve the TNF-α inhibitory activity of thalidomide for the treatment of autoimmune diseases Thalidomide may be represented by Formula (0 0.33):



Thalidomide

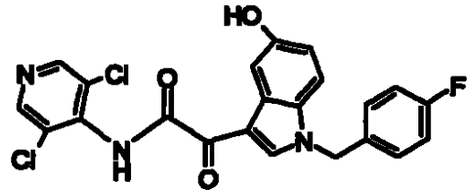
(0.0.33)

CDC-801 has also been studied for the treatment of Crohn's disease, a chronic granulomatous inflammatory disease of unknown etiology commonly involving the terminal ileum, with scarring and thickening of the bowel wall which frequently leads to intestinal obstruction and fistula and abscess formation Crohn's disease has a high rate of recurrence after treatment.

YM-58997 has an IC_{50} value of 1.2 nM against PDE4, Takayama *et al.*, "Synthetic studies on selective Type IV phosphodiesterase (PDE IV) inhibitors," *214th American Chemical Society*, Las Vegas, USA, MEDI 245, 1997 YM-58997 has a 1,8-naphthyridin-2-one structure, as does YM-976.

Roflumilast has been studied for the treatment of both COPD and asthma, and has an IC_{50} value of 3 5 nM in standard *in vitro* guinea-pig models of asthma. The use of roflumilast and a surfactant for the treatment of adult respiratory distress syndrome (ARDS) has also been described

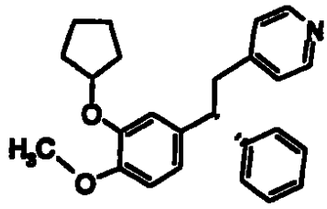
AWD-12,281, which is now designated as lotepredno1, has been shown to be active in a rat model of allergic rhinitis, as described further below in a section which deals with allergic rhinitis and the use of PDE4 inhibitors to treat it. AWD-12,281 may be represented by Formula (0.0.34):



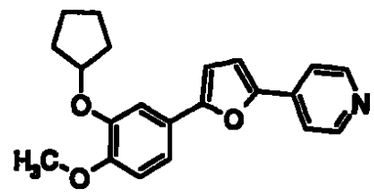
Lotepredno1 (AWD-12,281)

(0.0.34)

Compounds related in structure to CDP840, shown further above as Formula (0 0.9), include L-826,141, which has been reported to have activity in a rat model of bronchitis; Gordon *et al.*, "Anti-inflammatory effects of a PDE4 inhibitor in a rat model of chronic bronchitis," *Am. J Respir Crit. Care Med.* 159 A33, 1999 Another such compound is related in structure to those reported in Perrier *et al*, "Substituted furans as inhibitors of the PDE4 enzyme," *Bioorg. Med. Chem. Letts.* 9 323-328, 1999, and is represented by Formula (0.0.35):

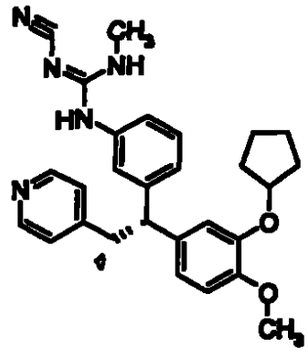


CDP840
(0.0.9)

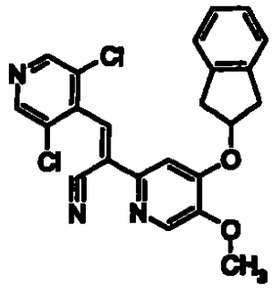


(0 0.35)

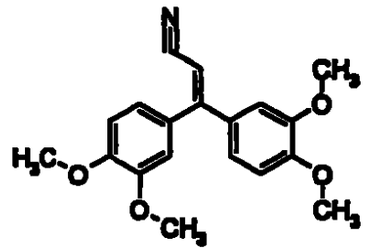
Other compounds which been found to be very potent PDE4 inhibitors are those represented by Formulas (0.0 36), (0 0.37), and (0 0.38).



(0.0.36)

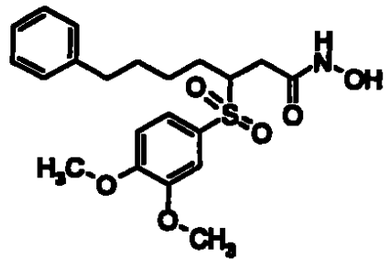


(0 0.37)

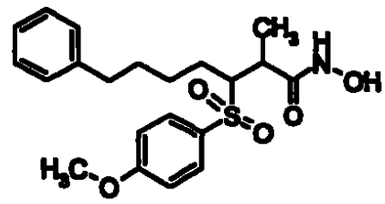


(0.0.38)

Compounds have been created which combine PDE4 and matrix metalloproteinase (MMP) inhibitory activity in a single molecule; Groneberg *et al.*, "Dual inhibition of phosphodiesterase 4 and matrix metalloproteinases by an (arylsulfonyl)hydroxamic acid template," *J Med. Chem.* 42(4) 541-544, 1999 Two examples of such compounds are represented by Formulas (0.0.39) and (0 0.40):



(0.0.39)

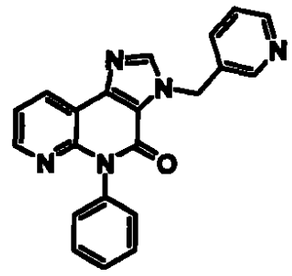


(0.0.40)

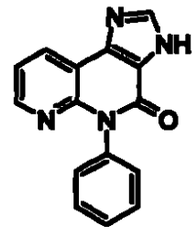
The respective IC_{50} values for the compounds of Formulas (0 1.36) and (0 1.37) using a guinea-pig macrophage PDE4 assay were 1 nM and 30 nM

The compounds identified as KF19514 and KF17625 have been shown in guinea-pig studies to have activity in the inhibition of the following histamine-induced and antigen-induced bronchoconstriction, PAF-induced lung eosinophilia and antigen-induced BAL eosinophilia, acetylcholine (ACh)-induced AHR, PAF-induced BAL eosinophilia and neutrophilia, and AHR, antigen-induced bronchospasm, and anaphylactic

bronchoconstriction, Fujimura *et al.*, "Bronchoprotective effects of KF-19514 and cilostazol in guinea-pigs *in vivo*," *Eur J Pharmacol.* 327 57-63, 1997, Manabe *et al.*, *Ibid.*, Manabe *et al.*, "KF19514, a phosphodiesterase 4 and 1 inhibitor, inhibits PAF-induced lung inflammatory responses by inhaled administration in guinea-pigs," *Int. Arch. Allergy Immunol.* 114 389-399, 1997, Suzuki *et al.*, "New bronchodilators. 3 Imidazo[4,5-c][1,8]naphthyridin-4(5H)-ones," *J Med. Chem.* 35 4866-4874, 1992, Matsuura *et al.*, "Substituted 1,8-naphthyridin-2(1H)-ones as selective phosphodiesterase IV inhibitors," *Biol. Pharm. Bull.* 17(4) 496-503, 1994, and Manabe *et al.*, "Pharmacological properties of a new bronchodilator, KF17625," *Jpn. J Pharmacol.* 58(Suppl. 1) 238P, 1992 KF19514 and KF17625 may be represented by Formulas (0 0.41) and (0.0.42):

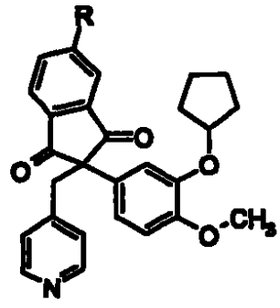


KF19514
(0.0.41)



KF17625
(0.0.42)

The reported potency and lack of emesis in a series of indandiones suggests that the hypothesis that has related side-effects such as emesis to the ratio of affinity for the PDE4 enzyme relative to that for the high affinity rolipram binding site (HARBS) is erroneous Such indandiones may be represented by Formulas (0 0.43) and (0.0.44):

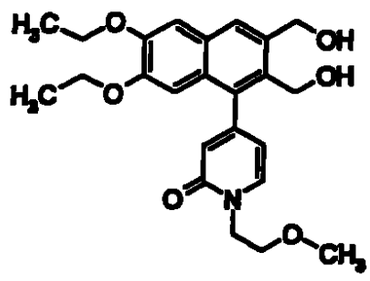


R = benzyloxy (0 0.43)

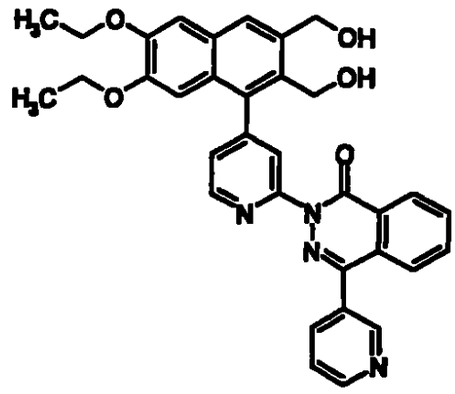
R = [1,4']-piperidinyl-1'-carbonyloxy (0.0.44)

The PDE4 inhibitors that have been created heretofore fall into a significant number of different classes in terms of their chemical structures. Such classes have been as diverse as phenanthridines and naphthyridines One class of PDE4 inhibitors are lignans such as T-440, which has been demonstrated to have activity in the inhibition of the following early phase bronchoconstriction induced by antigen, histamine, LTD4, U-46619, Ach, neurokinin A, and endothelin-1, allergen-induced early phase and late phase bronchoconstriction and BAL eosinophilia; and ozone-induced AHR and airway epithelial injury Optimization of the PDE4

Inhibitory potency of such compounds has led to the discovery of T-2585, one of the most potent PDE4 inhibitors described to date with an IC_{50} value of 0 13 nM against guinea-pig lung PDE4. T-440 and T-2585 may be represented by Formulas (0.0.45) and (0 0.46):

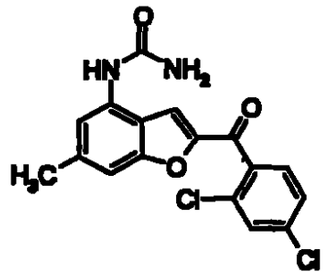


T-440
(0.0.45)



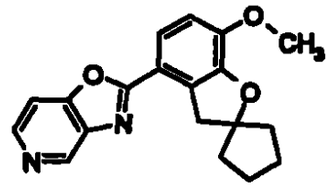
T-2585
(0.0.46)

Another class of PDE4 inhibitors consists of benzofurans and benzothiophenes In particular, furan and chroman rings have been utilized as surrogates for the cyclopentylether of the rolipram pharmacophore. An example of such a compound is one that is apparently related in structure to BAY 19-8004, and which may be represented by Formula (0.0.47)



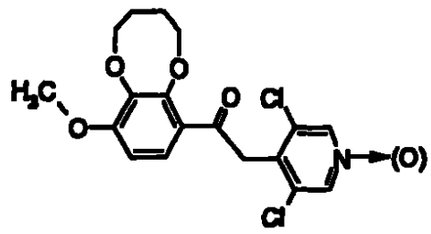
(0.0.47)

Another benzofuran-type compound has been reported to have an IC_{50} value of 2 5 nM, and may be represented by Formula (0.0.48)



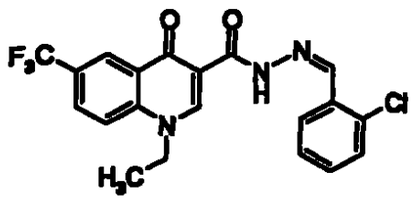
(0.0 48)

A compound with a related structure, which is not, however, a benzofuran, is characterized by a fused dioxdin ring and is reported to produce almost complete inhibition of canine tracheal PDE4 at 100 nM This compound may be represented by Formula (0 0.49)·

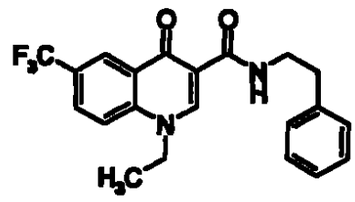


(0.0.49)

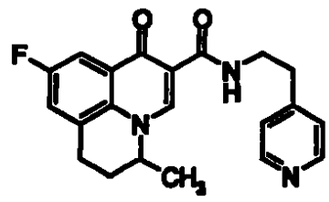
Quinolines and quinolones are a further class of PDE4 inhibitor structures, and they serve as surrogates for the catechol moiety of rolipram This compound and two compounds of similar structure may be represented by Formulas (0.0 50), (0.0.51), and (0.0.52).



(0 0 50)

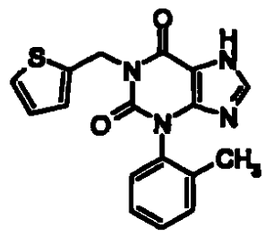


(0 0.51)



(0.0.52)

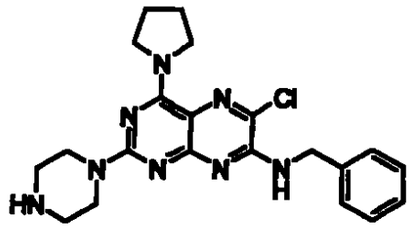
Purines, xanthines, and pteridines represent yet further classes of chemical compounds to which PDE4 inhibitors described heretofore in the art belong. The compound V-11294A described further above and represented by Formula (0.0.22), is a purine. A PDE4 inhibitor which is a xanthine compound, the class of compounds to which theophylline belongs, has been described in the art; Montana *et al.*, "PDE4 Inhibitors, new xanthine analogues," *Bioorg. Med Chem. Letts.* 8 2925-2930, 1998 The xanthine compound may be represented by Formula (0.0 54):



(0.0 54)

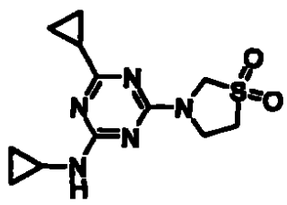
A potent PDE4 inhibitor belonging to the pteridine class of compounds has been demonstrated to have an IC_{50} value of 16 nM against a PDE4 derived from tumor cells and to inhibit the growth of tumor cells at micromolar concentrations; Merz *et al.*, "Synthesis of 7-

Benzylamino-6-chloro-2-piperazino-4-pyrrolidinopteridine and novel derivatives free of positional isomers Potent inhibitors of cAMP-specific phosphodiesterase and of malignant tumor cell growth," *J Med. Chem.* 41(24) 4733-4743, 1998 The pteridine PDE4 inhibitor may be represented by Formula (0.0 55)

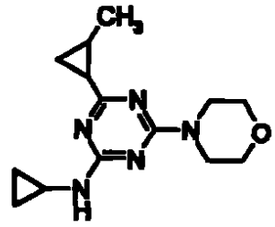


(0.0.55)

Triazines represent a still further class of chemical compounds to which PDE4 inhibitors belong that have been described in the art heretofore Two such triazines have been described which display bronchodilator activity and are potent relaxant agents in a guinea-pig trachea model These compounds, which may be represented by Formulas (0.0.56) and (0.0 57) below, are also moderately potent PDE4 inhibitors with IC_{50} values of 150 and 140 nM, respectively



(0.0.56)

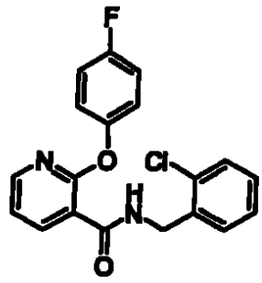


(0 0.57)

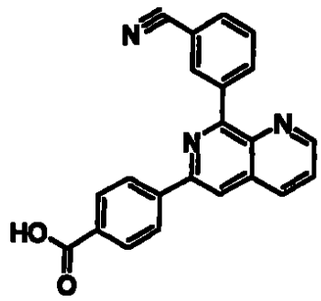
A triazine having a structure assumed to be closely related to that of the compounds of Formulas (0.0 56) and (0 0.57) is UCB-29936, which has been demonstrated to have activity in a murine model of septic shock; Danhaive *et al.*, "UCB29936, a selective phosphodiesterase Type IV inhibitor therapeutic potential in endotoxic shock," *Am. J Respir Crit. Care. Med.* 159 A811, 1999

Efforts have also been made in the art to improve the selectivity of PDE4 inhibitors with respect to the A through D subtypes described further above There are presently four known isoforms (subtypes) of the PDE4 isozyme, encompassing seven splice variants, also described further above. The PDE4D isoform mRNA is expressed in inflammatory cells such as neutrophils and eosinophils, and it has been suggested in the art that D-selective inhibitors of PDE4 will provide good clinical efficacy with reduced side-effects. A nicotinamide derivative displaying selectivity for inhibition of the PDE4D isoform has been described; WO 98/45268; as well as a naphthyridine derivative reported to be a PDE4D selective inhibitor;

WO 98/18796 These compounds may be represented by Formulas (0.0.58) and (0 0 59), respectively

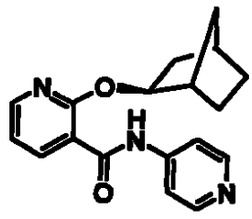


(0.0.58)

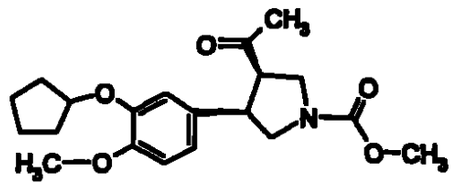


(0.0 59)

Another nicotinamide compound has been described in the art which may be useful in the treatment of CNS diseases such as multiple sclerosis, GB-2327675, and a rolipram derivative has been described in the art which is a PDE4 inhibitor which binds with equal affinity to both the catalytic and the HARB sites on human PDE4B2B; Tian *et al.*, "Dual inhibition of human Type 4 phosphodiesterase isostates by (*R,R*)-(+/-)-methyl-3-acetyl-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-methyl-1-pyrrolidine carboxylate," *Biochemistry* 37(19) 6894-6904, 1998 The nicotinamide derivative and the rolipram derivative may be represented by Formulas (0.0 60) and (0 0 61), respectively



(0.0 60)

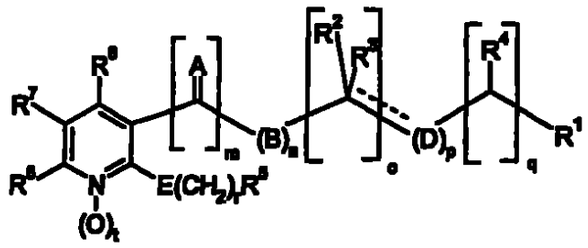


(0.0 61)

Further background information concerning selective PDE4 isozymes may be found in publications available in the art, *e g.*, Norman, "PDE4 Inhibitors 1999," *Exp. Opin. Ther Patents* 9(8) 1101-1118, 1999 (Ashley Publications Ltd); and Dyke and Montana, "The therapeutic potential of PDE4 inhibitors," *Exp Opin. Invest. Drugs* 8(9) 1301-1325, 1999 (Ashley Publications Ltd)

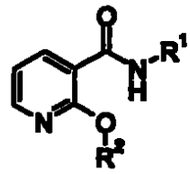
3.0 DESCRIPTION OF THE STATE OF THE ART

WO 98/45268 (Merfat *et al.*), published October 15, 1998, discloses nicotinamide derivatives having activity as selective inhibitors of PDE4D isozyme These selective inhibitors are represented by Formula (0 1 1)



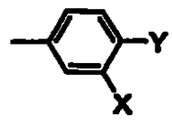
(0 1 1)

US 4,861,891 (Saccomano *et al*), issued August 29, 1989, discloses nicotinamide compounds which function as calcium independent c-AMP phosphodiesterase inhibitors useful as antidepressants, of Formula (0 1.2):



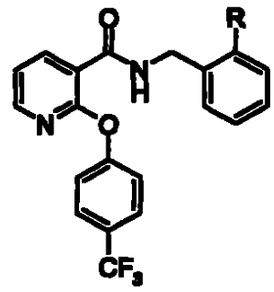
(0 1.2)

The nicotinamide nucleus of a typical compound disclosed in this patent is bonded directly to the R^1 group, which is defined as 1-piperidyl, 1-(3-indolyl)ethyl, C_1-C_4 alkyl, phenyl, 1-(1-phenylethyl), or benzyl optionally mono-substituted by methyl, methoxy, chloro or fluoro The R^2 substituent is bicyclo[2.2.1]hept-2-yl or



where Y is H, F or Cl; and X is H, F, Cl, OCH_3, CF_3, CN, COOH, -C(=O)(C_1-C_4) alkoxy, $NH(CH_3)C(=O)$- (methylcarbamoyl) or $N(CH_3)_2C(=O)$- (dimethylcarbamoyl).

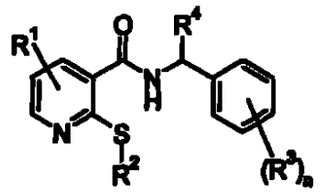
US 4,692,185 (Michaely *et al.*) discloses herbicides such as those of Formula (0 1.3):



(0 1.3)

where R is (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, or halo

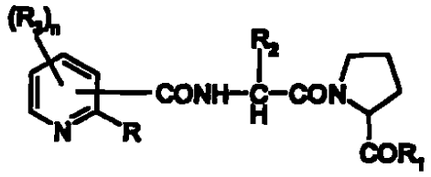
EP 550 900 (Jeschke *et al.*) discloses herbicides and plant nematicides of Formula (0 1.4).



(0 1.4)

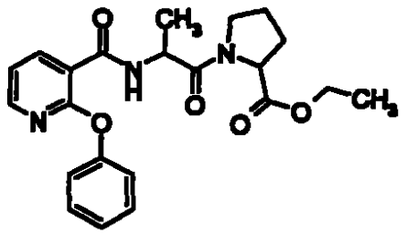
where n is 0-3, R^1 is selected from numerous groups, but is usually H, 6-CH_3, or 5-Cl, R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl, R1 and R2 is halo, CN, NO_2, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfonyl, haloalkylsulfonyl, aryl, aryloxy, or arylthio; and R^4 is alkyl

EP 500 989 (Mollner *et al.*) discloses ACE inhibitors of Formula (0 1.5):



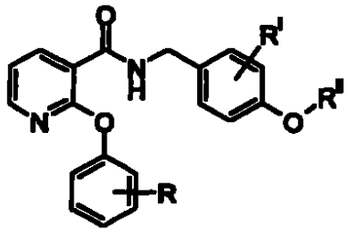
(0.1.5)

where n is 0-3, R is OH, SH, COOH, NH_2, halo, OR_4, SR_4, $COOR_4$, NHR_4 or $N(R_4)_2$, where R_4 is lower alkyl, optionally substituted aryl, or acyl, R_1 is OH, lower alkoxy, optionally substituted aryl lower alkoxy, aryloxy, or disubstituted amino, R_2 is lower alkyl or amino lower alkyl, and R1 and R2 is halo, NO_2, lower alkyl, halo lower alkyl, aryl lower alkyl, or aryl Specific embodiments disclosed include compounds such as that of Formula (0 1.6):



(0 1 6)

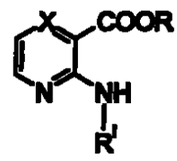
FR 2 140 772 (Aries) discloses compounds asserted to have utility as analgesics, tranquilizers, antipyretics, anti-inflammatories, and antirheumatics, of Formula (0 1 7):



(0 1 7)

where R is 1 or 2 substituents chosen from lower alkyl, trihalomethyl, alkoxy, and halo; R' is H or alkyl; and R" is hydrogen or alkyl

JP 07 304775 (Otsuka *et al.*) discloses naphthyridine and pyridopyrazine derivatives which have anti-inflammatory, immunomodulating, analgesic, antipyretic, antiallergic, and antidepressive action Also disclosed are intermediates of Formula (0 1.8).

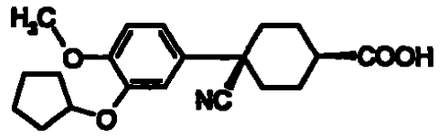


(0 1.8)

where X may be CH, and R and R' are each lower alkyl

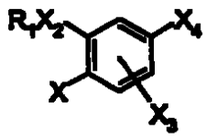
With regard to the disclosures of the above-identified patents and published patent applications, it will be appreciated that only the disclosure of WO 98/45268 (Marfat *et al.*) concerns the inhibition of PDE4 isozymes. The state of the art also contains information regarding compounds wholly dissimilar in chemical structure to those of Formula (1.0.0) of the present invention, but which, on the other hand, possess biological activity similar to that of the compounds of Formula (1.0.0). Representative patents and published patent applications disclosing said information are illustrated further below

US 5,552,438, US 5,602,157, and US 5,814,540 (all to Christensen), which all share the same April 2, 1992 priority date, relate to a therapeutic agent identified as ARIFLO®, which is a compound of Formula (0 1 9) and named as indicated below



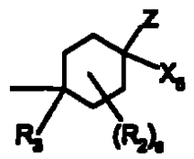
ARIFLO®
cis-[4-cyano-4-(3-cyclopentyl-oxy-4-methoxyphenyl)cyclo-hexane-1-carboxylic acid (0 1 9)

The compound of Formula (0 1 9) falls within the scope of US 5,552,438 which discloses a genus of compounds of Formula (0 1 10):



(0 1 10)

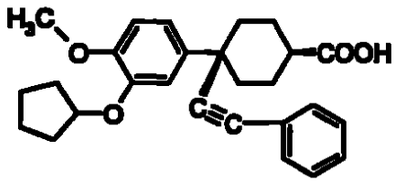
where R_1 = -$(CR_4R_5)_rR_6$ where r = 0 and R_6 = C_{3-6} cycloalkyl, X = YR_2 where Y = O and R_2 = $-CH_3$, X_2 = O; X_3 = H, and X_4 = a moiety of partial Formula (0 1 10 1)



(0 1 10 1)

where X_5 = H; s = 0, R_1 and R_2 = CN, and Z = C(O)OR_{14} where R_{14} = H The disclosures of US 5,602,157 and US 5,614,540 differ from that of US 5,552,438 and each other as to the definition of the R_3 group, which in the case of the ARIFLO® compound, is CN A preferred salt form of the ARIFLO® compound is disclosed to be the tris(hydroxymethyl)ammonium methane salt.

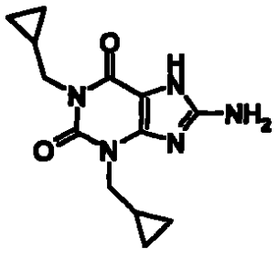
US 5,863,926 (Christensen *et al.*) discloses analogs of the ARIFLO® compound, *e.g.*, that of Formula (0 1 11):



(0 1 11)

WO 99/18793 (Webb *et al.*) discloses a process of making the ARIFLO® and related compounds. WO 95/00139 (Barnette *et al.*) claims a compound which has an IC_{50} ratio of about 0 1 or greater as regards the IC_{50} for the PDE IV catalytic form which binds rolipram with a high affinity, divided by the IC_{50} for the form which binds rolipram with a low affinity; but in a dependent claim restricts the scope thereof to a compound which was not known to be a PDE4 inhibitor prior to June 21, 1993

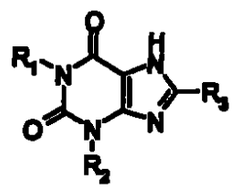
WO 99/20625 (Eggleston) discloses crystalline polymorphic forms of cipamfylline for treatment of PDE_4 and TNF mediated diseases, of Formula (0 1 12):



Cipamfylline

(0 1 12)

WO 99/20280 (Griswold *et al.*) discloses a method of treating pruritis by administering an effective amount of a PDE4 inhibitor, *e g* , a compound of Formula (0 1 13)·



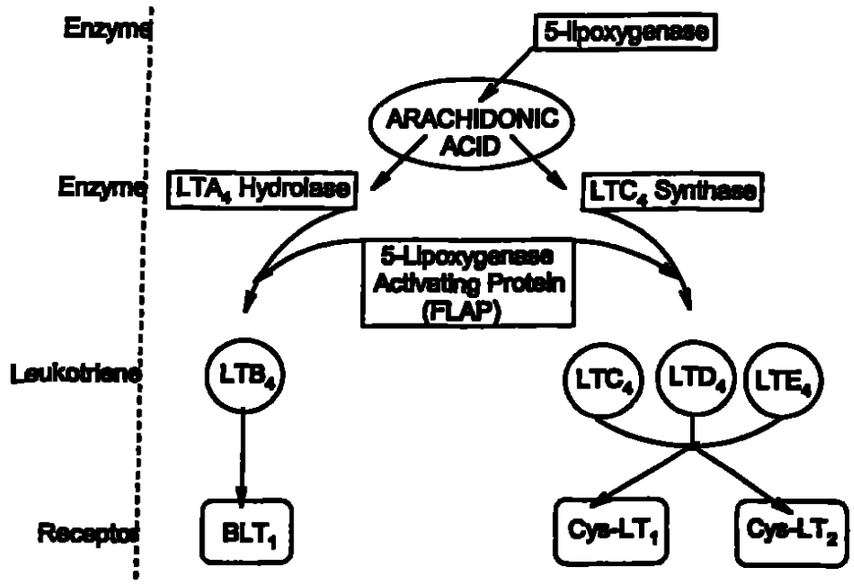
(0 1 13)

US 5,922,557 (Pon) discloses a CHO-K1 cell line which stably expresses high levels of a full length low-Km cAMP specific PDE4A enzyme, which has, in turn, been used to examine potent PDE4 enzyme inhibitors and compare the rank order of their potencies in elevating cAMP in a whole-cell preparation with their ability to inhibit phosphodiesterase activity in a broken-cell preparation. It is further said to be found that the soluble enzyme inhibition assay described in the prior art does not reflect behavior of the inhibitors acting *in vivo*. An improved soluble enzyme whole-cell assay is then disclosed which is said to reflect the behavior of inhibitors acting *in vivo*. It is further disclosed that there exist at least four distinct PDE4 isoforms or subtypes, and that each subtype has been shown to give rise to a number of splice variants, which in themselves can exhibit different cellular localization and affinities for inhibitors.

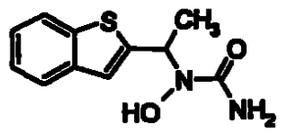
With regard to the disclosures of the above-identified patents and published patent applications, it will be appreciated that the compounds involved possess the same biological activity as the compounds of Formula (1.0.0). At the same time, however, the artisan will observe that the chemical structures of said compounds disclosed in the prior art are not only diverse from each other but dissimilar to that of the novel compounds of the present invention as well The state of the art contains still further information regarding compounds which are dissimilar in chemical structure to those of Formula (1.0.0), and which, moreover, do not possess PDE4 inhibitory activity similar to that of the compounds of Formula (1 0.0). Such compounds disclosed in the prior art do, nevertheless, often have therapeutic utility similar to that possessed by the compounds of Formula (1 0 0), *i.e.*, in the treatment of inflammatory, respiratory and allergic diseases and conditions In particular this is applicable to certain inhibitors of enzymes and antagonists of receptors in the so-called leukotriene pathway This is especially the case with regard to the leukotrienes LTB_4 and LTD_4. Accordingly, representative patents and published patent applications disclosing further information of this type are described below

Arachidonic acid is metabolized by cyclooxygenase-1 and by 5-lipoxygenase The 5-lipoxygenase pathway leads to the production of leukotrienes (LTs) which contribute to the inflammatory response through their effect on neutrophil aggregation, degranulation and chemotaxis, vascular permeability; smooth muscle contractility; and on lymphocytes. The

cysteinyl leukotrienes, LTC_4, LTD_4, and LTE_4, play an important role in the pathogenesis of asthma The components of the leukotriene pathway which afford targets for therapeutic intervention are illustrated in the following diagram



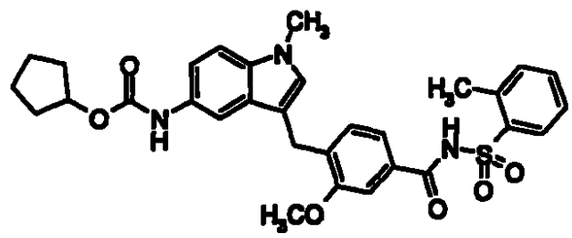
Accordingly, agents which are able to intervene in any of the steps of the 5-lipoxygenase pathway afford an opportunity for therapeutic treatment. An example of one such agent is the 5-lipoxygenase inhibitor, zileuton, a therapeutic agent identified as ZYFLO® which may be represented by Formula (0 1 14):



ZYFLO®

Zileuton (0 1 14)

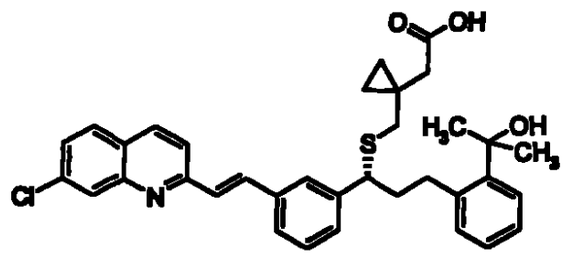
Another such agent is the LTD_4 receptor antagonist zafirlukast, a therapeutic agent identified as ACCOLATE® which may be represented by Formula (0 1 15):



ACCOLATE®

Zafirlukast (0 1 15)

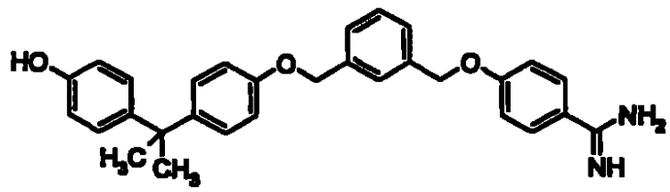
A further such LTD_4 receptor antagonist is montelukast, a therapeutic agent identified as SINGULAIR® which may be represented by Formula (0 1 16):



SINGULAIR®

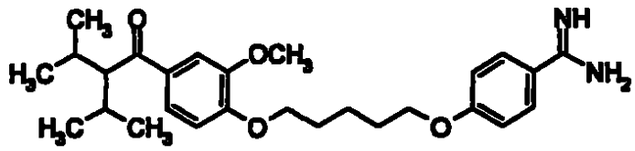
Montelukast (0 1 16)

Another type of the above-mentioned therapeutic targets is the LTB_4 receptor, and an example of an antagonist for said receptor is BIIL-260, a therapeutic agent which may be represented by Formula (0 1 17):



BIIL-260 (0 1 17)

Another example of a therapeutic agent which is an LTB_4 receptor antagonist is CGS-25019c which may be represented by Formula (0 1 18)



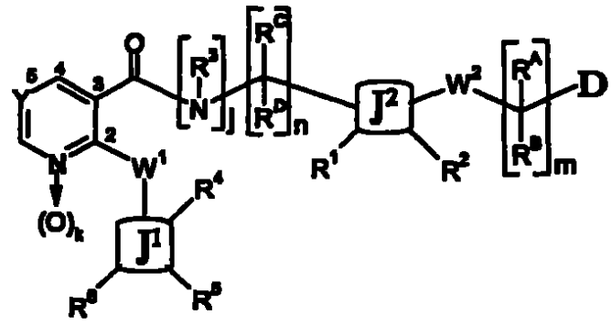
CGS-25019c (0 1 18)

Nothing in the above-described state of the art discloses or would suggest to the artisan the novel compounds of the present invention or their PDE4 inhibitory activity and the resulting significant improvement in therapeutic utility and therapeutic index in the treatment of inflammatory, respiratory and allergic diseases and conditions

4.0 SUMMARY OF THE INVENTION

The present invention is concerned with novel compounds which have biological activity as inhibitors of the phosphodiesterase so-called "Type IV" isoenzyme ("PDE4 isozyme") Embodiments of the novel compounds of the present invention are active as non-selective inhibitors of the PDE4 isozyme Other embodiments of said novel compounds have PDE4 isozyme substrate specificity, especially for the D subtype Said novel compounds having non-selective or D-selective PDE4 inhibitor activity are generally useful in the therapeutic treatment of various inflammatory, allergic, and respiratory diseases and conditions, and they afford in particular a significant improvement in the therapeutic treatment of obstructive respiratory diseases, especially asthma and chronic obstructive pulmonary disease (COPD).

The present invention relates to a compound of Formula (1.0 0):



(1.0 0)

— wherein —

-j Is 0 or 1, provided that when j is 0, n must be 2,

-k Is 0 or 1

-m Is 1, 2, or 3,

-n Is 1 or 2,

-W^1 and W^2 are independently —O—; —S(=O)$_t$— , where t is 0, 1, or 2, or -N(R^3)– where R^3 has the same meaning as defined below;

-Y is =C(R^1_a)—, where R^1_a has the same meaning as defined below; or -[N⇒(O)$_k$]— where k is 0 or 1,

— where —

—R^1_a is a member selected from the group consisting of –H, –F, –Cl, –CN, –NO_2, –(C_1-C_4) alkyl; –(C_2-C_4) alkynyl, fluorinated-(C_1-C_2) alkyl, fluorinated-(C_1-C_2) alkoxy; -OR^{16}; and –C(=O)$NR^{22}_aR^{22}_b$,

— where —

—R^{22}_a and R^{22}_b are each independently –H; –CH_3, –CH_2CH_3, –$CH_2CH_2CH_3$, -$CH_2(CH_3)_2$, –$CH_2CH_2CH_2CH_3$, –$CH(CH_3)CH_2CH_3$, –$CH_2CH(CH_3)_2$, –$C(CH_3)_3$, cyclopropyl; cyclobutyl, or cyclopentyl,

-R^A and R^B are each a member independently selected from the group consisting of –H; –F, –CF_3, –(C_1-C_4) alkyl, –(C_3-C_7) cycloalkyl, phenyl, and benzyl, wherein said cycloalkyl, phenyl, and benzyl moieties are each independently substituted with 0 to 3 substituents R^{10};

— where —

—R^{10} is a member selected from the group consisting of phenyl, pyridyl, –F; -Cl, -CF_3, oxo (=O); –OR^{16}; –NO_2, –CN, –C(=O)OR^{16}; -O-C(=O)R^{16}; –C(=O)$NR^{16}R^{17}$, -O-C(=O)$NR^{16}R^{17}$, –$NR^{16}R^{17}$, –NR^{16}C(=O)R^{17}, -NR^{16}C(=O)OR^{17}, –NR^{16}S(=O)$_2R^{17}$, and -S(=O)$_2NR^{16}R^{17}$, where said phenyl or pyridyl is substituted by 0 to 3 R^{11},

— where —

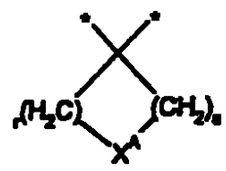
—R^{11} is –F; –Cl; –CF_3, –CN; –NO_2, –OH; –(C_1-C_3) alkoxy; –(C_1-C_3) alkyl, or -$NR^{16}R^{17}$,

— and —

—R^{16} and R^{17} are each a member independently selected from the group consisting of –H, –(C_1-C_4) alkyl, –(C_2-C_4) alkenyl, –(C_3-C_6) cycloalkyl, phenyl, benzyl, and pyridyl, wherein said alkyl, alkenyl, cycloalkyl, phenyl, benzyl, or pyridyl is substituted by 0 to 3 substituents selected from the group consisting of –F, –Cl, –CF_3, –CN, and –(C_1-C_3) alkyl,

— or —

-R^A and R^B are taken together, but only in the case where m is 1, to form a spiro moiety of Formula (1.2.0).



(1.2.0)

— where —

–r and s are independently 0 to 4 provided that the sum of r + s is at least 1 but not greater than 5,

— and —

–X^A is selected from $–CH_2–$, $–CH(R^{11})–$, or $C(R^{11})_2–$, where each R^{11} is selected independently of the other and each has the same meaning as defined above; $–NR^{15}–$, where R^{15} has the same meaning as defined below; –O–; and $–S(=O)_t–$, where t is 0, 1, or 2;

— and —

said spiro moiety of partial Formula (1.2.0) is substituted as to any one or more carbon atoms thereof, other than that defining X^A, by 0 to 3 substituents R^{14}, where R^{14} has the same meaning as defined below; as to a nitrogen atom thereof by 0 or 1 substituent R^{15}, where R^{15} has the same meaning as defined below; and as to a sulfur atom thereof by 0 or 2 oxygen atoms;

-R^C and R^D have the same meaning as defined above for R^A and R^B except that one of them must be –H, and they are selected independently of each other and of R^A and R^B;

-R^1 and R^2 may individually or together appear on any ring or rings comprising a meaning of the moiety J^2 as defined below; and R^1 and R^2 are each a member independently selected from the group consisting of –H, –F, –Cl; –CN, $–NO_2$, $–(C_1–C_4)$ alkyl, $–(C_2–C_4)$ alkynyl, fluorinated $–(C_1–C_3)$ alkyl, $–OR^{16}$; and $-C(=O)NR^{22}{}_aR^{22}{}_b$, where R^{16}, $R^{22}{}_a$, and $R^{22}{}_b$ have the same meanings as defined above,

-R^3 is –H, $–(C_1–C_3)$ alkyl, phenyl, benzyl, or $–OR^{16}$, where R^{16} has the same meaning as defined above;

$-R^4$, R^5 and R^6 may individually or together appear on any ring or rings comprising a meaning of the moiety J^1 as defined below; and R^4, R^5 and R^6 are each a member independently selected from the group consisting of

— the following: —

-(a) –H, –F, –Cl, -(C_2-C_4) alkynyl; $-R^{16}$; $-OR^{16}$; $-S(=O)_pR^{16}$; $-C(=O)R^{16}$; $-C(=O)OR^{16}$; $-OC(=O)R^{16}$; –CN, $-NO_2$, $-C(=O)NR^{16}R^{17}$, $-OC(=O)NR^{16}R^{17}$, $-NR^{22}_sC(=O)NR^{16}R^{17}$, $-NR^{22}_sC(=NR^{12})NR^{16}R^{17}$, $-NR^{22}_sC(=NCN)NR^{16}R^{17}$, $-NR^{22}_sC(=N-NO_2)NR^{16}R^{17}$, $-C(=NR^{22}_s)NR^{16}R^{17}$, $-CH_2C(=NR^{22}_s)NR^{16}R^{17}$, $-OC(=NR^{22}_s)NR^{16}R^{17}$, $-OC(=N-NO_2)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-CH_2NR^{16}R^{17}$, $-NR^{22}_sC(=O)R^{16}$; $-NR^{22}_sC(=O)OR^{16}$; $=NOR^{16}$; $-NR^{22}_sS(=O)_pR^{17}$ $-S(=O)_pNR^{16}R^{17}$, and $-CH_2C(=NR^{22}_s)NR^{16}R^{17}$,

— where —

–p is 0, 1, or 2, and R^{22}_s, R^{16}, and R^{17} have the same meanings as defined above,

-(b) -(C_1-C_4) alkyl, and –(C_1-C_4) alkoxy in the case where one or more of R^4, R^5, or R^6 has the meaning of $-OR^{16}$ under *(a)* above and R^{16} is defined as -(C_1-C_4) alkyl, wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents –F or –Cl; or 0 or 1 substituent (C_1-C_2) alkoxycarbonyl–; (C_1-C_2) alkylcarbonyl–; or (C_1-C_2) alkylcarbonyloxy–;

— and —

-(c) an aryl or heterocyclyl moiety selected from the group consisting of phenyl; benzyl, furanyl, tetrahydrofuranyl, oxetanyl; thienyl, tetrahydrothienyl, pyrrolyl, pyrrolidinyl, oxazolyl, oxazolidinyl, isoxazolyl; isoxazolidinyl; thiazolyl, thiazolidinyl; isothiazolyl; isothiazolidinyl; pyrazolyl, pyrazolidinyl, oxadiazolyl, thiadiazolyl, imidazolyl, imidazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, piperazinyl, triazolyl, triazinyl, tetrazolyl, pyranyl, azetidinyl, morpholinyl, parathiazinyl, indolyl, indolinyl; benzo[*b*]furanyl; 2,3-dihydrobenzofuranyl; 2-*H*-chromenyl, chromanyl, benzothienyl, 1-*H*-indazolyl; benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, and purinyl, wherein said aryl and heterocyclyl moieties are each independently substituted with 0 to 2 substituents R^{14}

— where —

$-R^{14}$ is a member selected from the group consisting of –(C_1-C_4) alkyl; -(C_3-C_7) cycloalkyl, phenyl, benzyl, pyridyl, and quinolinyl, where said alkyl, cycloalkyl, phenyl, benzyl, pyridyl, or quinolinyl is substituted by 0, 1, or 2 substituents –F, –Cl, $-CH_3$,

$-OR^{16}$, $-NO_2$, –CN, or $-NR^{16}R^{17}$, and said R^{14} group further consists of –F, -Cl; $-CF_3$, oxo (=O); $-OR^{16}$; $-NO_2$, –CN, $-C(=O)OR^{16}$; $-O-C(=O)R^{16}$, $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$, or $-S(=O)_2NR^{16}R^{17}$, where R^{16} and R^{17} have the same meanings as defined above;

— and further where —

—R^{15} is a member independently selected from the group consisting of –H, $-NR^{16}R^{17}$, $-C(=O)R^{16}$; $-OR^{16}$; $-(C_1-C_4)$ alkyl–OR^{16}; $-C(=O)OR^{16}$; $-(C_1-C_2)$ alkyl-$C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$, $-(C_1-C_4)$ alkyl, $-(C_2-C_4)$ alkenyl, $-(CH_2)_u-(C_3-C_7)$ cycloalkyl where u is 0, 1 or 2, phenyl, benzyl, pyridyl, and quinolinyl, wherein said alkyl, alkenyl, alkoxy, cycloalkyl, phenyl, benzyl, pyridyl or quinolinyl is substituted with 0 to 3 substituents R^{12}; where R^{16} and R^{17} have the same meanings as defined above; and

— where —

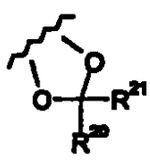
——R^{12} is a member independently selected from the group consisting of –F, –Cl; $-CO_2R^{18}$; $-OR^{18}$; –CN, $-C(=O)NR^{18}R^{19}$, $-NR^{18}R^{19}$, $-NR^{18}C(=O)R^{19}$, $-NR^{18}C(=O)OR^{19}$; $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, where p is 1 or 2, $-(C_1-C_4)$ alkyl; and $-(C_1-C_4)$ alkoxy in the case where R^{12} has the meaning of $-OR^{16}$ above and R^{16} is defined as $-(C_1-C_4)$ alkyl, wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from –F, –Cl, $-(C_1-C_2)$ alkoxycarbonyl, $-(C_1-C_2)$ alkylcarbonyl, and $-(C_1-C_2)$ alkylcarbonyloxy; where R^{18} has the same meaning as defined above; and

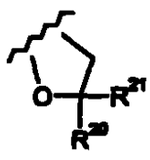
— where —

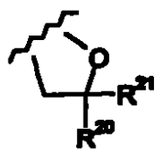
——R^{18} and R^{19} are independently selected from the group consisting of –H, $-(C_1-C_4)$ alkyl, and phenyl, where said alkyl or phenyl is substituted by 0-3 of –F; or –Cl;

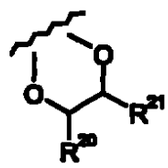
— or in the case where J^1 is phenyl —

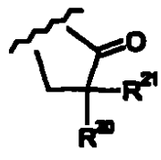
-(d) R^5 and R^6 are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3 1) through (1.3 15)

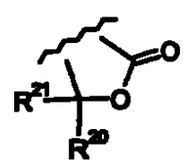

(1 3.1)

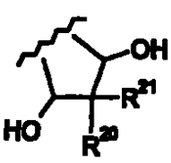

(1 3.2)

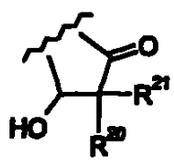

(1 3.3)

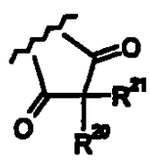

(1.3.4)

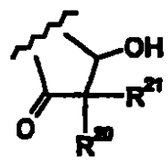

(1.3 5)

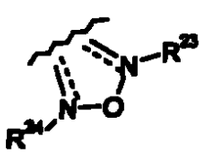

(1.3 6)

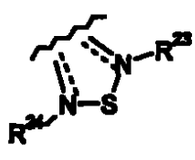

(1.3 7)

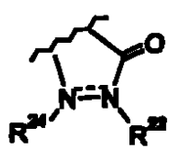

(1 3.8)

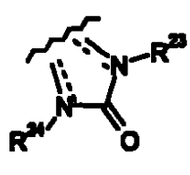

(1 3.9)

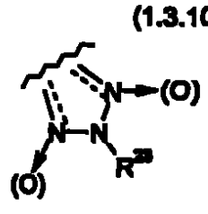

(1.3.10)


(1.3 11)


(1.3.12)


(1.3.13)


(1.3 14)


(1.3 15)

— wherein —

$-R^{20}$ and R^{21} are each a member independently selected from the group consisting of –H; –F, –Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_3$, and $-OCF_3$,

$-R^{23}$ and R^{24} are each independently –H, $-CH_3$, $-OCH_3$, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, or absent, in which case the dashed line ---- represents a double bond,

$-J^1$ is a moiety comprising a saturated or unsaturated carbon ring system that is a 3- to 7-membered monocyclic, or that is a 7- to 12-membered, fused polycyclic; provided that J^1 is not a discontinuous or restricted biaryl moiety; and wherein optionally one carbon atom of said carbon ring system may be replaced by a heteroatom selected from N, O, and S, where optionally a second carbon atom thereof, and further optionally a third carbon atom thereof may be replaced by N,

— wherein —

said moiety defining J^1 is substituted on any ring or rings thereof by R^4, R^5 and R^6, which have the same meaning as defined above,

$-J^2$ is a moiety comprising a saturated or unsaturated carbon ring system that is a 3- to 7-membered monocyclic, or that is a 7- to 12-membered, fused polycyclic; provided that J^2 is not a discontinuous or restricted biaryl moiety; and wherein optionally one carbon atom of said carbon ring system may be replaced by a heteroatom selected from N, O, and S, where optionally a second carbon atom thereof, and further optionally a third carbon atom thereof may be replaced by N,

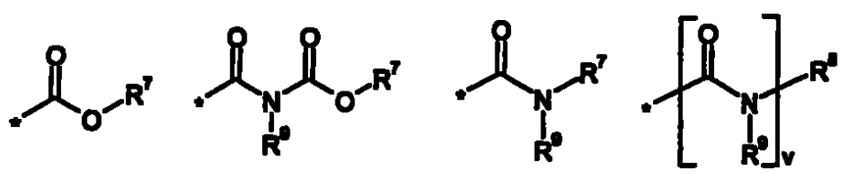
— wherein —

said moiety defining J^2 is substituted on any ring or rings thereof by R^1 and R^2, which have the same meaning as defined above;

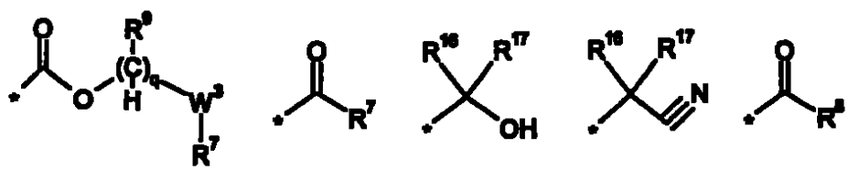
-D is a member independently selected from the group consisting of

— the following —

-(a) the group consisting of partial Formulas (1 1 1) through (1 1.9):



(1 1 1) (1 1.2) (1 1.3) (1 1.4)



(1 1.5) (1 1 6) (1 1 7) (1 1.8) (1 1.9)

— wherein —

—"*" Indicates the point of attachment of each partial Formula (1 1 1) through (1 1.9) to the remaining portion of Formula (1.0.0);

—q is 1, 2, or 3, provided that where q is 2 or 3, R^9 has the meaning of –H in at least one instance, or two instances, respectively;

—v 0 or 1,

$-W^3$ is —O—, —N(R^9)—, where R^9 has the same meaning as defined below; or —OC(=O)—;

$-R^7$ is a member independently selected from the group consisting of

— the following —

—(1) –H,

—(2) –(C_1-C_8) alkyl, –(C_2-C_8) alkenyl, or –(C_2-C_8) alkynyl, where said alkyl, alkenyl or alkynyl is substituted by 0 to 3 substituents R^{10}, where R^{10} has the same meaning as defined above;

—(3) $-(CH_2)_u-(C_3-C_7)$ cycloalkyl where u is 0, 1 or 2; and further where said (C_3-C_7) cycloalkyl is substituted by 0 to 3 substituents R^{10} where R^{10} has the same meaning as defined above,

— and —

—(4) phenyl or benzyl, where said phenyl or benzyl is independently substituted by 0 to 3 substituents R^{10} where R^{10} has the same meaning as defined above;

$-R^8$ is a member independently selected from the group consisting of

— the following —

—(1) phenyl, tetrazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-3-on-5-yl; 1,2,3-triazol-5-yl, imidazol-2-yl; imidazol-4-yl, imidazolidin-2-on-4-yl, 1,3,4-oxadiazolyl, 1,3,4-oxadiazol-2-on-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-on-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-on-5-yl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl; morpholinyl, perathiazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, succinimidyl, glutarimidyl, pyrrolidonyl, 2-piperidonyl, 2-pyridonyl, 4-pyridonyl, pyridazin-3-onyl, pyridyl, pyrimidinyl; pyrazinyl; pyridazinyl,

— and —

—(2) indolyl, indolinyl, isoindolinyl, *benzo[b]*furanyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, 2*H*-1-benzopyranyl, 2-*H*-chromenyl; chromanyl; benzothienyl; 1*H*-indazolyl; benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl, benzotriazinyl, phthalazinyl, 1,8-naphthyridinyl, quinolinyl, isoquinolinyl, quinazolinyl; quinoxalinyl, pyrazolo[3,4-*d*]pyrimidinyl, pyrimido[4,5-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridinyl; pyridopyridinyl; pteridinyl, and 1*H*-purinyl,

— where —

any moiety recited in *(1)* or *(2)* above is optionally substituted with respect to *(I)* any one or more carbon atoms thereof optionally by a substituent R^{14} where R^{14} has the same meaning as defined above, *(II)* any one or more nitrogen atoms thereof that is not a point of attachment of said moiety, optionally by a substituent R^{18} where R^{18} has the same meaning as defined above, and all tautomer forms thereof; and *(III)* any sulfur atom thereof that is not a point of attachment of said moiety, by 0, 1, or 2 oxygen atoms;

$-R^8$ is a member selected from the group consisting of —H; $-(C_1-C_4)$ alkyl, $-(C_3-C_7)$ cycloalkyl, phenyl, benzyl, pyridyl, $-C(=O)OR^{18}$; $-C(=O)R^{18}$; $-OR^{18}$; $-(C_1-C_2)$ alkyl–OR^{18}; and $-(C_1-C_2)$ alkyl–$C(=O)OR^{18}$; where R^{18} has the same meaning as defined above,

— and D is further selected from —

-(b) a moiety comprising a member selected from the group consisting of -O-P(=O)(OH)$_2$ (phosphoric); –PH(=O)OH (phosphinic); -P(=O)(OH)$_2$ (phosphonic); -[P(=O)(OH)–O(C_1-C_4) alkyl] (alkylphosphono); -P(=O)(OH)-O(C_1-C_4) alkyl) (alkylphosphinyl); –P(=O)(OH)NH_2 (phosphoramido); -P(=O)(OH)NH(C_1-C_4) alkyl and -P(=O)(OH)NHR^{28} (substituted phosphoramido); -O-S(=O)$_2$OH (sulfuric); –S(=O)$_2$OH (sulfonic), –S(=O)$_2$$NHR^{28}$ or -NHS(=O)$_2$$R^{28}$ (sulfonamido) where R^{28} is –CH_3, –CF_3, or *o*-toluyl, and acylsulfonamido selected from the group consisting of -C(=O)NHS(=O)$_2$$R^{28}$; -C(=O)NHS(=O)$_2$$NH_2$, -C(=O)NHS(=O)$_2$($C_1$-$C_4$) alkyl, -C(=O)NHS(=O)$_2$NH($C_1$-$C_4$) alkyl, -C(=O)NHS(=O)$_2$N[($C_1$-$C_4$) alkyl]$_2$, -S(=O)$_2$NHC(=O)($C_1$-$C_4$) alkyl, –S(=O)$_2$NHC(=O)$NH_2$, -S(=O)$_2$NHC(=O)NH($C_1$-$C_4$) alkyl, -S(=O)$_2$NHC(=O)N[($C_1$-$C_4$) alkyl]$_2$, –S(=O)$_2$NHC(=O)$R^{28}$; -S(=O)$_2$NHCN, -S(=O)$_2$NHC(=S)$NH_2$, –S(=O)$_2$NHC(=S)NH($C_1$-$C_4$) alkyl, -S(=O)$_2$NHC(=S)N[($C_1$-$C_4$) alkyl]$_2$, and -S(=O)$_2$NHS(=O)$_2$$R^{28}$;

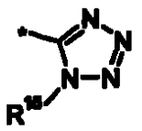
— where —

–R^{28} is –H, –(C_1-C_4) alkyl, phenyl, or –OR^{15}, where R^{15} has the same meaning as defined above;

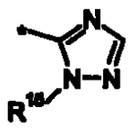
— or —

a pharmaceutically acceptable salt thereof

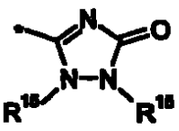
The present invention is concerned in particular with a compound of Formula (1.0.0) as above-recited wherein the moiety D comprises as a preferred meaning of R^7, phenyl, benzyl, or cyclohexyl illustrated in partial Formulas (1 1.45) through (1 1.47) below; or the moiety D comprises R^8 of partial Formula (1 1.4) where v is 0 or 1, comprising a member selected from the group consisting of partial Formulas (1 1 11) through (1 1.44) illustrated below



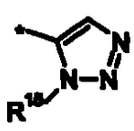
tetrazol-5-yl
(1 1 11)



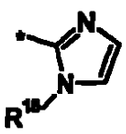
1,2,4-triazol-3-yl
(1 1 12)



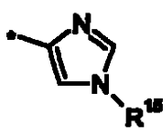
1,2,4-triazol-3-on-5-yl
(1 1 13)



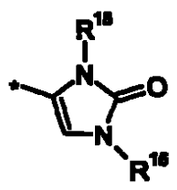
1,2,3-triazol-5-yl
(1 1 14)



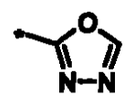
imidazol-2-yl
(1 1 15)



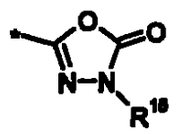
imidazol-4-yl
(1 1 16)



imidazolidin-2-on-4-yl
(1 1 17)

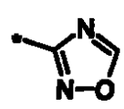


1,3,4-oxadiazolyl
(1 1 18)



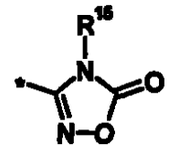
1,3,4-oxadiazol-2-on-5-yl

(1 1 19)



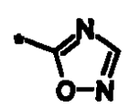
1,2,4-oxadiazol-3-yl

(1 1.20)



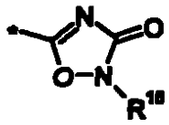
1,2,4-oxadiazol-5-on-3-yl

(1 1.21)



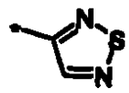
1,2,4-oxadiazol-5-yl

(1 1.22)



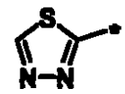
1,2,4-oxadiazol-3-on-5-yl

(1 1.23)



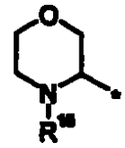
1,2,5-thiadiazol-2-yl

(1 1.24)



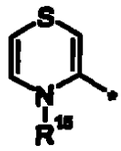
1,3,4-thiadiazolyl

(1 1.25)



morpholin-3-yl

(1 1.26)



parathiazin-3-yl

(1 1.27)



oxazolyl

(1 1.28)



isoxazolyl

(1 1.29)



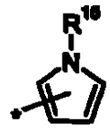
thiazolyl

(1 1.30)



isothiazolyl

(1 1.31)



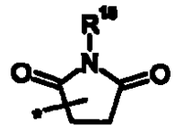
pyrrolyl

(1 1.32)



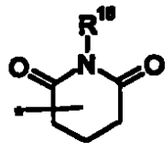
pyrazolyl

(1 1.33)



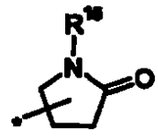
succinimidyl

(1 1.34)



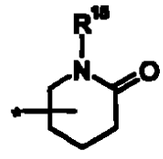
glutarimidyl

(1 1.35)



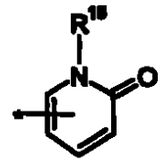
pyrrolidonyl

(1 1.36)



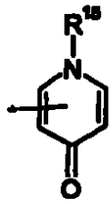
2-piperidonyl

(1 1.37)



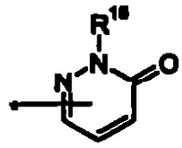
2-pyridonyl

(1 1.38)



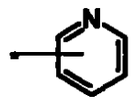
4-pyridonyl

(1 1.39)



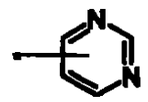
pyridazin-3-onyl

(1 1.40)



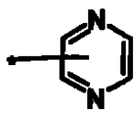
pyridyl

(1 1.41)



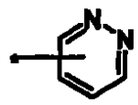
pyrimidinyl

(1 1.42)



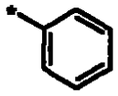
pyrazinyl

(1 1.43)



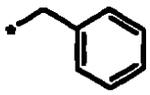
pyridazinyl

(1 1.44)



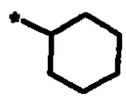
phenyl

(1 1.45)



benzyl

(1 1.46)

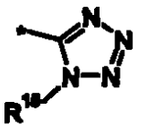


cyclohexyl

(1 1.47)

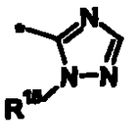
wherein "*" indicates the point of attachment of each partial Formula (1 1 11) through (1 1.47) to the remaining portion of Formula (1.0 0); and wherein each carbon atom of partial Formulas (1 1 11) through (1 1.44) is optionally substituted by a substituent R^{14}; where R^{14} and R^{15} have the same meaning as defined above; and all tautomer forms, and optionally N-oxide forms, thereof; and further wherein each carbon atom of partial Formulas (1 1.45) through (1 1.47) is optionally substituted by a substituent R^{10}; where R^{10} has the same meaning as defined above.

The present invention is further concerned more particularly with a compound of Formula (1 0.0) as above-recited wherein the moiety D is especially the below-indicated member selected from the above-recited group consisting of partial Formulas (1 1 11) through (1 1.47):



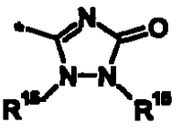
tetrazol-5-yl

(1 1 11)



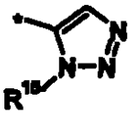
1,2,4-triazol-3-yl

(1 1 12)



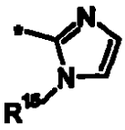
1,2,4-triazol-3-on-5-yl

(1 1 13)



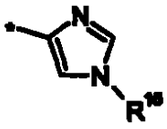
1,2,3-triazol-5-yl

(1 1 14)



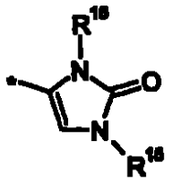
imidazol-2-yl

(1 1 15)



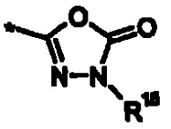
imidazol-4-yl

(1 1 16)



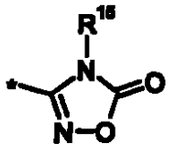
imidazolidin-2-on-4-yl

(1 1 17)



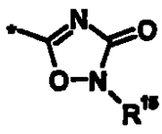
1,3,4-oxadiazol-2-on-5-yl

(1 1 19)



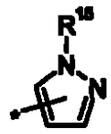
1,2,4-oxadiazol-5-on-3-yl

(1 1.21)



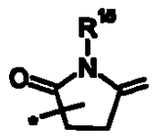
1,2,4-oxadiazol-3-on-5-yl

(1 1.23)



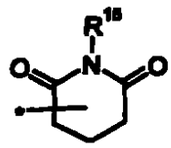
pyrazolyl

(1 1.33)



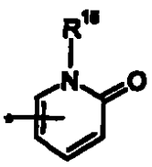
succinimidyl

(1 1.34)



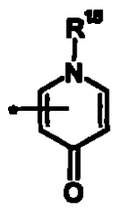
glutarimidyl

(1 1.35)



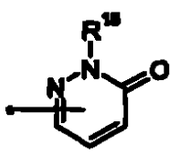
2-pyridonyl

(1 1.38)



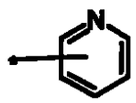
4-pyridonyl

(1 1.39)



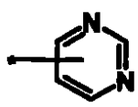
pyridazin-3-onyl

(1 1.40)



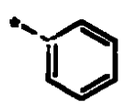
pyridyl

(1 1.41)



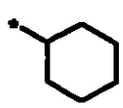
pyrimidinyl

(1 1.42)



phenyl

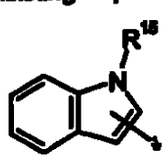
(1 1.45)



cyclohexyl

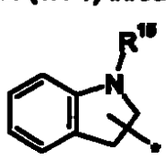
(1 1.47)

The present invention is further concerned in particular with a compound of Formula (1 0.0) as above-recited wherein the moiety D comprises R^8 of partial Formula (1 1.4) where v is 0 or 1, and R^8 of said partial Formula (1 1.4) is a member selected from the group consisting of partial Formulas (1.4 1) through (1.4.28):



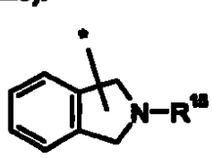
indolyl

(1.4 1)



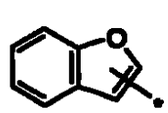
indolinyl

(1.4.2)



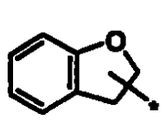
isoindolinyl

(1.4.3)



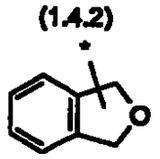
benzo[*b*]furanyl

(1.4.4)



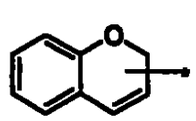
2,3-dihydrobenzo-furanyl

(1.4.5)



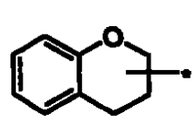
1,3-dihydroisobenzo-furanyl, phthalanyl

(1.4.6)



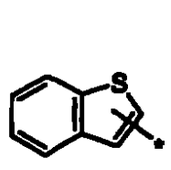
2*H*-1-benzopyranyl

(1.4 7)

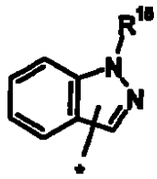


chromanyl

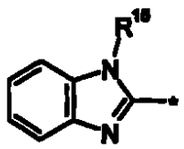
(1.4.8)



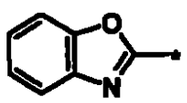
benzothienyl (1.4.9)



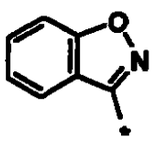
1*H*-indazolyl (1.4.10)



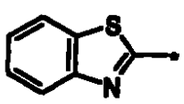
benzimidazolyl (1.4.11)



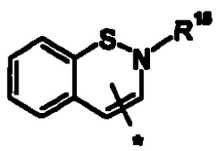
benzoxazolyl (1.4.12)



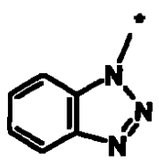
benzisoxazolyl (1.4.13)



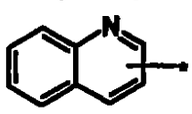
benzothiazolyl (1.4.14)



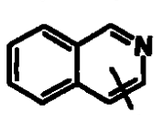
2H-1,2-benzothiazinyl (1.4.15)



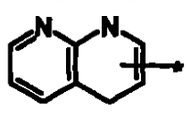
benzotriazolyl (1.4.16)



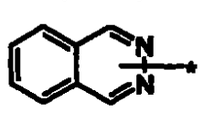
quinolinyl (1.4.17)



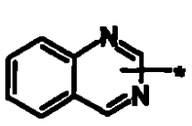
isoquinolinyl (1.4.18)



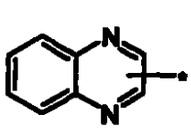
1,8-naphthyridinyl (1.4.19)



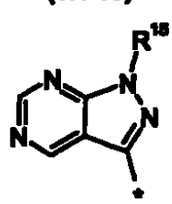
phthalazinyl (1.4.20)



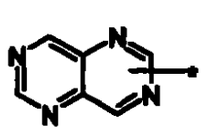
quinazolinyl (1.4.21)



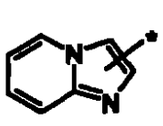
quinoxalinyl (1.4.22)



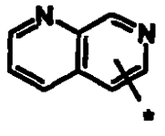
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl (1.4.23)



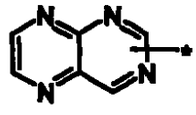
pyrimido[5,4-*d*]-pyrimidinyl (1.4.24)



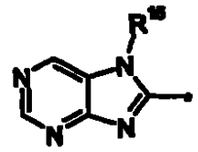
imidazo-[1,2-*a*]-pyridinyl (1.4.25)



pyridopyridinyl (1.4.26)



pteridinyl (1.4.27)



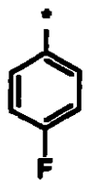
1*H*-purinyl (1.4.28)

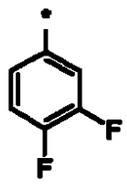
where "*" indicates the point of attachment to the remaining portion of Formula (1.0.0); and where each carbon atom is optionally substituted by a substituent R^{14}, and where R^{14} and R^{15} have the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms, thereof

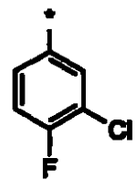
The present invention is further concerned with a compound of Formula (1.0.0) wherein J^1 comprises especially a member selected from the group consisting of phenyl; pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl, imidazolyl,

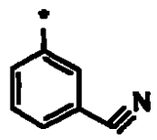
imidazolidinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, quinuclidinyl, and azabicyclo[3 3 0]octanyl; a monocyclic -(C_3-C_7) cycloalkyl moiety; a monocyclic -(C_5-C_7) cycloalkenyl moiety that is a member selected from the group consisting of cyclopentenyl, cyclohexenyl, and cycloheptenyl, and a bicyclic -(C_7-C_{10}) cycloalkyl or -(C_7-C_{10}) cycloalkenyl moiety that is a member selected from the group consisting of norbornanyl, norbornenyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.1]octanyl, bicyclo[3.3 0]octanyl, bicyclo[2.2.2]oct-5-enyl, bicyclo[2.2.2]oct-7-enyl, bicyclo[3.3 1]nonanyl, cyclodecanyl, and adamantanyl

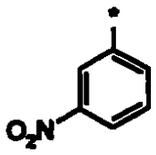
The present invention is still further concerned especially with a compound of Formula (1.0 0) wherein particularly J^1 and the substituents R^4, R^5, and R^6 are selected in such a way that the left-hand terminus of said compound of Formula (1.0.0) is represented by the following partial Formulas (2.0 1) through (2.0 72):

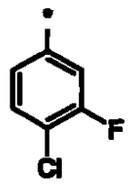

(2.0 1)

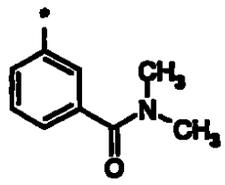

(2.0.2)

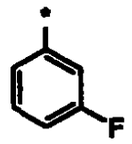

(2.0.3)

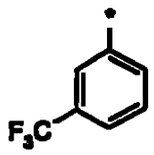

(2.0.4)

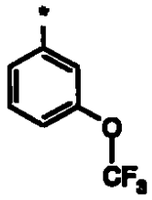

(2.0.5)

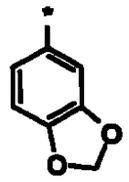

(2.0 6)

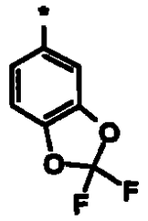

(2.0 7)

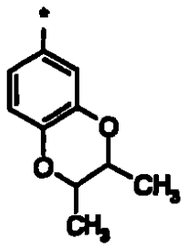

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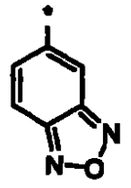

(2.0.9)

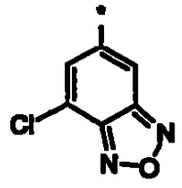

(2.0 10)

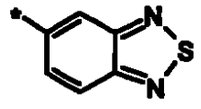

(2 0 11)

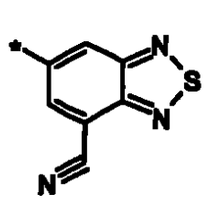

(2.0 12)


(2 0 13)

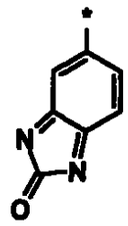

(2 0 14)


(2.0 15)

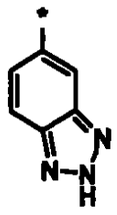

(2.0 16)



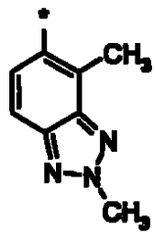
(2 0 17)



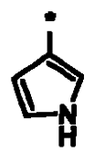
(2.0 18)



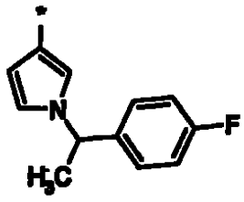
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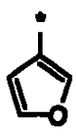
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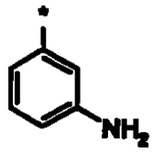
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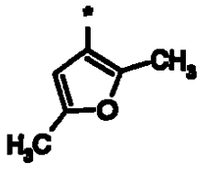
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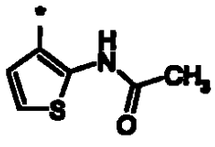
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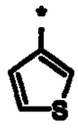
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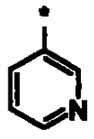
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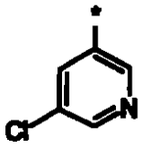
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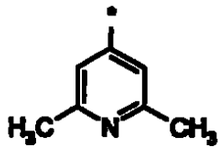
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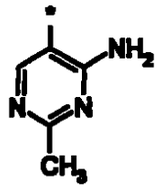
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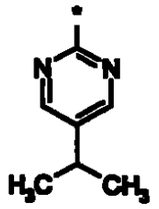
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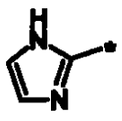
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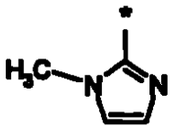
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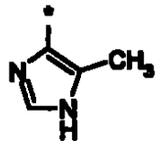
(2.0.32)



(2.0.33)



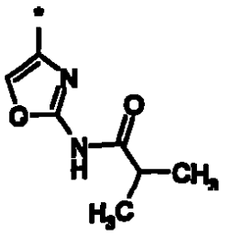
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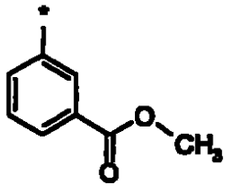
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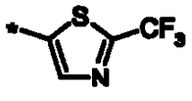
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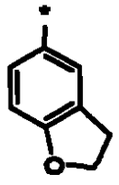
(2.0.37)



(2.0.38)



(2 0.39)



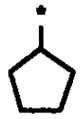
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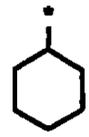
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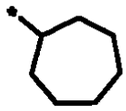
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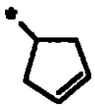
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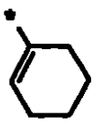
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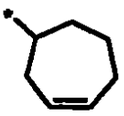
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(2.0.46)



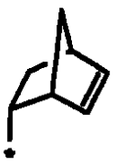
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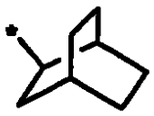
(2.0.48)



(2.0.49)



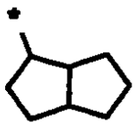
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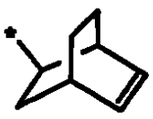
(2.0 51)



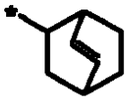
(2.0.52)



(2.0 53)



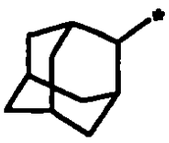
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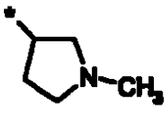
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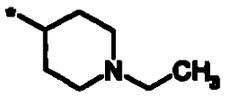
(2 0 56)



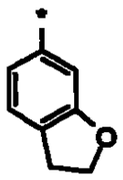
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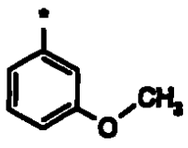
(2.0.58)



(2 0 59)



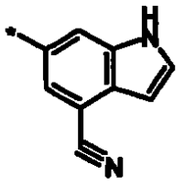
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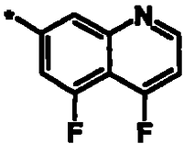
(2.0 61)



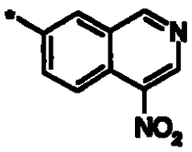
(2.0 62)



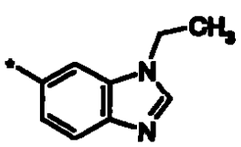
(2.0 63)



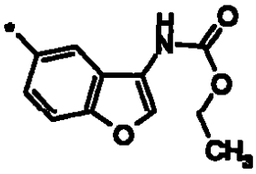
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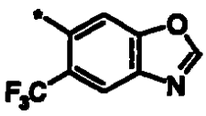
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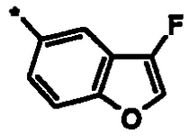
(2 0 66)



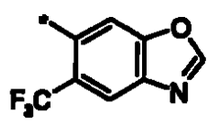
(2 0.67)



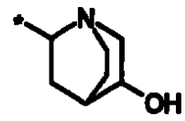
(2.0.68)



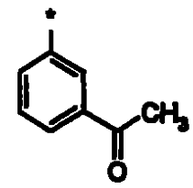
(2 0 69)



(2 0 70)



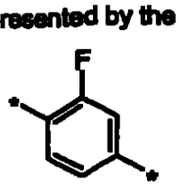
(2.0 71)



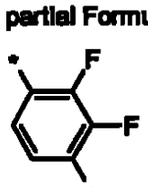
(2.0 72)

The present invention is further concerned with a compound of Formula (1 0 0) wherein J^2 comprises especially a member selected from the group consisting of phenyl, pyrrolyl, pyrrolidinyl; furanyl; thienyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl, imidazolyl; imidazolidinyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, morpholinyl, quinuclidinyl, and azabicyclo[3.3 0]octanyl; a monocyclic -(C_5-C_7) cycloalkyl moiety; a monocyclic -(C_5-C_7) cycloalkenyl moiety that is a member selected from the group consisting of cyclopentenyl, cyclohexenyl, and cycloheptenyl; and a bicyclic -(C_7-C_{10}) cycloalkyl or -(C_7-C_{10}) cycloalkenyl moiety that is a member selected from the group consisting of norbornanyl, norbornenyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.1]octanyl, bicyclo[3 3 0]octanyl, bicyclo[2.2.2]oct-5-enyl, bicyclo[2.2.2]oct-7-enyl, bicyclo[3.3 1]nonanyl, cyclodecanyl, and adamantanyl

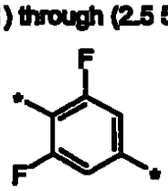
The present invention is also further concerned especially with a compound of Formula (1 0 0) wherein particularly J^2 and the substituents R^1 and R^2 are selected in such a way that this portion of the right-hand terminus of said compound of Formula (1.0.0) is represented by the following partial Formulas (2 5 1) through (2.5 50) set out below



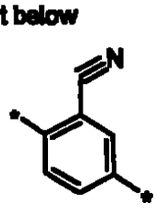
(2.5.1)



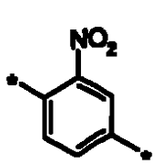
(2.5.2)



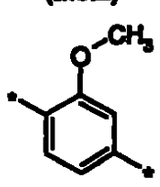
(2.5.3)



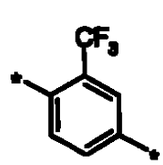
(2.5.4)



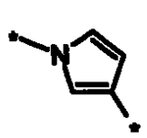
(2.5 5)



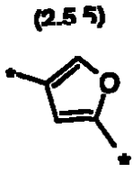
(2 5 6)



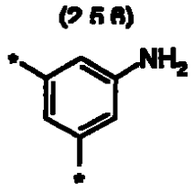
(2 5 7)



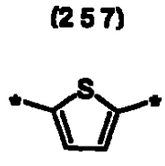
(2 5.8)



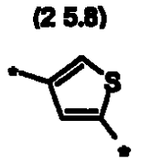
(2.5.9)



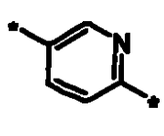
(2 5.10)



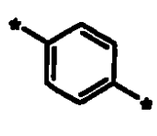
(2 5.11)



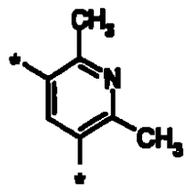
(2.5 12)



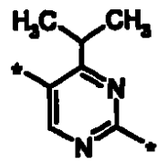
(2 5 13)



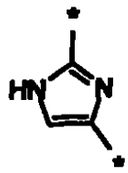
(2 5.14)



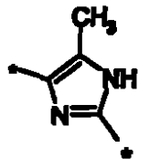
(2.5.15)



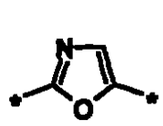
(2.5 16)



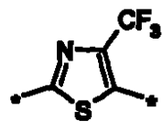
(2.5 17)



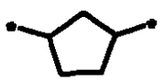
(2 5 18)



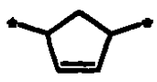
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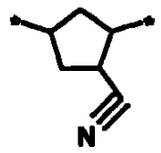
(2.5.20)



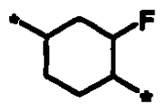
(2.5.21)



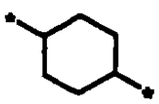
(2.5.22)



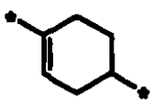
(2.5.23)



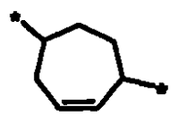
(2 5.24)



(2.5.25)



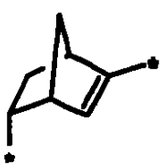
(2.5.26)



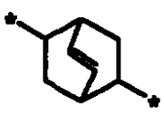
(2.5.27)



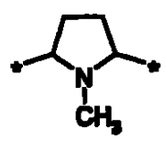
(2.5.28)



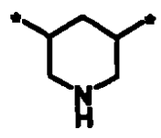
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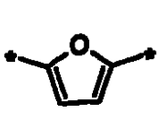
(2.5.30)



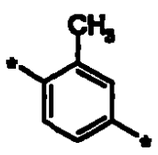
(2 5.31)



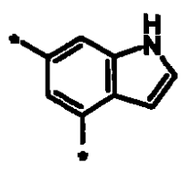
(2 5.32)



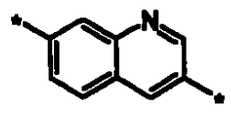
(2.5.33)



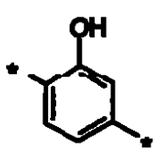
(2.5.34)



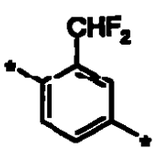
(2 5.35)



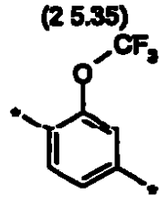
(2.5.36)



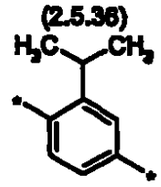
(2.5.37)



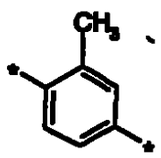
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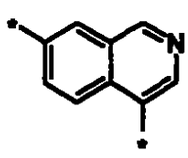


(2 5.39)

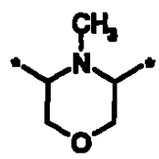


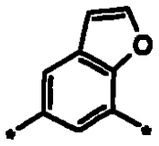
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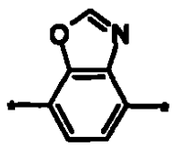

(2 5.41)

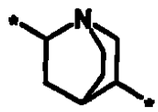

(2 5.42)

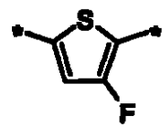

(2 5.43)

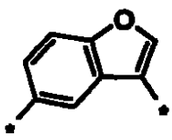

(2 5.44)

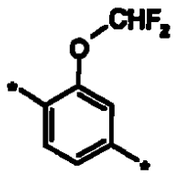

(2.5.45)


(2.5.46)

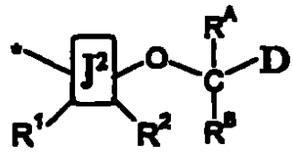

(2 5.47)


(2 5.48)


(2 5.49)

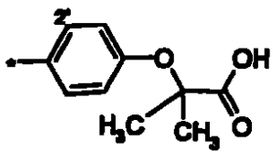

(2.5.50)

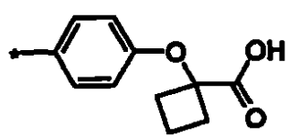
The present invention is still further concerned with a compound of Formula (1.0.0) characterized as to the right-hand side thereof, where m is 1, by partial Formula (1.0.5):

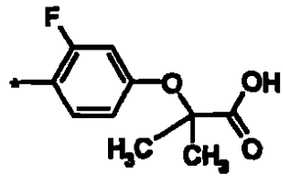


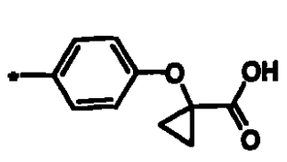
(1.0.5)

where " * " is a symbol representing the point of attachment of the group of partial Formula (1.0.5) to the remaining portion of a compound of Formula (1.0 0) where R^A and R^B are both -H, or one is –H and the other is $–CH_3$, or both are $–CH_3$, or both are taken together to form spiro-cyclopropyl or spiro-cyclobutyl, R^1 is –H, $-OCH_3$, or 2'–F, R^2 is -H, and the moieties J^2 and D are selected such that, said group of partial Formula (1 0 5) is a member selected from the group consisting of partial Formulas (1 5 1) through (1 5 54), as set out below Where the moiety J^2 is phenyl, the 2'-position thereof is located as indicated in partial Formula (1 5 1):

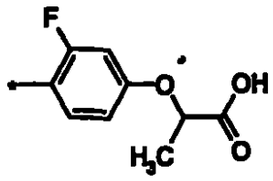

(1.5 1)


(1 5.2)

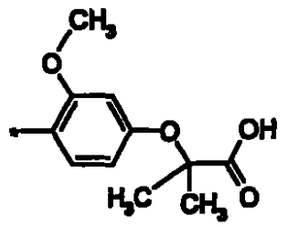

(1.5 3)



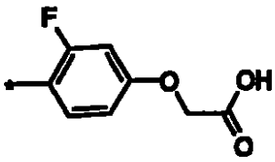
(1.5.4)



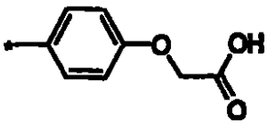
(1.5 5)



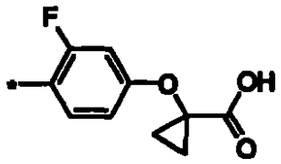
(1 5.6)



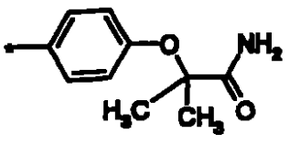
(1 5 7)



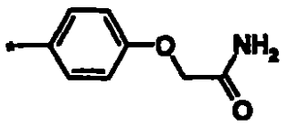
(1.5.8)



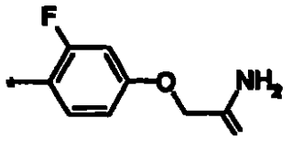
(1.5.9)



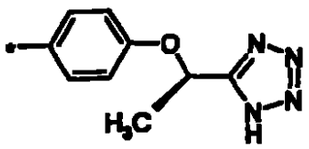
(1 5 10)



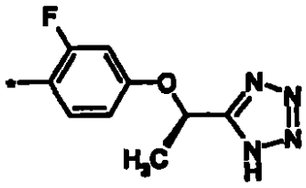
(1.5 11)



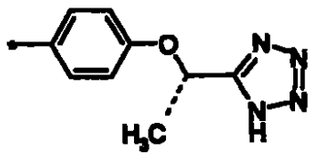
(1.5.12)



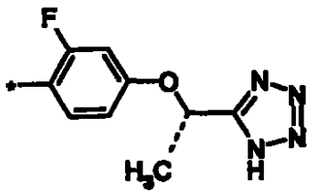
(1 5.13)



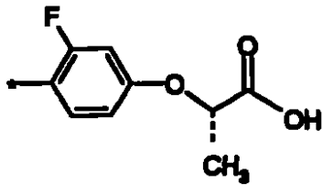
(1.5.14)



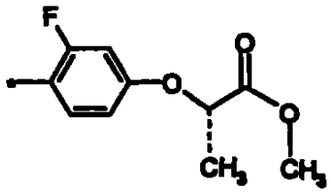
(1.5 15)



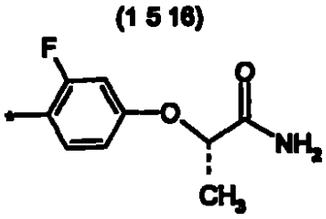
(1 5 16)



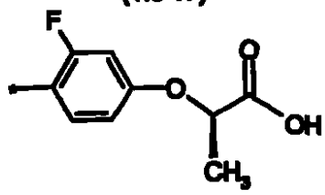
(1.5 17)



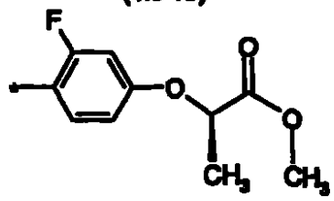
(1.5 18)



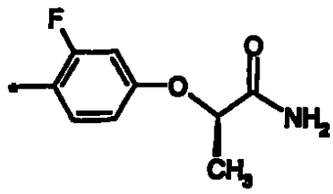
(1.5 19)



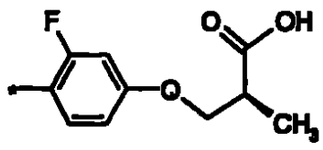
(1.5.20)



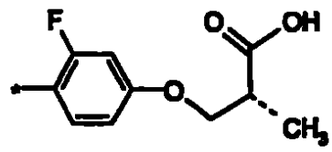
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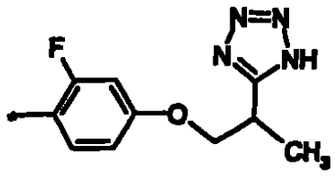
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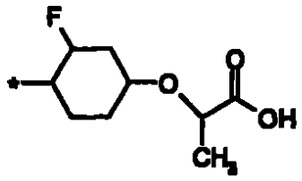
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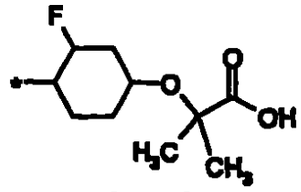
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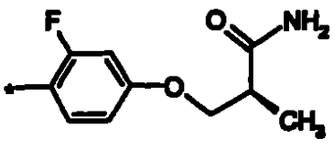
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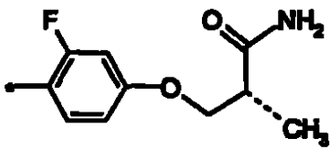
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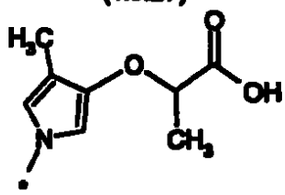
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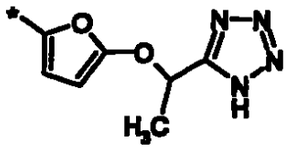
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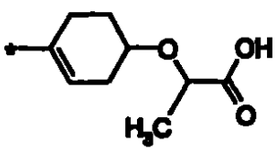
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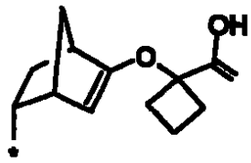
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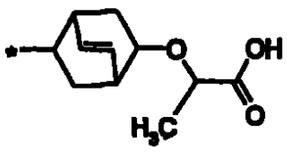
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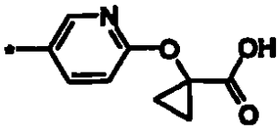
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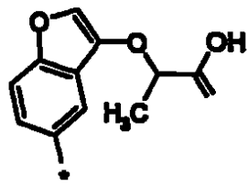
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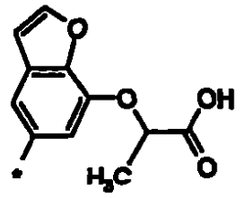
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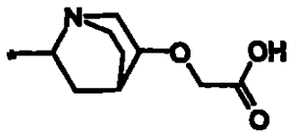
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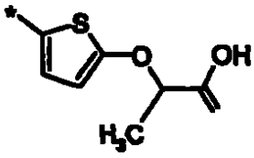
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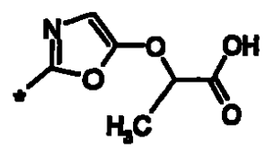
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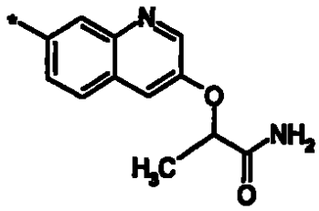
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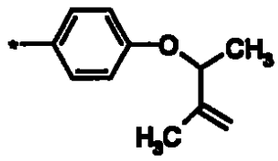
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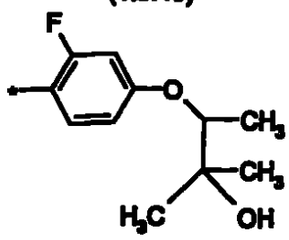
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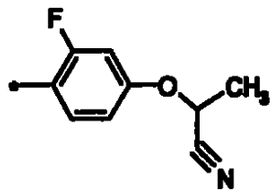
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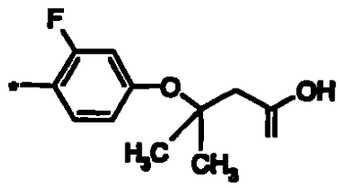
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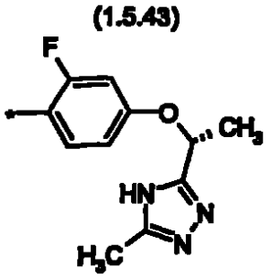
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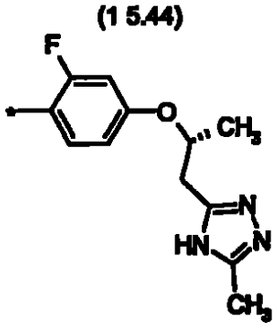
(1 5.44)



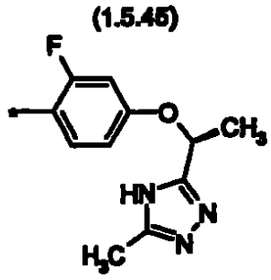
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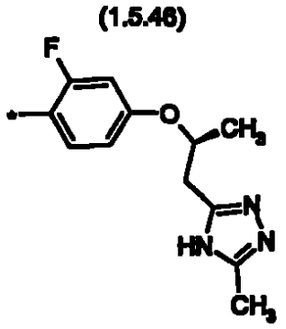
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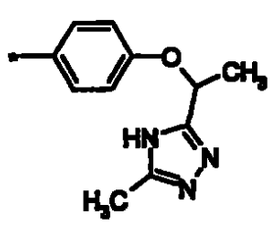
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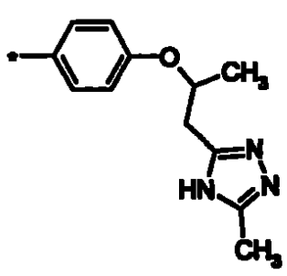
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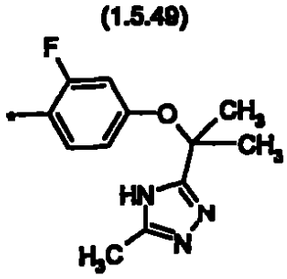
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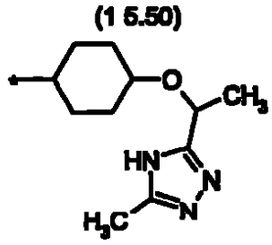
(1 5.50)



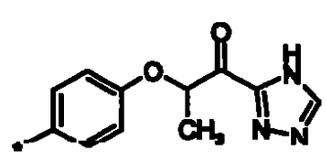
(1.5.51)



(1.5 52)



(1.5 53)



(1.5.54)

– wherein –

"***" indicates the point of attachment of each said group of partial Formula (1.0 5) represented by partial Formulas (1.5 1) through (1.5 54) to the remaining portion of Formula (1 0 0)

The present invention is further concerned with a method of treating a subject suffering from a disease or condition mediated by the PDE4 isozyme in its role of regulating the activation and degranulation of human eosinophils, comprising administering to said subject in need of said treatment a therapeutically effective amount of a compound of Formula (1 0 0) as described above. Similarly, the present invention is also concerned with a pharmaceutical composition for use in such a therapeutic treatment, comprising a compound of Formula (1.0 0) as described above together with a pharmaceutically acceptable carrier

The present invention relates to PDE4 isozyme inhibitors comprising a compound of Formula (1.0 0) as described above which is useful in treating or preventing one or members selected from the groups of diseases, disorders, and conditions consisting of:

– asthma of whatever type, etiology, or pathogenesis, or asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma; atopic, bronchial, IgE-mediated asthma, bronchial asthma, essential asthma; true asthma; intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause; non-atopic asthma; bronchitic asthma, emphysematous asthma, exercise-induced asthma, occupational asthma; infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma; incipient asthma; wheezy infant syndrome,

– chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction; and emphysema;

– obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, or an obstructive or inflammatory airways disease that is a member selected from the group consisting of asthma, pneumoconiosis, chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD), COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated therewith, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS), and exacerbation of airways hyper-reactivity consequent to other drug therapy

– pneumoconiosis of whatever type, etiology, or pathogenesis, or pneumoconiosis that is a member selected from the group consisting of aluminosis or bauxite workers' disease; anthracosis or miners' asthma, asbestosis or steam-fitters' asthma, chalicosis or flint disease, ptilosis caused by inhaling the dust from ostrich feathers, siderosis caused by the

Inhalation of iron particles, silicosis or grinders' disease, byssinosis or cotton-dust asthma, and talc pneumoconiosis;

– bronchitis of whatever type, etiology, or pathogenesis, or bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis; dry bronchitis, infectious asthmatic bronchitis; productive bronchitis, staphylococcus or streptococcal bronchitis, and vesicular bronchitis,

– bronchiectasis of whatever type, etiology, or pathogenesis, or bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis; sacculated bronchiectasis, fusiform bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis, and follicular bronchiectasis,

– seasonal allergic rhinitis, or perennial allergic rhinitis, or sinusitis of whatever type, etiology, or pathogenesis, or sinusitis that is a member selected from the group consisting of purulent or nonpurulent sinusitis, acute or chronic sinusitis, and ethmoid, frontal, maxillary, or sphenoid sinusitis,

– rheumatoid arthritis of whatever type, etiology, or pathogenesis, or rheumatoid arthritis that is a member selected from the group consisting of acute arthritis; acute gouty arthritis, chronic inflammatory arthritis, degenerative arthritis, infectious arthritis, Lyme arthritis, proliferative arthritis, psoriatic arthritis, and vertebral arthritis,

– gout, and fever and pain associated with inflammation;

– an eosinophil-related disorder of whatever type, etiology, or pathogenesis, or an eosinophil-related disorder that is a member selected from the group consisting of eosinophilia, pulmonary infiltration eosinophilia, Loffler's syndrome; chronic eosinophilic pneumonia, tropical pulmonary eosinophilia, bronchopneumonic aspergillosis, aspergilloma; granulomas containing eosinophils, allergic granulomatous angiitis or Churg-Strauss syndrome, polyarteritis nodosa (PAN); and systemic necrotizing vasculitis,

– atopic dermatitis, or allergic dermatitis, or allergic or atopic eczema;

– urticaria of whatever type, etiology, or pathogenesis, or urticaria that is a member selected from the group consisting of immune-mediated urticaria, complement-mediated urticaria; urticariogenic material-induced urticaria, physical agent-induced urticaria; stress-induced urticaria, idiopathic urticaria, acute urticaria, chronic urticaria; angioedema, cholinergic urticaria, cold urticaria in the autosomal dominant form or in the acquired form, contact urticaria, giant urticaria, and papular urticaria,

– conjunctivitis of whatever type, etiology, or pathogenesis, or conjunctivitis that is a member selected from the group consisting of actinic conjunctivitis; acute catarrhal conjunctivitis, acute contagious conjunctivitis, allergic conjunctivitis, atopic conjunctivitis, chronic catarrhal conjunctivitis, purulent conjunctivitis, and vernal conjunctivitis

–uveitis of whatever type, etiology, or pathogenesis, or uveitis that is a member selected from the group consisting of inflammation of all or part of the uvea, anterior uveitis, iritis, cyclitis, iridocyclitis, granulomatous uveitis, nongranulomatous uveitis; phacoantigenic uveitis, posterior uveitis; choroiditis, and chorioretinitis,

– psoriasis;

– multiple sclerosis of whatever type, etiology, or pathogenesis, or multiple sclerosis that is a member selected from the group consisting of primary progressive multiple sclerosis; and relapsing remitting multiple sclerosis,

– autoimmune/inflammatory diseases of whatever type, etiology, or pathogenesis, or an autoimmune/inflammatory disease that is a member selected from the group consisting of autoimmune hematological disorders, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, polychondritis; scleroderma, Wegner's granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis; Stevens-Johnson syndrome, idiopathic sprue; autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease; endocrin opthamopathy; Grave's disease; sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary bilary cirrhosis; juvenile diabetes or diabetes mellitus type I, anterior uveitis, granulomatous or posterior uveitis, keratoconjunctivitis sicca, epidemic keratoconjunctivitis, diffuse interstitial pulmonary fibrosis or interstitial lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, psoriatic arthritis, glomerulonephritis with and without nephrotic syndrome, acute glomerulonephritis; idiopathic nephrotic syndrome; minimal change nephropathy; inflammatory/hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, allergic contact dermatitis, benign familial pemphigus, pamphigus erythematosus, pemphigus follaceus, and pemphigus vulgaris,

– prevention of allogeneic graft rejection following organ transplantation,

– inflammatory bowel disease (IBD) of whatever type, etiology, or pathogenesis, or inflammatory bowel disease that is a member selected from the group consisting of ulcerative colitis (UC); collagenous colitis, colitis polyposa, transmural colitis, and Crohn's disease (CD),

– septic shock of whatever type, etiology, or pathogenesis, or septic shock that is a member selected from the group consisting of renal failure, acute renal failure; cachexia,

malarial cachexia, *hypophysial* cachexia, uremic cachexia, cardiac cachexia; cachexia suprarenalis or Addison's disease, cancerous cachexia, and cachexia as a consequence of infection by the human immunodeficiency virus (HIV);

– liver injury;

– pulmonary hypertension; and hypoxia-induced pulmonary hypertension,

– bone loss diseases, primary osteoporosis, and secondary osteoporosis,

– central nervous system disorders of whatever type, etiology, or pathogenesis, or a central nervous system disorder that is a member selected from the group consisting of depression, Parkinson's disease, learning and memory impairment; tardive dyskinesia, drug dependence, arteriosclerotic dementia, and dementias that accompany Huntington's chorea, Wilson's disease, paralysis agitans, and thalamic atrophies,

– infection, especially infection by viruses wherein such viruses increase the production of TNF-α in their host, or wherein such viruses are sensitive to upregulation of TNF-α in their host so that their replication or other vital activities are adversely impacted, including a virus which is a member selected from the group consisting of HIV-1, HIV-2, and HIV-3, cytomegalovirus, CMV; influenza; adenoviruses, and Herpes viruses, including *Herpes zoster* and *Herpes simplex*;

– yeast and fungus infections wherein said yeast and fungi are sensitive to upregulation by TNF-α or elicit TNF-α production in their host, *e.g.*, fungal meningitis; particularly when administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections, including but are not limited to, polymixins, *e.g.*, Polymycin B, imidazoles, *e.g.*, clotrimazole, econazole, miconazole, and ketoconazole; triazoles, *e.g.*, fluconazole and itranazole, and amphotericins, *e.g.*, Amphotericin B and liposomal Amphotericin B

– ischemia-reperfusion injury; autoimmune diabetes, retinal autoimmunity; chronic lymphocytic leukemia, HIV infections, lupus erythematosus, kidney and ureter disease; urogenital and gastrointestinal disorders, and prostate diseases

In particular, the compounds of Formula (1 0 0) are useful in the treatment of (1) inflammatory diseases and conditions comprising joint inflammation rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, inflammatory bowel disease, ulcerative colitis, chronic glomerulonephritis, dermatitis, and Crohn's disease, (2) respiratory diseases and conditions comprising asthma, acute respiratory distress syndrome, chronic pulmonary inflammatory disease, bronchitis, chronic obstructive airway disease, and silicosis, (3) infectious diseases and conditions comprising. sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock

syndrome, fever and myalgias due to bacterial, viral or fungal infection, and influenza; (4) immune diseases and conditions comprising. autoimmune diabetes, systemic lupus erythematosis, graft vs. host reaction, allograft rejections, multiple sclerosis, psoriasis, and allergic rhinitis, and (5) other diseases and conditions comprising bone resorption diseases, reperfusion injury; cachexia secondary to infection or malignancy; cachexia secondary to human acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV) infection, or AIDS related complex (ARC); keloid formation, scar tissue formation; type 1 diabetes mellitus, and leukemia.

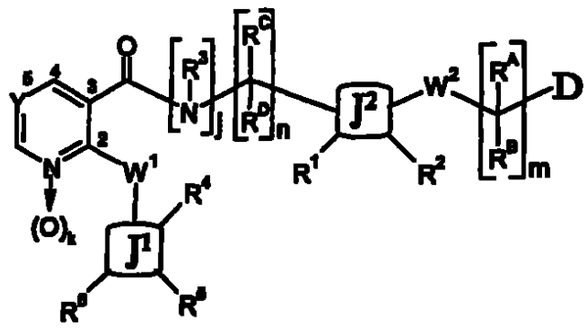
The present invention still further relates to the combination of a compound of Formula (1 0.0) together with one or more members selected from the group consisting of the following (a) leukotriene biosynthesis inhibitors 5-lipoxygenase (5-LO) inhibitors and 5-lipoxygenase activating protein (FLAP) antagonists selected from the group consisting of zileuton, ABT-761, fenleuton, tepoxalin, Abbott-79175, Abbott-85761, *N*-(5-substituted)-thiophene-2-alkylsulfonamides of Formula (5.2.8); 2,6-di-*tert*-butylphenol hydrazones of Formula (5.2 10), the class of methoxytetrahydropyrans which includes Zeneca ZD-2138 of Formula (5.2 11), the compound SB-210661 of Formula (5.2 12) and the class to which it belongs, the class of pyridinyl-substituted 2-cyanonaphthalene compounds to which L-739,010 belongs, the class of 2-cyanoquinoline compounds to which L-746,530 belongs, the classes of indole and quinoline compounds to which MK-591, MK-886, and BAY x 1005 belong, (b) receptor antagonists for leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4 selected from the group consisting of the phenothiazin-3-one class of compounds to which L-651,392 belongs, the class of amidino compounds to which CGS-25019c belongs; the class of benzoxaolamines to which ontazolast belongs, the class of benzenecarboximidamides to which BIIL 284/260 belongs, and the classes of compounds to which zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195 belong; (c) PDE4 inhibitors including inhibitors of the isoform PDE4D, (d) 5-Lipoxygenase (5-LO) inhibitors, or 5-lipoxygenase activating protein (FLAP) antagonists, (e) dual inhibitors of 5-lipoxygenase (5-LO) and antagonists of platelet activating factor (PAF); (f) leukotriene antagonists (LTRAs) including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4, (g) antihistaminic H_1 receptor antagonists including cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine; (h) gastroprotective H_2 receptor antagonists, (i) α_1– and α_2 adrenoceptor agonist vasoconstrictor sympathomimetic agents administered orally or topically for decongestant use, including propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride, (j) α_1– and α_2–adrenoceptor agonists in combination with inhibitors of 5-lipoxygenase (5-LO), (k) anticholinergic agents including

ipratropium bromide, tiotropium bromide; oxitropium bromide, pirenzepine; and telenzepine; (l) β_1– to β_4–adrenoceptor agonists including metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol, (m) methylxanthanines including theophylline and aminophylline; (n) sodium cromoglycate; (o) muscarinic receptor (M1, M2, and M3) antagonists, (p) COX-1 inhibitors (NSAIDs), COX-2 selective inhibitors including rofecoxib, and nitric oxide NSAIDs, (q) insulin-like growth factor type I (IGF-1) mimetics, (r) ciclesonide, (s) inhaled glucocorticoids with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate; (t) tryptase inhibitors, (u) platelet activating factor (PAF) antagonists, (v) monoclonal antibodies active against endogenous inflammatory entities; (w) IPL 576, (x) anti-tumor necrosis factor (TNFα) agents including Etanercept, Infliximab, and D2E7; (y) DMARDs including Leflunomide; (z) TCR peptides, (aa) interleukin converting enzyme (ICE) inhibitors, (*bb*) IMPDH inhibitors, (cc) adhesion molecule inhibitors including VLA-4 antagonists; (dd) cathepsins, (ee) MAP kinase inhibitors; (ff) glucose-6 phosphate dehydrogenase inhibitors, (gg) kinin-B_1- and B_2-receptor antagonists, (hh) gold in the form of an aurothio group together with various hydrophilic groups, (ii) immunosuppressive agents, e.g., cyclosporine, azathioprine, and methotrexate, (jj) anti-gout agents, *e g.*, colchicine; (kk) xanthine oxidase inhibitors, *e g.*, allopurinol, (ll) uricosuric agents, *e g.*, probenecid, sulfinpyrazone, and benzbromarone; (mm) antineoplastic agents, especially antimitotic drugs including the vinca alkaloids such as vinblastine and vincristine, (nn) growth hormone secretagogues, (oo) inhibitors of matrix metalloproteases (MMPs), *i.e* , the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11); (*pp*) transforming growth factor (TGFβ); (qq) platelet-derived growth factor (PDGF); (rr) fibroblast growth factor, *e g.*, basic fibroblast growth factor (bFGF); (ss) granulocyte macrophage colony stimulating factor (GM-CSF); (tt) capsaicin cream, (uu) Tachykinin NK_1 and NK_3 receptor antagonists selected from the group consisting of NKP-608C, SB-233412 (talnetant), and D-4418, and (vv) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892

DETAILED DESCRIPTION OF THE INVENTION

5.0 Compounds

The present invention is concerned with novel compounds which may be represented by Formula (1 0.0) as follows



(1.0.0)

The broadest scope of the compounds of the present invention is circumscribed above under Section 4 0 relating to the Summary of the Invention A further description of said compounds is provided hereafter in terms of a range of different types and groups of embodiments, as well as specific embodiments which characterize and exemplify the compounds of Formula (1 0 0). Preferred and more preferred embodiments of said compounds are also set forth, but it will be understood that the recital of such preferances is in no way intended to, and does not limit the scope of the present invention with regard to said compounds

As used herein, the expressions "–(C_1-C_2) alkyl", "–(C_1-C_4) alkyl", and "-(C_1-C_8) alkyl", as well as equivalent variations of the same, are intended to include branched as well as straight chain conformations of these aliphatic groups Thus, the above-quoted expressions include, in addition to the straight chain entities *methyl*, *ethyl*, *n*-propyl, *n*-butyl, *n*-pentyl, and *n*-hexyl, the branched chain entities *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *iso*-pentane (2-methylbutane), 2-methylpentane, 3-methylpentane, 1-ethylpropane, and 1-ethylbutane The meanings of the above-quoted expressions are also intended to apply to said expressions whether or not they are substituted Thus, the expression "fluorinated–(C_1-C_3) alkyl" is intended to encompass the various fluorinated species of the *n*-propyl and iso-propyl aliphatic groups.

As used herein, the expression "saturated or unsaturated carbon ring system that is 3- to 7-membered monocyclic" is intended to include such saturated monocyclic carbon ring systems as cyclopropane, cyclobutane, cyclopentane, cyclohexane, and cycloheptane The above-quoted expression is also intended to include such mono-unsaturated monocyclic carbon ring systems as cyclopentene, cyclohexene, and cycloheptene; as well as such aromatic monocyclic carbon ring systems as phenylene

As used herein, the expressions "fused or discontinuous, polycyclic" and "fused polycyclic" are intended to mean first, a carbon ring system having two or more rings, especially bicyclic and tricyclic, more especially bicyclic, in which the rings are fused, *i.e.*,

there is at least one pair of bridgehead carbon atoms present. These polycyclic ring systems may be saturated or unsaturated Second, the above-quoted expression is intended to mean a carbon ring system having two or more rings in which said rings are discontinuous, *i.e* , they are attached to each other by a single or double covalent bond and there are no bridgehead carbon atoms present. These polycyclic ring systems may also be saturated or unsaturated

The moiety J^1 may be discontinuous, while the moiety J^2 may not be discontinuous It is also provided herein that J^2 may not have the meaning of a moiety which is biaryl or discontinuous. The expression "biaryl" as used herein is intended to mean a fused polycyclic ring system as defined immediately above in which (1) bridgehead carbon atoms are joined by a bond, *i.e* , there are no additional carbon atoms present between said bridgehead carbon atoms, and (2) heteroatoms, if present, are contained only in a tricyclic or higher polycyclic fused ring system Further, as already mentioned, J^2 may not be discontinuous, as that expression is defined immediately above.

Consequently, the types of biaryl and discontinuous ring systems that may comprise a meaning of of J^1, but that may not comprise a meaning of J^2 include, *inter alia*, the following: biphenyl; biphenylene; fluorene, 9*H*-carbazole; phenanthridine; phenanthrene; 2,2'-bipyridine; iminodibenzyl, 2,2'-biquinoline, naphthalene, 2-phenylnaphthalene; 1-phenylnaphthalene; diphenylmethane, 1-phenylpiperadine, 1-phenylpiperazine; bibenzyl; azulene; 4,4'-diphenyl-2,2'-dipyridyl, 1-(diphenylmethyl)azetidine; 4,5-diphenyloxazole; 2,5-diphenyloxazole; diphenyl-2-pyridylmethane and diphenyl-4-pyridylmethane; 3,6-diphenyl-1,2,4,5-tetrazine; 1-benzylpiperazine, 1-benzylpiperidine; 2-benzylpyridine, 3-benzylpyridine and 4-benzylpyridine, 4,5-diphenylimidazole; phenothiazine; phenoxazine, phenazine, 1-phenyl-3,4-dihydronaphthalene, 2-phenylindene, 2-phenylindole; 4-phenylmorpholine, 2-phenylbenzothiazole, 2-phenylbenzoxazole, and 2-phenylbenzimidazole.

The above-recited types of biaryl and discontinuous ring systems may, on the other hand, comprise a meaning of J^1 As a further illustration, it will be understood that, *e g* , a naphthyl moiety is biaryl as defined herein, since it is a fused bicyclic with a bond between the bridgehead carbon atoms, and there are no heteroatoms present. A quinolinyl moiety, on the other hand, while also a fused bicyclic with a bond between the bridgehead carbon atoms, is not biaryl as defined herein, since a nitrogen heteroatom is also present. and the definition of "biaryl" requires that in such a case the fused ring system be tricyclic or higher polycyclic. The biphenyl moiety is an example of a discontinuous ring system that, accordingly, may be a meaning of J^1, but may not be a meaning of J^2

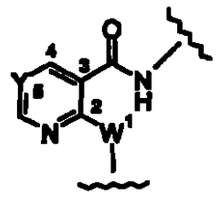
As used herein, the expression "saturated or unsaturated carbon ring system that is 7- to 12-membered, fused or discontinuous, polycyclic" is intended to include such

saturated fused bi- and tricyclic carbon ring systems as norbornane, bicyclo[2.2.2]octanyl, bicyclo[3.2 1]octanyl, bicyclo[3 3 0]octanyl, bicyclo[3.3 1]nonanyl, cyclodecanyl, and adamantanyl The above-quoted expression is also intended to include such mono-unsaturated bi- and tricyclic carbon ring systems as norbornenyl, bicyclo[2.2.2]oct-5-enyl, and bicyclo[2.2.2]oct-7-enyl, as well as such aromatic bi- and tricyclic carbon ring systems as naphthylene and biphenylene. The above-quoted expression is further intended to include such aromatic disonthnuous bicyclic carbon ring systems as biphenylene

The carbon ring systems included within the scope of the above-quoted expression and described above also include moieties wherein optionally one carbon atom thereof may be replaced by a heteroatom selected from N, O, or S, and where N is selected, optionally a second carbon atom thereof may be replaced by a heteroatom selected from N, O, and S The resulting moieties incude pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyridyl; pyrimidinyl, piperidinyl; piperazinyl; imidazolyl, imidazolidinyl, oxazolyl, isoxazolyl; thiazolyl; indolyl; quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl; morpholinyl; quinuclidinyl, and azabicyclo[3.3 0]octanyl

As used herein with respect to compounds of Formula (1.0.0), as well as other formulas and partial formulas relating thereto, where one or more nitrogen atom components thereof is or are represented as [N⇒(O)], it or they comprise(s) an optional nitrogen oxide form of said nitrogen atom(s). Where there is more than one such nitrogen oxide form, they are selected independently of each other Further, it will be appreciated that said nitrogen oxide form(s) may also be represented as "[N⇒(O)$_u$]" where u is 0 or 1

A portion of the core nucleus of the compounds of Formula (1 0 0) is that of a nicotinamide of Formula (1 0 1):



(1.0 1)

derived from nicotinic acid This portion of the core nucleus is then elaborated by defining the Y moiety as being =C(R^1_a)—, or —[N⇒(O)$_k$]— where k is 0 or 1, and where the symbol ⇒(O) indicates a nitrogen heteroatom in the form of its N-oxide when k is 1 It should be noted that in the N-containing heterocyclyl moieties which define R^a, it is provided that optionally one or more of the N-heteroatoms comprising said heterocyclyl moieties may be in the form of the N-

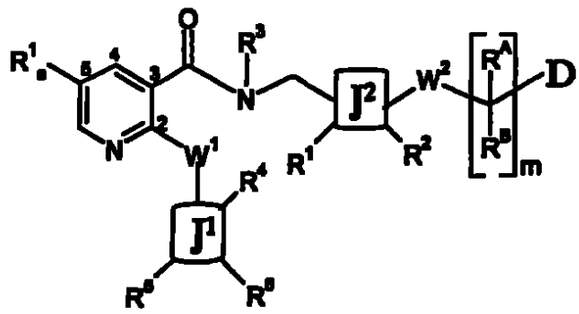
oxide of said N-heteroatoms Accordingly, the considerations concerning N-oxides just described also apply to such N-oxide-containing moieties defining R^5

Where Y has the meaning of —[N⇒(O)$_k$]— the compounds of the present invention are pyrimidines The pyrimidine group of compounds of Formula (1 0 0) is a significant part of the scope of the present invention It is preferred, nevertheless, that the compounds of Formula (1.0 0) have the Y moiety defined as =C(R^1_a)— where the substituent R^1_a is selected independently from the other substituents that form the compounds of Formula (1 0 0).

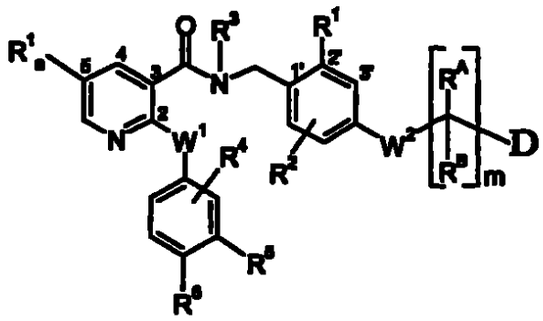
In addition to –H, R^1_a of the =C(R^1_a)— moiety is defined as a member selected from the group consisting of –F, –Cl, –CN, –NO_2, –(C_1-C_4) alkyl, –(C_2-C_4) alkynyl, fluorinated–(C_1 -C_3) alkyl, fluorinated-(C_1 -C_3) alkoxy; -OR^{12}; and –C(=O)$NR^{12}_aR^{12}_b$, where R^{12}_a and R^{12}_b are each independently –H; –CH_3, –CH_2CH_3, –$CH_2CH_2CH_3$, -$CH_2(CH_3)_2$, –$CH_2CH_2CH_2CH_3$, –$CH(CH_3)CH_2CH_3$, –$CH_2CH(CH_3)_2$, –$C(CH_3)_3$, cyclopropyl; cyclobutyl, or cyclopentyl;

However, it is preferred that the R^1_a substituent of the =C(R^1_a)— moiety have the meaning of –H; –F, –Cl; –CH_3, -OCH_3, or –(C_2-C_4) alkynyl, more preferably R^1_a is –F or -H

It will be noted that R^1_a has several substituent definitions, especially –F, in common with those for the R^1 and R^2 substituents on the J^2 moiety In the embodiments of the compounds of Formula (1 0 0) where Y is =C(R^1_a)—, and both the J^1 moiety and the J^2 moiety have the preferred meaning of phenyl, the substituents at the 5-position of the nicotinamide core nucleus and at the 2'-position, of the benzyl group attached to the amide portion thereof, are selected from the same group of definitions, although on an independent basis The embodiments of the present invention wherein such substituents are involved, and where j is 1, k is 0, n is 1, both R^C and R^D are –H, and Y is =C(R^1_a)—, may be illustrated by generic Formula (1 0.2a) and sub-generic Formula (1 0.2b) as follows.



(1.0.2a)



(1.0.2b)

In such embodiments of the present invention, the 5-position (R^1_n) and 2'-position (R^1) substituents serve the same function of modulating the properties of the overall compound of Formula (1.0 0) with respect to its pharmacological and pharmacokinetic properties such as potency, substrate specificity (selectivity), and physico-chemical properties In preferred embodiments of the compounds of the present invention of this type, both the R^1 and R^1_n substituents will have the same meaning, which will be –H or –F

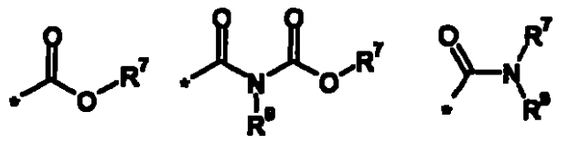
5 1.0 Terminal Moiety D is a Moiety of Partial Formulas (1.1.1) – (1.1.9)

D is a member selected from the group of moieties defined by partial Formulas (1 1 1) through (1 1 9) illustrated further above. The moieties of partial Formulas (1.1 1) through (1 1 5) which define the D group are typically but not necessarily acids, amides, and heterocyclyl groups that act as acid and amide mimetics, but they are not limited to these types of functional groups The moieties of partial Formulas (1 1 6) through (1 1.9) which define the D group are typically but not necessarily tertiary alcohols and their mimetics, especially analogous acyl and nitrile moieties, but they are not limited to these types of functional groups. Other moieties as described herein may be employed at the right-hand-side of the compounds of Formula (1 0 0) These moieties are bioisosteric in that they permit the compounds of Formula (1 0 0) containing them to achieve PDE4 inhibition

essentially equivalent to that achieved by other moieties, especially acid, amide, and alcohol moieties

5.1.1 D is a Moiety of Partial Formulas (1.1.1), (1.1.2), or (1.1.3)

Embodiments of the present invention wherein the definition of the D group is illustrated by partial Formulas (1.1.1), (1.1.2), and (1.1.3), are as follows



(1.1.1) (1.1.2) (1.1.3)

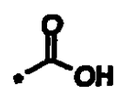
One of a number of preferred moieties for defining the D group is that of partial Formula (1.1.1) where R^7 has the meaning of –H, which is a preferred meaning of this substituent. Where R^7 is hydrogen and m is 1, 2, or 3 in Formula (1.0.0), a simple carboxylic acid -COOH results, and the group becomes a lower alkanoic acid. Benzoic acid as a meaning of the D group, however, is a less preferred embodiment of the present invention.

R^{10} is an optional substituent of the moieties that define R^7, and there may be up to three such substituents when present. The meaning of the R^{10} substituent includes phenyl or pyridyl where said phenyl or pyridyl is in turn optionally substituted by up to 3 substituents R^{11} where R^{11} is –F, –Cl, –CN, $–NO_2$, –OH, $–(C_1-C_3)$ alkoxy, $–(C_1-C_3)$ alkyl, or $–NR^{16}R^{17}$. In preferred embodiments that include such R^{11} substitution, there will be 1 or 2 substituents R^{11} that have the meaning of –F, –Cl, $-CH_3$, $–OCH_3$, –OH, –CN, or $–N(CH_3)_2$. Preferably, there is 0 or 1 such R^{11} substituent and when present it is –F or –Cl. The meaning of the R^{10} substituent further includes –F, –Cl, $–CF_3$, oxo (=O), $–OR^{16}$, $–NO_2$, –CN, $–C(=O)OR^{16}$, $-O-C(=O)R^{16}$, $–C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $–NR^{16}R^{17}$, $–NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $–NR^{16}S(=O)_2R^{17}$, or $-S(=O)_2NR^{16}R^{17}$.

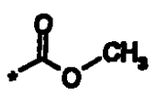
The sub-substituents R^{16} and R^{17} comprise –H, $–(C_1-C_4)$ alkyl, preferably $-CH_3$, $-(C_2-C_4)$ alkenyl, $–(C_3-C_6)$ cycloalkyl, preferably cyclopropyl, phenyl, benzyl, or pyridyl. Said alkyl, alkenyl, cycloalkyl, phenyl, benzyl, or pyridyl groups are in turn optionally substituted by up to 3 substituents –F, –Cl, or –CN. Among the above-recited additional meanings of R^{10}, it is preferred that the R^{10} substituent when present be pyridyl optionally substituted by –F, –Cl, $-OCH_3$, –CN, $–NO_2$, or $–NR^{16}R^{17}$ where R^{16} and R^{17} are independently –H or $–CH_3$, or that the R^{10} substituent when present be –F, –Cl, $–CF_3$, –CN, $–NO_2$, $–C(=O)OR^{16}$, or $–NR^{16}R^{17}$ where R^{16} and R^{17} are independently –H or $–CH_3$.

These and other preferred embodiments of the compounds of Formula (1.0.0) comprising the moieties of partial Formula (1.1.1) based on the preferred meanings of R^7 and

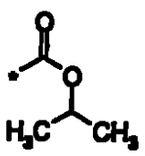
R^9 as described above, include, *inter alia*, the following groups illustrated by partial Formulas (3.5.1) through (3.5 15):



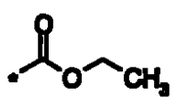
(3 5 1)



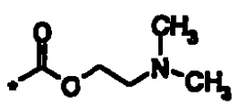
(3 5.2)



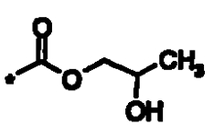
(3 5.3)



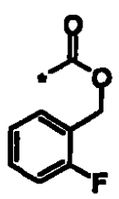
(3.5.4)



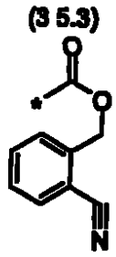
(3.5.5)



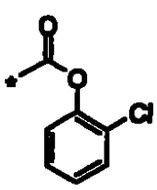
(3.5.6)



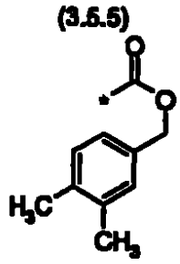
(3.5 7)



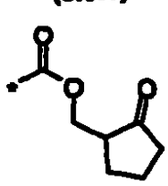
(3.5.8)



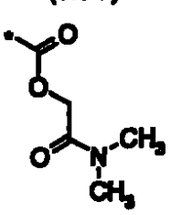
(3.5.9)



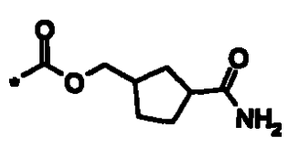
(3.5.10)



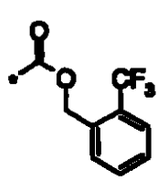
(3.5.11)



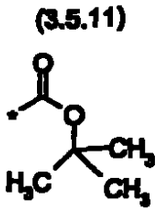
(3.5 12)



(3.5.13)



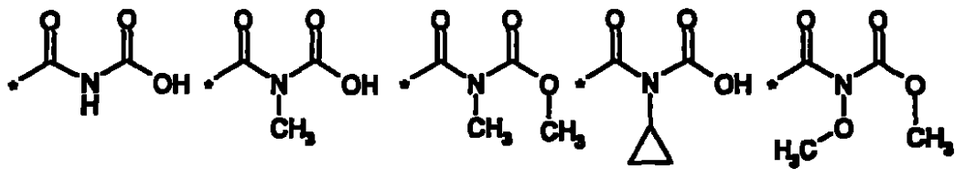
(3.5 14)



(3.5 15)

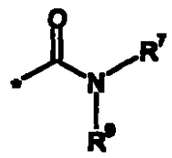
The D group is represented by partial Formula (1 1.2) in which the nitrogen atom is substituted by R^9 where R^9 has the meaning of –H; -(C_1-C_4) alkyl, –(C_3-C_7) cycloalkyl, phenyl; benzyl, –C(=O)OR^{18}; –C(=O)R^{18}; –OR^{18}; -(C_1-C_2) alkyl–OR^{18}, or –(C_1-C_2) alkyl–C(=O)OR^{18}; where R^{18} is –H or -(C_1-C_4) alkyl R^{18} is preferably –H or –CH_3.

Accordingly, embodiments of the present invention where the D group is represented by partial Formula (1 1.2) may be illustrated as follows by partial Formulas (4 1 1) through (4 1.5):



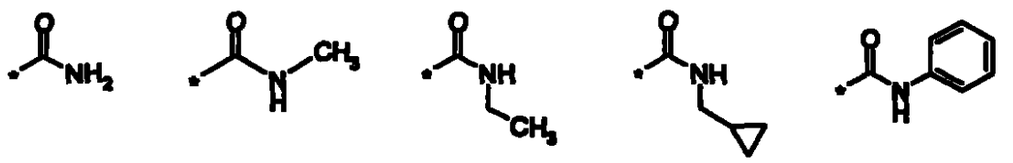
(4 1 1) (4 1.2) (4 1.3) (4 1.4) (4 1.5)

Those embodiments wherein the definition of D is that of an amide group, are illustrated by partial Formula (1 1.3)

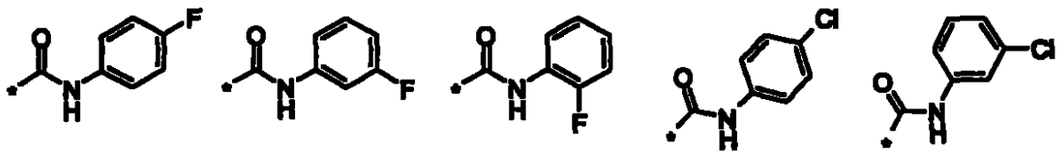


(1 1.3)

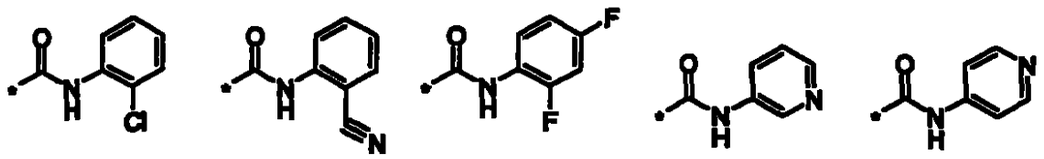
These and other preferred embodiments of the compounds of Formula (1 0.0) comprising moieties of partial Formula (1 1.3), based on the meanings of R^7 and R^9 described above, include, *inter alia*, the following groups illustrated by partial Formulas (4.5.1) through (4.5.20)



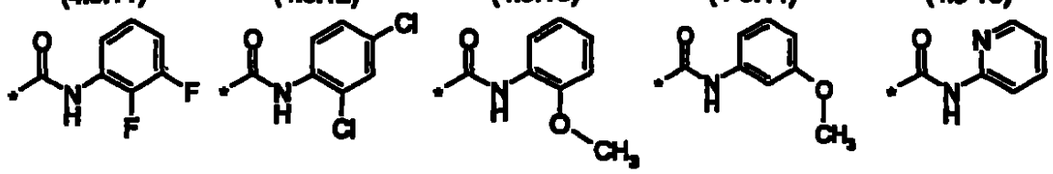
(4.5.1) (4.5.2) (4.5.3) (4 5.4) (4.5.5)



(4.5.6) (4.5.7) (4.5.8) (4.5.9) (4.5.10)



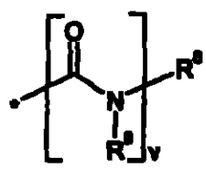
(4.5.11) (4.5.12) (4.5.13) (4 5.14) (4.5 15)



(4.5.16) (4.5.17) (4.5 18) (4 5 19) (4.5.20)

5 1.2 D is a Moiety of Partial Formula (1.1.4)

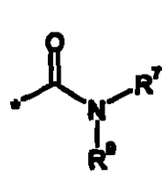
Preferred embodiments of the present invention also comprise those compounds of Formula (1.0 0) wherein terminal moiety D falls within the scope of partial Formula (1 1.4), *i.e* , embodiments of this type are encompassed within the scope of the D moiety when it has the meaning of partial Formula (1 1.4):



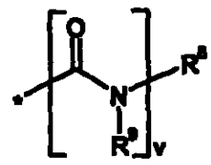
(1 1.4)

wherein R^8 is a monocyclic or bicyclic heterocyclyl which is a member selected from the group consisting of tetrazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-3-on-5-yl, 1,2,3-triazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazolidin-2-on-4-yl; 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-on-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-on-5-yl, 1,3,4-oxadiazolyl, 1,3,4-oxadiazol-2-on-5-yl, oxazolyl; isoxazolyl, pyrrolyl, pyrazolyl, succinimidyl, glutarimidyl, pyrrolidonyl, 2-piperidonyl, 2-pyridonyl, 4-pyridonyl, pyridazin-3-onyl; pyridazin-3-onyl, thiazolyl; isothiazolyl; thiadiazolyl, morpholinyl, parathiazinyl; pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, indolinyl; isoindolinyl, benzo[*b*]furanyl; 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl; 2*H*-1-benzopyranyl, 2-*H*-chromenyl, chromanyl, benzothienyl, 1*H*-indazolyl; benzimidazolyl; benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl, benzotriazinyl, phthalazinyl, 1,8-naphthyridinyl, quinolinyl; isoquinolinyl, quinazolinyl, quinoxalinyl, pyrazolo[3,4-*d*]pyrimidinyl; pyrimido[4,5-d]pyrimidinyl, imidazo[1,2-a]pyridinyl, pyridopyridinyl; pteridinyl, and 1*H*-purinyl

Partial Formulas (1 1.3) and (1 1.4) are similar and the distinction between them should be noted Partial Formulas (1 1.3) and (1 1.4) are as follows



(1 1.3)



(1 1.4)

Where v is 0, R^8 is linked in a direct fashion to the remaining portion of a compound of Formula (1.0 0) and it is, accordingly, readily distinguishable from a moiety of partial Formula (1 1 3) in which R^7 is linked to the remaining portion of a compound of Formula (1 0 0) through the amide bridging moiety —C(=O)NR^9—. Where v is 1, on the other hand, both the R^8 and the R^7 moieties are linked to the remaining portion of a compound of Formula (1 0.0) through the amide bridging moiety —C(=O)NR^9— In this instance, the distinction

between the moieties of partial Formulas (1 1.3) and (1 1.4) comprises the difference between the meanings of the R^9 and the R^7 moieties This difference has already been described above in detail

In order to facilitate the following description, the monocyclic heterocyclyl moieties and the bicyclic heterocyclyl moieties are first treated together and thereafter are discussed as separate groups

Any one or more of the carbon atoms of the phenyl, benzyl, or heterocyclyl moiety is substituted by 0 to 3 substituents R^{14} where R^{14} has the meanings and preferred meanings already described above with regard to partial Formulas (1 1 1), (1 1.2), and (1 1.3). Any one or more of the nitrogen atoms, which it will be appreciated occur only in the case of the heterocyclyl moieties, and which are not a point of attachment of said heterocyclyl moiety, are optionally substituted by up to 3 substituents R^{15} Any sulfur atom which happens to occur in a heterocyclyl moiety, that is not a point of attachment of said heterocyclyl moiety, is substituted by 0, 1, or 2 oxygen atoms.

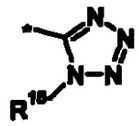
The optional nitrogen heterocyclyl substituent R^{15} comprises –H, $-NR^{16}R^{17}$, $-C(=O)R^{16}$; $-OR^{16}$, preferably $-OCH_3$, $-(C_1-C_4)$ alkyl–OR^{16}; $-C(=O)OR^{16}$; $-(C_1-C_2)$ alkyl-$C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$, $-(C_1-C_4)$ alkyl, preferably $-CH_3$, $-(C_2-C_4)$ alkenyl, $-(CH_2)_u-(C_3-C_7)$ cycloalkyl where u is 0, 1 or 2, preferably cyclopropyl; phenyl, benzyl, pyridyl; or quinolinyl The alkyl, alkenyl, alkoxy, cycloalkyl, phenyl, benzyl, pyridyl and quinolinyl groups thus included are optionally substituted with up to 2 substituents R^{12}

The sub-substituent R^{12} comprises –F, –Cl, $-CO_2R^{18}$; $-OR^{18}$; –CN, $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$; $-NR^{18}C(=O)OR^{19}$, $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, where p is 1 or 2, preferably 2, $-(C_1-C_4)$ alkyl, preferably $-CH_3$, and $-(C_1-C_4)$ alkoxy, where R^{12} has the meaning of $-OR^{18}$ above and R^{19} is defined as $-(C_1-C_4)$ alkyl, and preferably R^{12} is $-OCH_3$, where said alkyl and alkoxy are in turn optionally substituted with up to 3 substituents –F, –Cl, $-(C_1-C_2)$ alkoxycarbonyl, $-(C_1-C_2)$ alkylcarbonyl, and $-(C_1-C_2)$ alkylcarbonyloxy The R^{18} and R^{19} substituents are independently selected from –H, $-(C_1-C_2)$ alkyl, preferably $-CH_3$, or phenyl, and are optionally substituted with up to 3 –F, or –Cl

No R^9 substituents are shown in partial Formulas (1 1 11) through (1 1.34) above, as well as further below, because the R^9 substituent is attached only to a nitrogen atom that does not form an integral, component part of an attached heterocyclic moiety The R^9 substituent is optional in character in that "–H" is included as a definition of the R^9 substituent, and in many of the embodiments of the compounds of Formula (1.0 0) this is the preferred meaning of R^9 Another preferred meaning of R^9 is $-CH_3$.

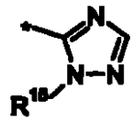
There is also pointed out the distinction between the substituents R^8 and R^{16}, both of which are attached only to nitrogen atoms in any of the meanings of the moiety D. The substituent R^{16} is attached only to a nitrogen atom that is an integral, component part of any heterocyclic moiety that may be defined *via* the R^8 substituent of partial Formula (1.1.4) and in particular with reference to the more specific heterocyclic moieties of partial Formulas (1.1.11) through (1.1.34), shown above as well as further below. The R^8 substituent, on the other hand, is attached only to a nitrogen atom that in turn is attached to, but is not an integral, component part of any of the heterocyclic moieties that is defined by partial Formulas (1.1.2), (1.1.3), and (1.1.5). The R^{16} substituent may be attached to one or more nitrogen atoms and said nitrogen atoms may be present in any moieties falling within the scope of partial Formula (1.1.4) that can be characterized as containing or comprising a nitrogen-containing heterocyclic moiety.

As an illustration of preferred subgeneric embodiments of the present invention wherein the D group has the meaning of a moiety that falls within the scope of partial Formula (1.1.4), there is set out below the groups of partial Formulas (1.1.11) through (1.1.44):



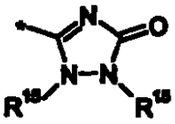
tetrazol-5-yl

(1.1.11)



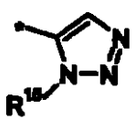
1,2,4-triazol-3-yl

(1.1.12)



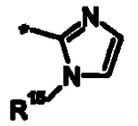
1,2,4-triazol-3-on-5-yl

(1.1.13)



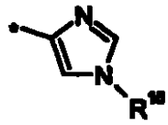
1,2,3-triazol-5-yl

(1.1.14)



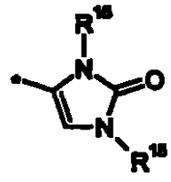
imidazol-2-yl

(1.1.15)



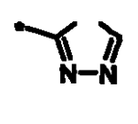
imidazol-4-yl

(1.1.16)



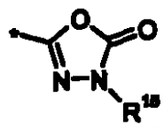
imidazolidin-2-on-4-yl

(1.1.17)



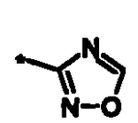
1,3,4-oxadiazolyl

(1.1.18)



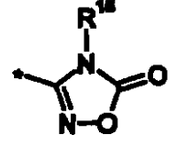
1,3,4-oxadiazol-2-on-5-yl

(1.1.19)



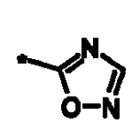
1,2,4-oxadiazol-3-yl

(1.1.20)



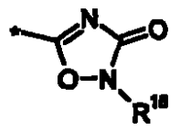
1,2,4-oxadiazol-5-on-3-yl

(1.1.21)



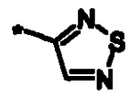
1,2,4-oxadiazol-5-yl

(1.1.22)



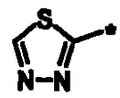
1,2,4-oxadiazol-3-on-5-yl

(1 1.23)



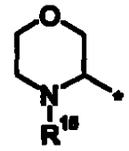
1,2,5-thiadiazol-2-yl

(1 1.24)



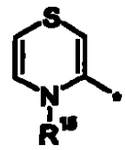
1,3,4-thiadiazolyl

(1 1.25)



morpholin-3-yl

(1 1.26)



parathiazin-3-yl

(1 1.27)



oxazolyl

(1 1.28)



isoxazolyl

(1 1.29)



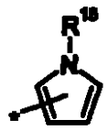
thiazolyl

(1 1.30)



isothiazolyl

(1 1.31)



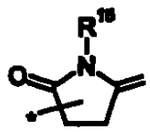
pyrrolyl

(1 1.32)



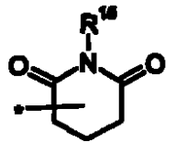
pyrazolyl

(1 1.33)



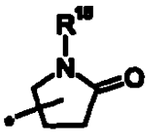
succinimidyl

(1 1.34)



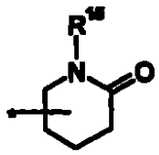
glutarimidyl

(1 1.35)



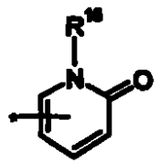
pyrrolidonyl

(1 1.36)



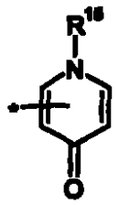
2-piperidonyl

(1 1.37)



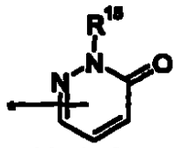
2-pyridonyl

(1 1.38)



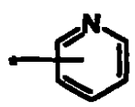
4-pyridonyl

(1 1.39)



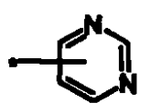
pyridazin-3-onyl

(1 1.40)



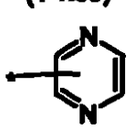
pyridyl

(1 1.41)



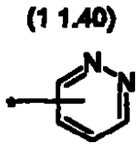
pyrimidinyl

(1 1.42)



pyrazinyl

(1 1.43)

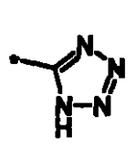


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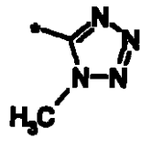
(1 1.44)

In order to provide another demonstration of preferred embodiments of the compounds of Formula (1 0 0) with reference to the D group where it is a moiety of partial

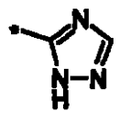
Formula (1 1.4) and v is 0 or 1, and R^8 is a monocyclic heterocyclic group, there is set out below the groups consisting of partial Formulas (4 8 1) through (4.8 80) from which the D moiety is selected in such preferred embodiments.



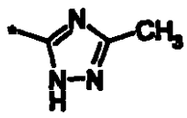
(4.8.1)



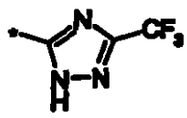
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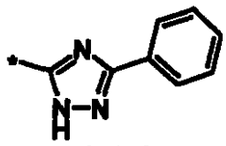
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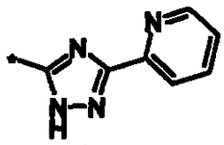
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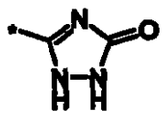
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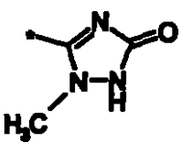
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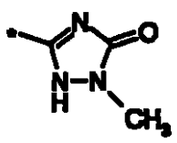
(4.8 7)



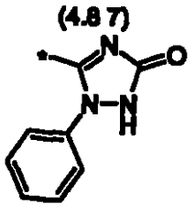
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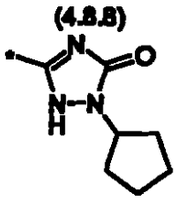
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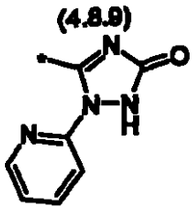
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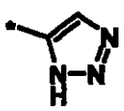
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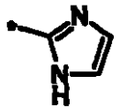
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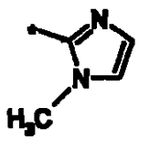
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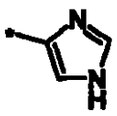
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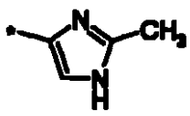
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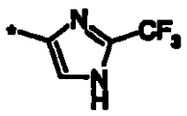
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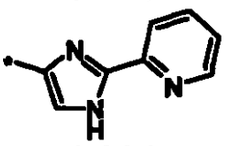
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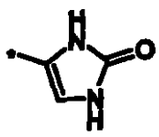
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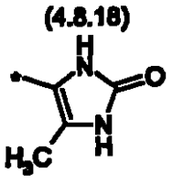
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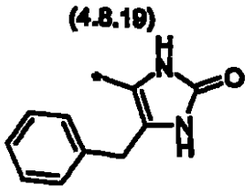
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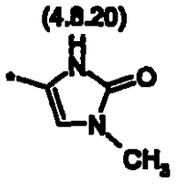
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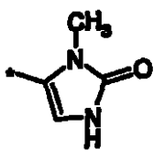
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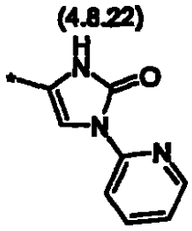
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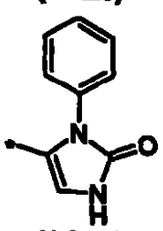
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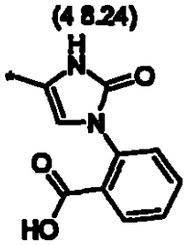
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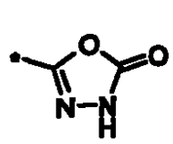
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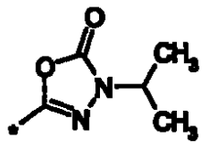
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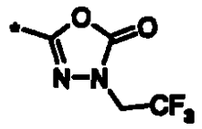
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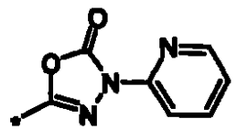
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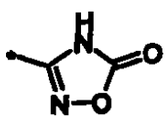
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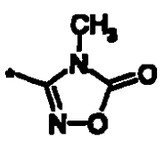
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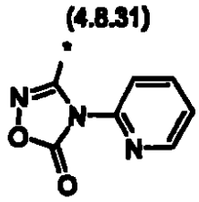
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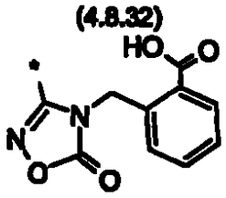
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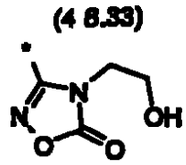
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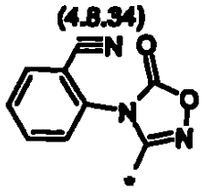
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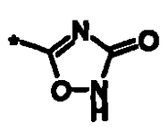
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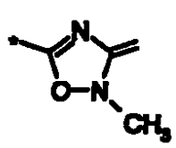
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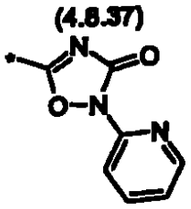
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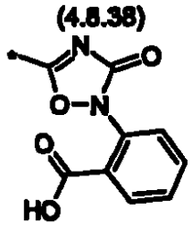
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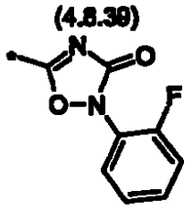
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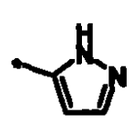
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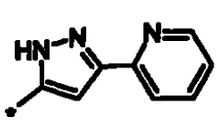
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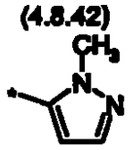
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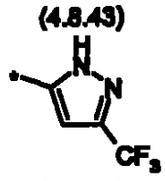
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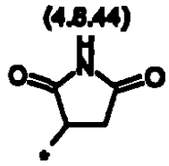
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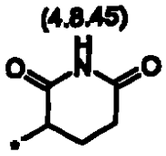
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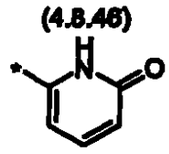
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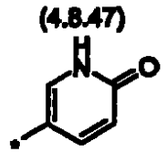
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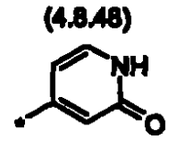
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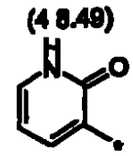
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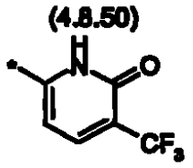
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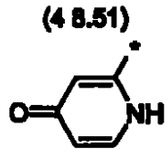
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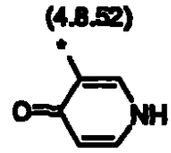
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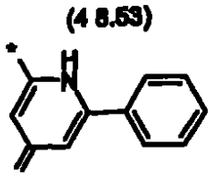
(4.8 54)



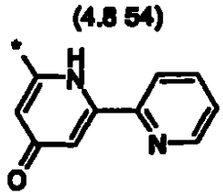
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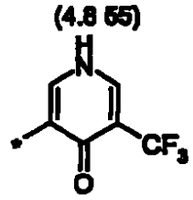
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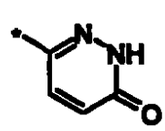
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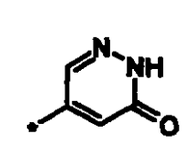
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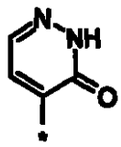
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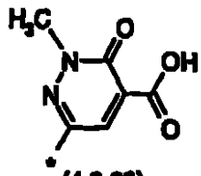
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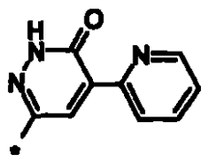
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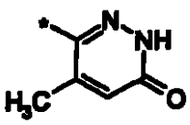
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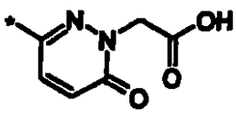
(4.8 63)



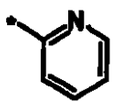
(4.8 64)



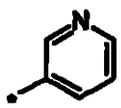
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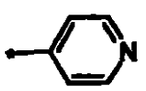
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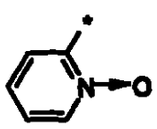
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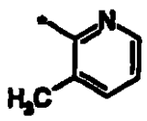
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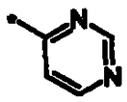
(4 8 69)



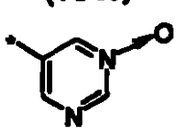
(4.8 70)



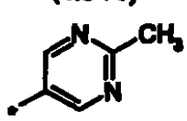
(4.8 71)



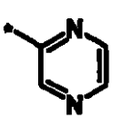
(4.8 72)



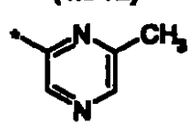
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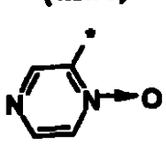
(4.8 74)



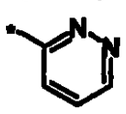
(4.8 75)



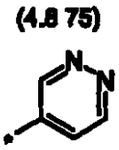
(4.8 76)



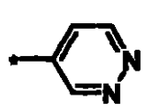
(4.8.77)



(4.8 78)



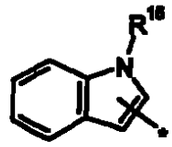
(4.8 79)



(4.8.80)

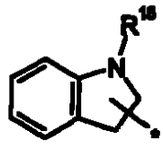
Preferred embodiments of the present invention where the group **D** is a moiety of partial Formula (1 1.4) and v is 0 or 1, also include those wherein the moiety R^8 is a bicyclic heterocyclic group selected from the group consisting of indolyl, indolinyl, isoindolinyl, benzo[*b*]furanyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl; 2*H*-1-benzopyranyl, 2-*H*-chromanyl, chromanyl, benzothienyl; 1*H*-indazolyl, benzimidazolyl, benzoxazolyl; benzisoxazolyl, benzothiazolyl, benzotriazolyl; benzotriaznyl, phthalazinyl, 1,8-naphthyridinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyrazolo[3,4-*d*]pyrimidinyl, pyrimido[4,5-*d*]pyrimidinyl, imidazo[1,2-a]pyridinyl, pyridopyridinyl, pteridinyl, and 1*H*-purinyl

In order to provide a still further demonstration of preferred embodiments of the compounds of Formula (1.0 0) with reference to the **D** group where it is a moiety of partial Formula (1 1.4), v is 0 or 1, and R^8 is a bicyclic heterocyclic group, there is set out below the groups consisting of partial Formulas (5.0 1) through (5 0.28) from which the **D** moiety is selected in such preferred embodiments



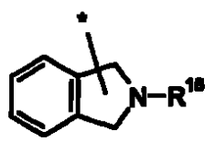
indolyl

(5 0 1)



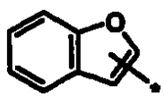
indolinyl

(5 0.2)



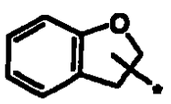
isoindolinyl

(5 0 3)



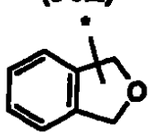
benzo[*b*]furanyl

(5 0.4)



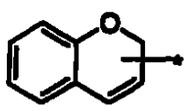
2,3-dihydrobenzo-furanyl

(5 0.5)



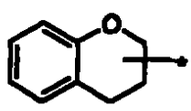
1,3-dihydroisobenzo-furanyl; phthalanyl

(5.0.6)



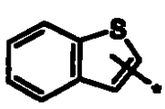
2*H*-1-benzopyranyl

(5 0.7)



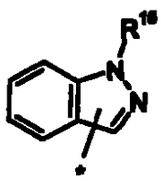
chromanyl

(5.0.8)



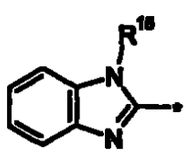
benzothienyl

(5.0.9)



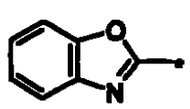
1*H*-indazolyl

(5.0 10)



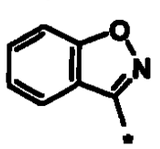
benzimidazolyl

(5.0 11)



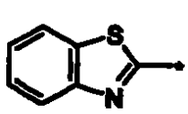
benzoxazolyl

(5.0 12)



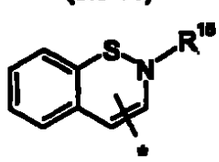
benzisoxazolyl

(5 0 13)



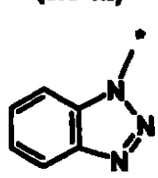
benzothiazolyl

(5.0 14)



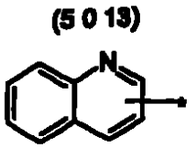
2H-1,2-benzothiazinyl

(5.0 15)



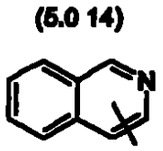
benzotriazolyl

(5.0.16)



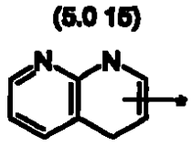
quinolinyl

(5 0 17)



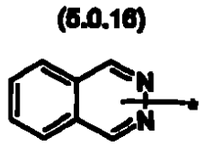
isoquinolinyl

(5.0 18)



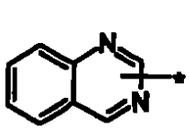
1,8-naphthyridinyl

(5.0 19)



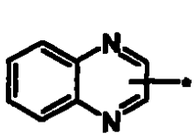
phthalazinyl

(5.0.20)



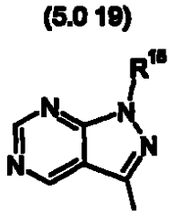
quinazolinyl

(5.0.21)



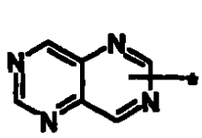
quinoxalinyl

(5.0.22)



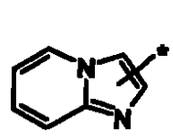
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(5.0.23)

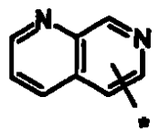


pyrimido[5,4-*d*]-pyrimidinyl

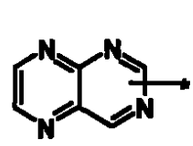
(5.0.24)



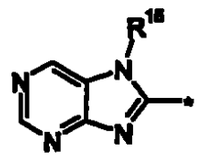
imidazo-[1,2-a]-pyridinyl (5 0.25)



pyridopyridinyl (5.0.26)



pteridinyl (5.0.27)

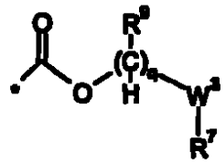


1*H*-purinyl (5.0.28)

where "*" indicates the point of attachment to the remaining portion of Formula (1 0 0), and where each carbon atom is optionally substituted by a substituent R^{14}, and where R^{14} and R^{15} have the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms, thereof

5 **5 1.3 D is a Moiety of Partial Formula (1.1.5)**

There are further embodiments of the compounds of Formula (1 0.0) in which the D moiety comprises a group falling within the scope of partial Formula (1 1 5).

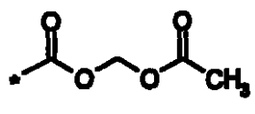


(1 1.5)

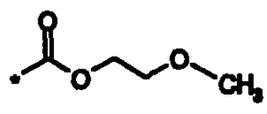
wherein q is 1, 2, or 3, provided that where q is 2 or 3, R^9 has the meaning of –H in at least one instance, or two instances, respectively; W^3 is –O–, –N(R^9)–; or –OC(=O)– where R^9 has the same meaning as defined above; and R^7 has the same meaning as defined above

In preferred embodiments of the compounds of partial Formula (1 1 5), q is 1 or 2, R^9 is –H, or $-CH_3$, W^3 is –O–, –O(C=O)–, or -NH–, and R^7 is one of the preferred moieties already described above.

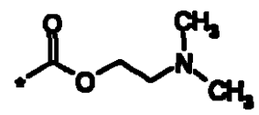
Representative embodiments of the compounds of Formula (1.0 0) in which the D moiety falls within the scope of partial Formula (1 1.5) are those illustrated by partial Formulas (6 0 1) through (6 0.6):



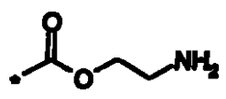
(6.0.1)



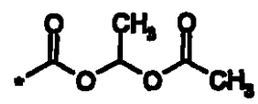
(6.0.2)



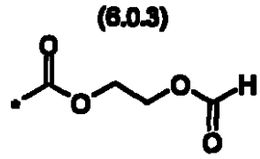
(6.0.3)



(6.0.4)



(6.0.5)

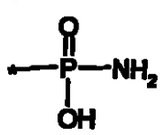


(6.0.6)

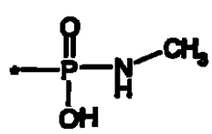
5.1.4 D is Other Than a Carboxylic Acid

Embodiments of the compounds of Formula (1.0.0) include those wherein the D moiety is other than a carboxylic acid and is, instead, a phosphorus or sulfur acid or a derivative thereof. There are a significant number of such derivatives from which the D moiety may be selected, and they include the following: -O-P(=O)(OH)$_2$ (phosphoric); -PH(=O)OH (phosphinic); -P(=O)(OH)$_2$ (phosphonic); -[P(=O)(OH)-O(C_1-C_4) alkyl] (alkylphosphono); -P(=O)(OH)-O(C_1-C_4) alkyl) (alkylphosphinyl); -P(=O)(OH)NH_2 (phosphoramido); -P(=O)(OH)NH(C_1-C_4) alkyl and -P(=O)(OH)NHR^{28} (substituted phosphoramido); -O-S(=O)$_2$OH (sulfuric); -S(=O)$_2$OH (sulfonic); -S(=O)$_2$$NHR^{28}$ or -NHS(=O)$_2$$R^{28}$ (sulfonamido) where R^{28} is $-CH_3$, $-CF_3$, or o-toluyl, and acylsulfonamido selected from the group consisting of -C(=O)NHS(=O)$_2$$R^{28}$; -C(=O)NHS(=O)$_2$$NH_2$, -C(=O)NHS(=O)$_2$($C_1$-$C_4$) alkyl; -C(=O)NHS(=O)$_2$NH($C_1$-$C_4$) alkyl, -C(=O)NHS(=O)$_2$N[($C_1$-$C_4$) alkyl]$_2$, -S(=O)$_2$NHC(=O)($C_1$-$C_4$) alkyl, -S(=O)$_2$NHC(=O)$NH_2$, -S(=O)$_2$NHC(=O)NH($C_1$-$C_4$) alkyl, -S(=O)$_2$NHC(=O)N[($C_1$-$C_4$) alkyl]$_2$, -S(=O)$_2$NHC(=O)$R^{28}$; -S(=O)$_2$NHCN, -S(=O)$_2$NHC(=S)$NH_2$, -S(=O)$_2$NHC(=S)NH($C_1$-$C_4$) alkyl, -S(=O)$_2$NHC(=S)N[($C_1$-$C_4$) alkyl]$_2$, and -S(=O)$_2$NHS(=O)$_2$$R^{28}$; where R^{28} is -H, -(C_1-C_4) alkyl; phenyl, or $-OR^{15}$, where R^{15} has the same meaning as defined above.

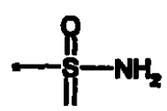
Preferred embodiments of the compounds of Formula (1.0.0) wherein D is a phosphorus or sulfur acid or a derivative thereof, are those wherein D is -P(=O)(OH)NHR^{28} (substituted phosphoramido); -S(=O)$_2$$NHR^{28}$ or -NHS(=O)$_2$$R^{28}$ (sulfonamido); or -C(=O)NHS(=O)$_2$$R^{28}$ (acylsulfonamido); where R^{28} and R^{28} has the same meaning as defined above. Some of these preferred embodiments may be illustrated by partial Formulas (6.5.1) through (6.5.9):



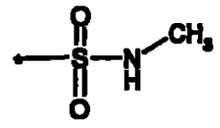
(6.5.1)



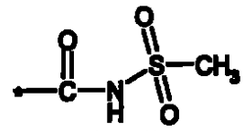
(6.5.2)



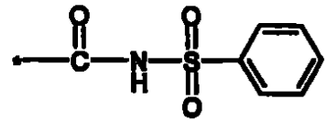
(6.5.3)



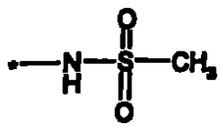
(6.5.4)



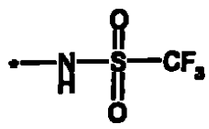
(6 5.5)



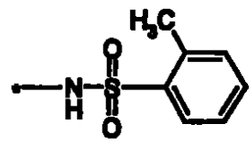
(6.5.6)



(6.5 7)



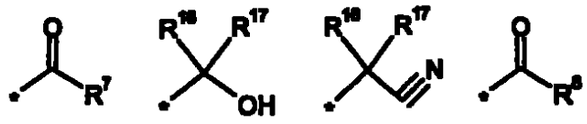
(6.5.8)



(6.5.9)

5.1.5 D is a Moiety of Partial Formulas (1.1 6) through (1 1.9)

There are further embodiments of the compounds of Formula (1 0 0) in which the D moiety comprises a group falling within the scope of partial Formulas (1 1.6) through (1 1.9)



(1 1 6) (1 1 7) (1 1.8) (1 1.9)

where R^7, R^8, R^{16}, and R^{17} have the same meaning as defined above For example, R^{16} and R^{17} are each independently selected from –H, –(C_1-C_4) alkyl, –(C_2-C_4) alkenyl, -(C_3-C_6) cycloalkyl, phenyl, benzyl, and pyridyl, wherein said alkyl, alkenyl, cycloalkyl, phenyl, benzyl, or pyridyl is substituted by 0 to 3 substituents selected from the group consisting of -F, –Cl, –CF_3, –CN, and –(C_1-C_3) alkyl

The keto groups of partial Formulas (1 1 6) and (1 1.9) are the same with respect to the carbonyl linking entity, but differ with respect to the attached group, R^7 or R^8



(1 1.6) (1 1 9)

R^7 in the moiety of partial Formula (1 1 6) has the same meaning as defined further above, but in preferred embodiments of the compounds of Formula (1.0 0) R^7 has especially the meaning of –H, –(C_1-C_8) alkyl, preferably methyl, ethyl, *iso*-propyl, or *tert*-butyl, –(C_2-C_8) alkenyl, preferably 2-propenyl, -(C_2-C_8) alkynyl, preferably ethynyl Each of these meanings of R^7 is optionally substituted by up to 3 substituents R^{10} The meaning of R^{10} is the same as defined above, but is preferably phenyl or pyridyl optionally substituted by up to 3 R^{11} where R^{11} is preferably –F, –CF_3, –CN, –CH_3, or –OCH_3. R^{10} also preferably has the meaning of –F, -CF_3, –OR^{16}, –CN, –C(=O)OR^{16}, –C(=O)$NR^{16}R^{17}$, –$NR^{16}R^{17}$, or –

$NR^{16}S(=O)_2R^{17}$, where R^{16} and R^{17} are preferably –H, methyl, ethyl, cyclopropyl, phenyl, benzyl, or pyridyl optionally substituted by up to 3 of –F, or 1 of $-CF_3$, -CN, or $-CH_3$.

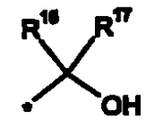
R^7 also has the meaning of $-(CH_2)_u-(C_3-C_7)$ cycloalkyl where u is preferably 0 or 1 and where (C_3-C_7) cycloalkyl is preferably cyclopropyl, cyclopentyl, or cyclohexyl optionally substituted by up to 3 substituents R^{10} where R^{10} has the same preferred meanings as defined in the paragraph immediately above

R^7 also has the meaning of phenyl or benzyl, where said phenyl or benzyl optionally substituted by up to 3 substituents R^{10} where R^{10} has the same preferred meanings as defined in the paragraph immediately above

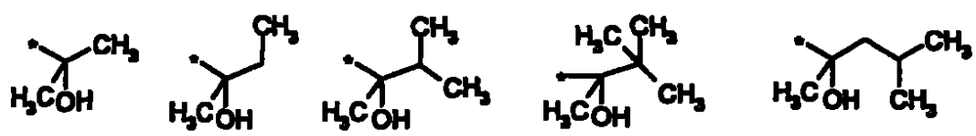
R^8 in the moiety of partial Formula (1 1 9) has the same meaning as defined further above, but in preferred embodiments of the compounds of Formula (1 0 0) R^8 has especially the meaning of tetrazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-5-yl, imidazol-2-yl, imidazol-4-yl, 1,3,4-oxadiazolyl; 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,5-thiadiazolyl; 1,3,4-thiadiazolyl, morpholinyl, oxazolyl, isoxazolyl; thiazolyl; isothiazolyl, pyrrolyl, pyrazolyl, pyridyl; indolyl, benzo[*b*]furanyl, 2,3-dihydrobenzofuranyl, 1*H*-indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl; benzothiazolyl, benzotriazolyl; quinolinyl, isoquinolinyl, quinazolinyl; or quinoxalinyl

Any of the above-recited especially preferred meanings of R^8 is optionally substituted on a carbon atom by R^{14} where R^{14} has the same meaning as defined above; and on a nitrogen atom by R^{15} where R^{15} has the same meaning as defined above. Especially included in the case of such nitrogen atom substituents, are all tautomer forms of the moieties of partial Formula (1 1.9). Sulfur atoms of said moieties are optionally substituted by 1 or 2 oxygen atoms

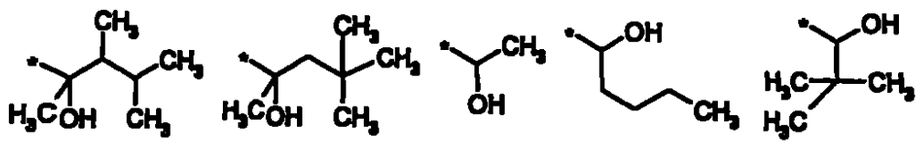
In order to illustrate further meanings of D that fall within the scope of partial Formulas (1 1 6), (1 1 7), (1 1.8), and (1 1.9), there are depicted below moieties of partial Formulas (3.3 1) through (3.3 15) that represent different meanings that fall within the scope partial Formula (1 1 7):



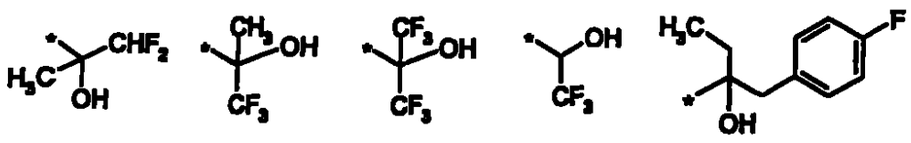
(1 1 7)



(3.3 1) (3.3.2) (3 3.3) (3 3.4) (3 3 5)



(3.3 6) (3.3 7) (3.3.8) (3.3 9) (3.3 10)

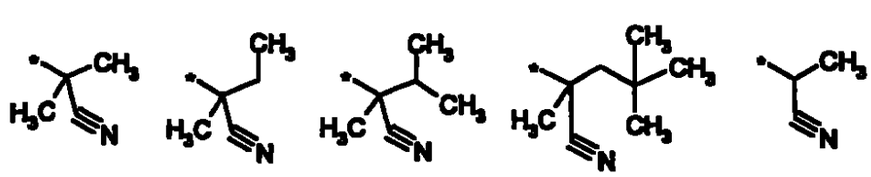


(3.3.11) (3.3 12) (3.3 13) (3.3 14) (3.3 15)

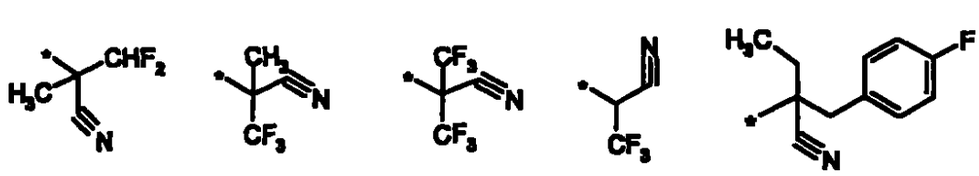
Further meanings of D are those that fall within the scope of partial Formula (1 1.8), in which a nitrile group, –C≡N, serves as a bioisosteric replacement for the hydroxyl group of partial Formula (1 1 7). Accordingly, there are depicted below moieties of partial Formulas (3.8.1) through (3.8 10) that represent different meanings that fall within the scope partial Formula (1 1.8):



(1 1.8)



(3.8 1) (3.8.2) (3.8.3) (3.8.4) (3.8 5)



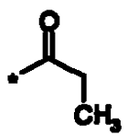
(3.8.6) (3 8.7) (3 8 8) (3.8 9) (3.8 10)

In order to illustrate additional meanings of D that fall within the scope of partial Formulas (1 1 6), (1 1 7), (1 1 8), and (1 1 9), there are depicted below moieties of partial

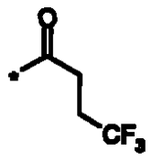
Formulas (3.9 1) through (3 9 9) that represent different meanings that fall within the scope partial Formulas (1 1 6) and (1 1.9)



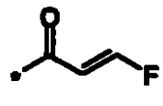
(1 1.6) (1 1.9)



(3 9 1)



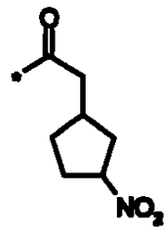
(3.9.2)



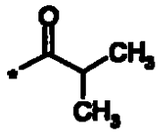
(3 9.3)



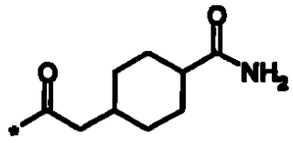
(3 9.4)



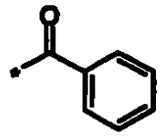
(3 9.5)



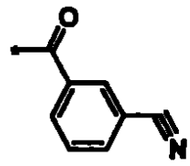
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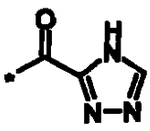
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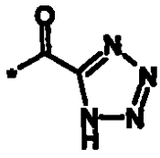
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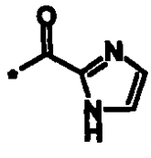
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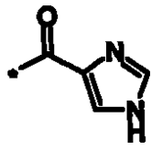
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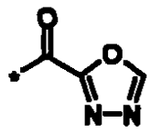
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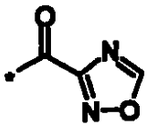
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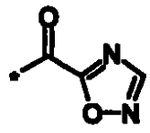
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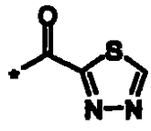
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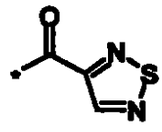
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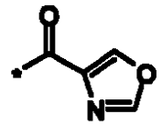
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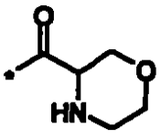
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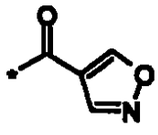
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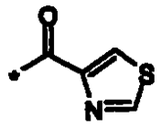
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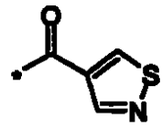
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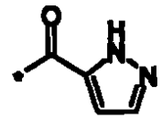
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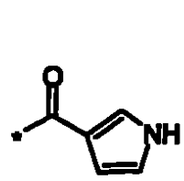
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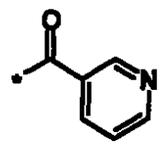
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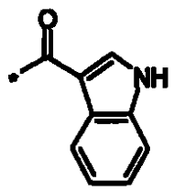
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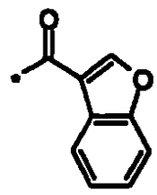
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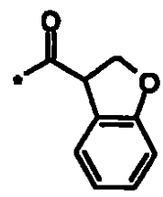
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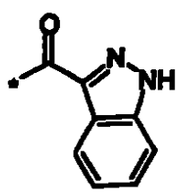
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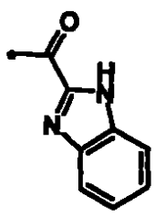
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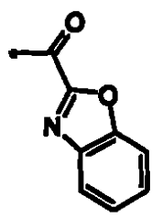
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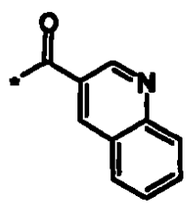
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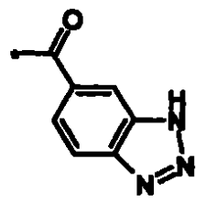
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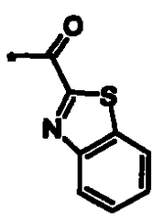
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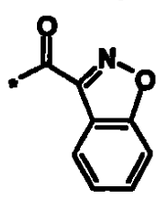
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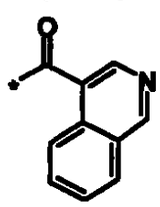
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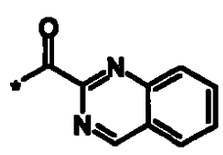
(3 9.35)



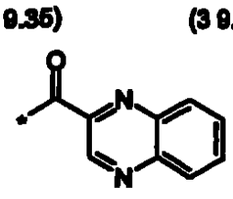
(3 9.36)



(3.9.37)



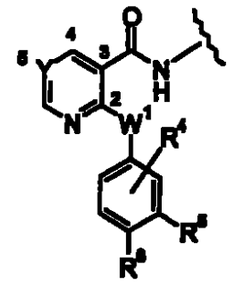
(3.9.38)



(3.9.39)

5.2 Linkage W^1 and (R^4–, R^5–, and R^5)–Substituted Moiety J^1

The nicotinamide core nucleus is further elaborated by allowing the 2-carbon atom in the pyridyl or pyrimidinyl ring of said nucleus to form a linkage to a ring comprising the moiety J^1. In preferred embodiments, the moiety J^1 has the meaning of a phenyl ring which is *para*-substituted by a moiety R^5, *meta*-substituted by a moiety R^5, or substituted on any of the remaining positions by a moiety R^4, resulting in a moiety of partial Formula (1 0.3):



(1.0.3)

where W^1 has the meaning –O–, $–S(=O)_t–$, where t is 0, 1, or 2, or $–N(R^3)–$ where R^3 is –H, $–(C_1–C_3)$ alkyl, phenyl, benzyl, or $–OR^{16}$; and is preferably –H or $–CH_3$.

In other embodiments of the present invention, W^1 has the meaning $–S(=O)_t–$, where t is 0, 1, or 2, and preferably has the meaning –S– whereby a thioether linkage is formed Where the sulfur atom of the thioether linkage is oxygenated, a sulfinyl or a sulfonyl linkage results In still further embodiments, where W^1 has the meaning of $–N(R^3)–$, an amino linkage is formed, which preferably will be –NH– Nevertheless, the nitrogen atom may be substituted and where this is the case, it is preferred that said substituent be $–CH_3$.

The meanings of the R^4, R^5 and R^6 substituents are selected from the same set of definitions, but it will be understood that said meanings are selected on an independent basis from each other R^5 and R^6 may also be –H Accordingly, where the moiety J^1 has the meaning of a phenyl ring, the *para*- (R^6), *meta*- (R^5), or *ortho*- (R^4)-position of the phenyl ring may be substituted, or all three positions may be substituted, or any combination of said positions may be substituted It is preferred, however, in the compounds of Formula (1.0.0) that the *para*- and/or *meta*-positions be substituted, rather than the *ortho*-position.

Where the moiety J^1 has the preferred meaning of a phenyl ring, R^5 and R^6 may also be taken together to form a member selected from a group of partial formulas described in more detail further below Some of these meanings of R^5 and R^6 taken together also constitute preferred embodiments of the compounds of Formula (1 0.0)

R^5 and R^6 may be –H In addition to –H, R^5 and R^6 may, *inter alia*, be –F, –Cl, –CN, $–NO_2$, $–C(=O)R^{16}$; $–OR^{16}$; $–C(=O)OR^{16}$; or $–NR^{16}R^{17}$ Where R^5 is –H and R^6 is –F, preferred embodiments of the present invention result. In a further preferred embodiment of the present invention, R^5 and R^6 may also be $–OR^{16}$, where R^{16} is hydrogen, $(C_1–C_4)$ alkyl; or $(C_3–C_6)$ cycloalkyl, wherein said alkyl and cycloalkyl are substituted by 0 to 3 substituents selected from the group consisting of –F and –Cl Other preferred embodiments are those wherein R^{16} is methyl, difluoromethyl, ethyl, or cyclopentyl

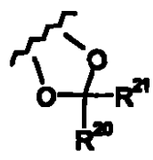
The medicinal chemist will appreciate that the choice of substituents from those described above will be influenced by the effect which such substituents have in turn on the physico-chemical properties of the overall molecules which result. The present state of the art provides the capability of quickly and facilely synthesizing a very large number of chemically very similar compounds based on the substituent choices outlined above, and of thereafter testing the relative effectiveness of the resulting molecules in rapid *in vitro* testing methods. Combinatorial chemistry synthesis and testing procedures currently available in the art have even more considerably expanded the number of substituent combinations which can be rapidly evaluated. The information which has thereby been produced through use of these techniques permits a reasonable prediction herein of certain preferences which exist as to various embodiments of the present invention. Such preferred embodiments are described in detail herein.

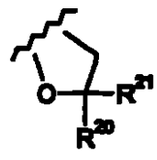
Preferred embodiments of the present invention further include those wherein both R^5 and R^6 are both –F, wherein R^5 is –H and R^6 is –F, and wherein R^5 is –H and R^6 is –F, $-OR^{10}$, *e.g.*, $-OCH_3$, $-OCH_2F$, $-OCHF_2$, or $-OCF_3$, -CN, –COOH; $-COOCH_3$, $-CONH_2$, $-OCOCH_3$, or NH_2. The most preferred embodiments are those wherein R^5 is –H and R^6 is -F, R^5 is –CN and R^6 is –H, and R^5 is $-NO_2$, $-NH_2$, –CN, $-OCH_3$, or $-C(=O)CH_3$, and R^6 is –H.

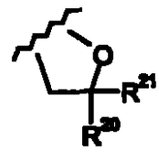
R^5 and R^6 may also be selected from substituents comprising $-(C_1-C_4)$ alkyl and $-(C_1-C_4)$ alkoxy wherein said alkyl and alkoxy are substituted with 0 to 3 substituents –F or -Cl; or 0 or 1 substituent (C_1-C_2) alkoxycarbonyl–; (C_1-C_2) alkylcarbonyl–; or (C_1-C_2) alkylcarbonyloxy–.

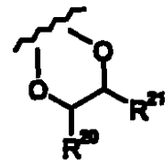
5 3 0 J^1 is Phenyl and R^5 and R^6 Are Taken Together

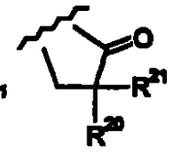
Where the moiety J^1 has the preferred meaning of a phenyl ring, R^5 and R^6 may also be taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3 1) through (1.3 15):

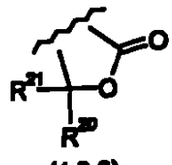

(1.3 1)

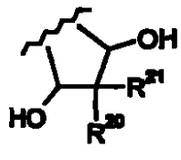

(1 3.2)

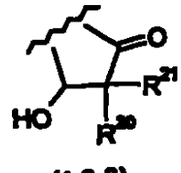

(1 3.3)

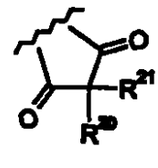

(1.3.4)

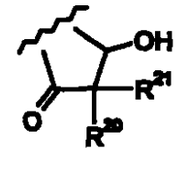

(1.3 5)

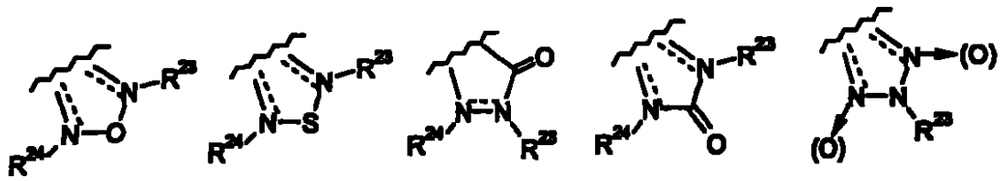

(1.3.6)


(1.3 7)


(1.3.8)


(1.3 9)


(1.3 10)

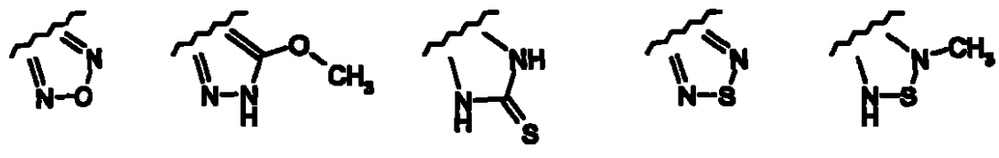


(1 3 11) (1.3 12) (1.3 13) (1 3.14) (1.3 15)

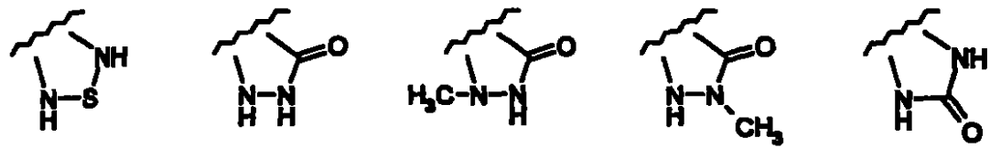
wherein R^{20} and R^{21} are each a member independently selected from the group consisting of –H, –F, –Cl; $–CH_3$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–OCH_3$, and $–OCF_3$, and R^{23} and R^{24} are each independently –H, $–CH_3$; $—OCH_3$, $–CH_2CH_3$, $–OCH_2CH_3$, $–CH_2CH_2CH_3$, $–CH_2(CH_3)_2$, $–CH_2CH_2CH_2CH_3$, $–CH(CH_3)CH_2CH_3$, $–CH_2CH(CH_3)_2$, $–C(CH_3)_3$, or absent, in which case the dashed line – – – – represents a double bond. For the moiety of partial Formula (1.3.13) the nitrogen atom components thereof are represented as –[N(⇒O)]– and thus comprise optional nitrogen oxide forms of said nitrogen atoms, selected independently of each other It will be appreciated that said nitrogen oxide form may also be represented as $–N(⇒O)_j–$ where j is 0 or 1, as in Formula (1 0 0).

Where the moiety J^1 has the preferred meaning of a phenyl ring, and where R^5 and R^6 are taken together to form the moiety of partial Formula (1.3 1), and R^{20} and R^{21} are both hydrogen, there is formed together with the phenyl group to which it is attached, a 1,3-benzodioxole group Analogously, the structure of partial Formula (1.3.4) forms a 1,4-benzodioxan group

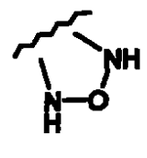
Where the moiety J^1 has the preferred meaning of a phenyl ring, and where R^5 and R^6 are taken together to form the moieties of partial Formulas (1.3 1) through (1.3.15), and R^{23} and R^{24} are as defined, benzofurazan, benzothiazan, triazole, and other analogous groups, as well as substituted derivatives thereof are formed, including, *inter alia*, the following moieties of partial Formulas (2.1 1) through (2 1.20):



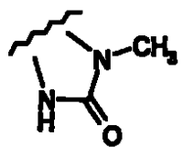
(2.1 1) (2.1.2) (2.1.3) (2.1.4) (2 1.5)



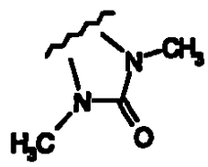
(2.1 6) (2 1 7) (2.1.8) (2 1 9) (2.1 10)



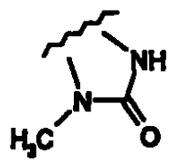
(2 1 11)



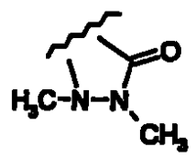
(2.1 12)



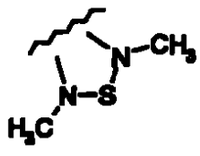
(2 1 13)



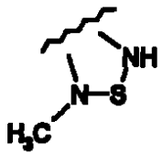
(2.1 14)



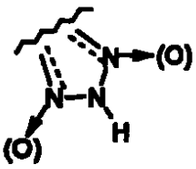
(2.1 15)



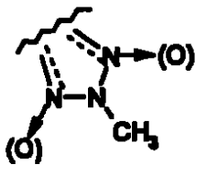
(2.1 16)



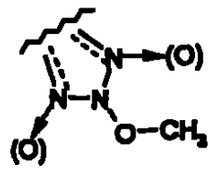
(2.1 17)



(2 1 18)



(2 1 19)

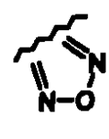


(2 1.20)

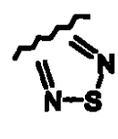
wherein the dashed line ---- in partial Formulas (2.1 16), (2 1 19), and (2.1.20) represents a double bond where no oxygen atom is attached to the corresponding nitrogen atom, and represents a single bond where an oxygen atom is attached to said corresponding nitrogen atom

The artisan of ordinary skill in the preparation of organic molecules will appreciate that the compounds of Formula (1.0 0) wherein R^5 and R^6 are taken together to form moieties of the above-illustrated partial Formulas (2 1.2), (2 1.3), (2 1 7), (2 1 8), (2 1 10), (2.1 12), and (2.1 14) exist in tautomeric form, and each moiety of said partial Formulas (2 1.2), (2 1.3), (2 1 7), (2.1.8), (2 1 10), (2.1 12), and (2 1 14) has a tautomer counterpart. These tautomers are related by the shift of a hydrogen and one or more π-bonds, and whenever necessary, the skilled artisan will be able to readily discern or determine which tautomeric form is present or is the most stable

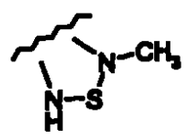
Still more preferred embodiments of the type comprising the moieties of partial Formulas (2 1 1) through (2 1.20) illustrated above are those wherein R^5 and R^6 are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (2.1 1), (2.1.4) through (2 1 6), (2.1 11), and (2 1 16) through (2.1.20):



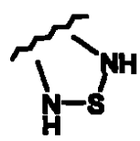
(2 1 1)



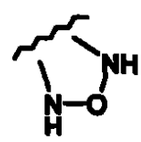
(2 1.4)



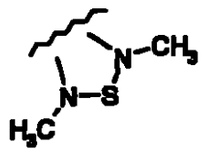
(2 1.5)

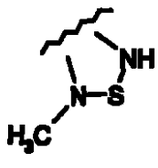


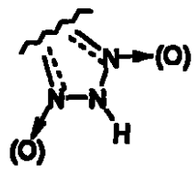
(2.1.6)

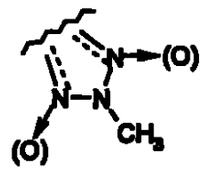


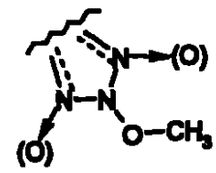
(2 1 11)


(2 1 16)


(2.1 17)

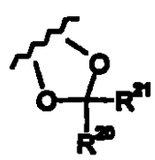

(2 1 18)

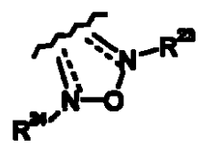

(2.1 19)

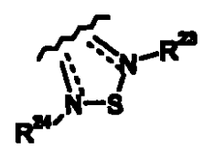

(2.1.20)

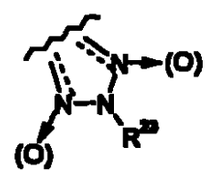
wherein the dashed line ---- in partial Formulas (2.1 18), (2 1 19), and (2 1.20) represents a double bond where no oxygen atom is attached to the corresponding nitrogen atom, and represents a single bond where an oxygen atom is attached to said corresponding nitrogen atom.

Preferred embodiments of the present invention result directly from the definition of R^5 and R^6 as taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3.1), (1.3 11), (1.3.12), and (1.3 15):

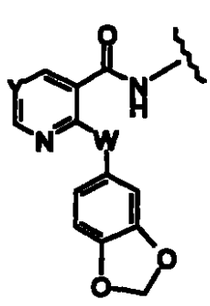

(1.3 1)

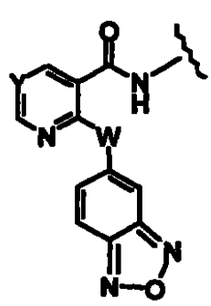

(1.3.11)

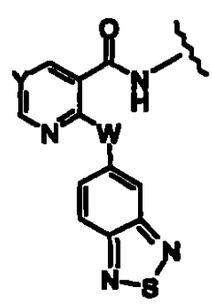

(1.3.12)

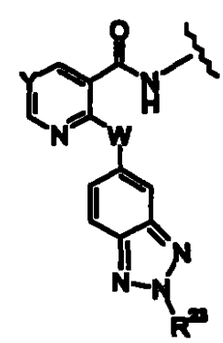

(1.3 15)

Accordingly, there further results moieties of partial Formulas (1.0 15) through (1.0.18):


(1 0 15)


(1.0 16)


(1 0 17)


(1 0.18)

where R^{23} is –H or $–CH_3$, and W has the meaning of –O–; $–S(=O)_t–$ where t is 0,1, or 2, or $–N(R^3)–$ where R^3 is as defined herein and is preferably –H or $–CH_3$. In preferred compounds of Formula (1 0 0), W has the meaning of –O– whereby an ether linkage is created to attach the benzo-fused, bicyclic heterocycle to the nicotinamide core nucleus

In preferred embodiments of the compounds of Formula (1.0.0), R^{23} and R^{24} are both absent, except in compounds of the type illustrated by partial Formula (1.3.11), where only one of R^{23} or R^{24} may be absent. It will be recognized that where R^{23} and R^{24} are both absent, and the dashed lines - - - accordingly represent double bonds, that the phenyl

portion of the resulting benzo-fused bicyclic heterocycles depicted cannot have all of the double bonds depicted in said partial Formulas, since the result would be prohibited pentavalent carbon atoms in said phenyl portion

Accordingly, where R^{23} and R^{24} are both absent, the resulting compounds are characterized by such structures as those shown in partial Formulas (1.0 16) and (1 0 17) above.

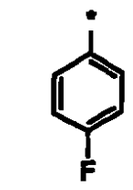
In other embodiments of the compounds of Formula (1.0.0) the substituents R^{20} and R^{21} on the benzo-fused, bicyclic heterocycles represented by partial Formula (1.3.1) are –H, –F, –Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. Preferably, R^{20} and R^{21} are both –H or –F, in which case the resulting compounds are characterized by the structure shown in partial Formula (1.0 15) above, or its corresponding difluoro analog (not shown). The substituents R^{23} and R^{24} on the benzo-fused, bicyclic heterocycles represented by the moieties of partial Formulas (1.3 9) through (1.3 13) are each independently –H, $-CH_3$, $-OCH_3$, or absent in which case the dashed line – – – – represents a double bond It will be understood, of course, that where R^{23} and R^{24} are absent; there are no pentavalent carbon atoms in the phenyl portion of said benzo-fused, bicyclic heterocyles. The resulting benzo-fused, bicyclic heterocyclic structures are shown in partial Formulas (1.0 16) through (1 0 18) above.

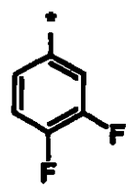
5.3.1 J^1 is Other Than Phenyl

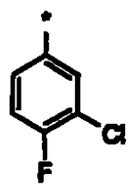
In addition to those embodiments of the present invention where J^1 has the preferred meaning of phenyl, the present invention has also been defined above as being concerned with a compound of Formula (1.0 0) wherein J^1 has the meaning defined above as a moiety comprising a saturated or unsaturated carbon ring system that is 3- to 7-membered monocyclic, or that is 7- to 12-membered, fused or discontinuous, polycyclic; wherein optionally one carbon atom thereof may be replaced by a heteroatom selected from N, O, or S, and where N is selected, optionally a second carbon atom thereof may be replaced by a heteroatom selected from N, O, or S The present invention is further concerned with a compound of Formula (1.0 0) wherein J^1 comprises especially a member selected from the group consisting of phenyl, pyrrolyl, pyrrolidinyl, furanyl; thienyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl, imidazolyl, imidazolidinyl, oxazolyl, isoxazolyl, morpholinyl; thiazolyl, indolyl, quinolinyl; isoquinolinyl, benzimidazolyl, benzoxazolyl, quinuclidinyl, and azabicyclo[3.3.0]octanyl, a monocyclic $-(C_3-C_7)$ cycloalkyl moiety; a monocyclic $-(C_5-C_7)$ cycloalkenyl moiety that is a member selected from the group consisting of cyclopentanyl, cyclohexanyl, and cycloheptanyl, and a bicyclic $-(C_7-C_{10})$ cycloalkyl or $-(C_7-C_{10})$ cycloalkenyl moiety that is a member selected from the group consisting of norbomanyl, norbomenyl, bicyclo[2.2.2]octanyl, bicyclo[3.2 1]octanyl, bicyclo[3.3 0]octanyl,

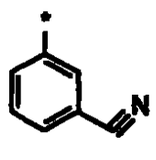
bicyclo[2.2.2]oct-5-enyl, bicyclo[2.2.2]oct-7-enyl, bicyclo[3.3.1]nonanyl, cyclodecanyl, and adamantanyl

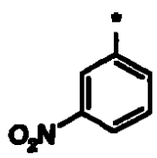
The present invention is still further concerned especially with a compound of Formula (1.0.0) wherein particularly J^1 and the substituents R^4, R^5, and R^6 are selected in such a way that the left-hand terminus of said compound of Formula (1.0.0) is represented by the following partial Formulas (1.8.1) through (1.8.72):

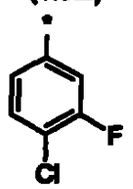

(1.8.1)

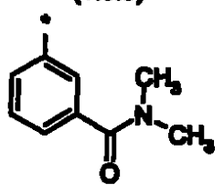

(1.8.2)

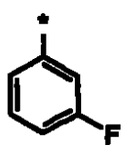

(1.8.3)

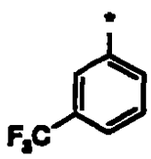

(1.8.4)

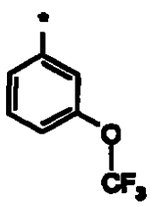

(1.8.5)

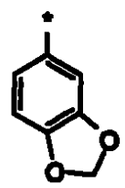

(1.8.6)

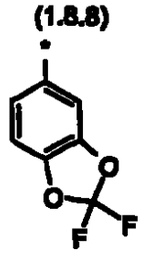

(1.8.7)

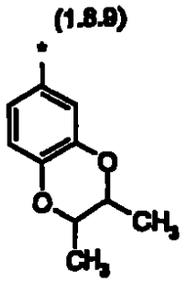

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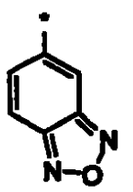

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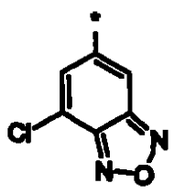

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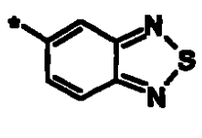

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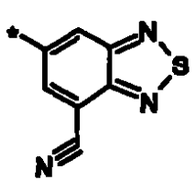

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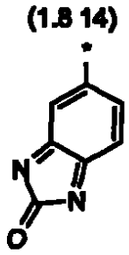

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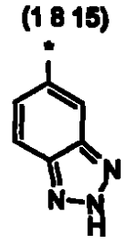

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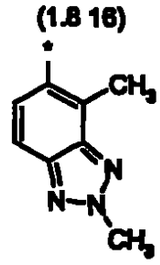

(1.8.15)


(1.8.16)


(1.8.17)

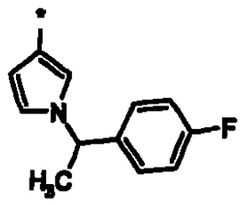

(1.8.18)


(1.8.19)

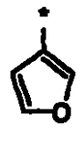

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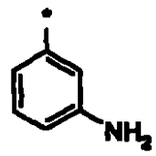
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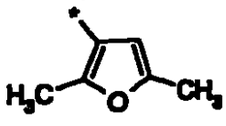
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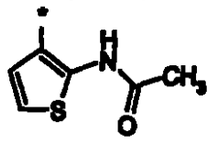
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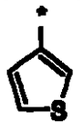
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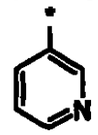
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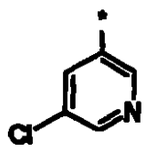
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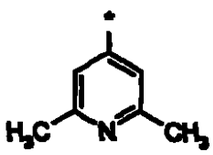
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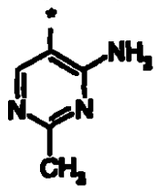
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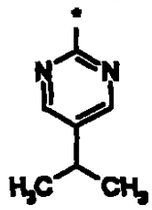
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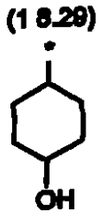
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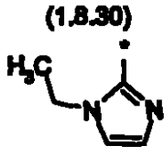
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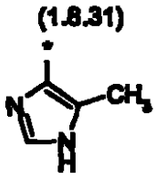
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(1.8.33)



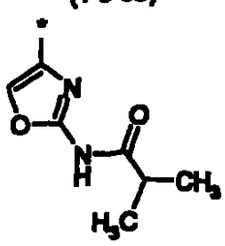
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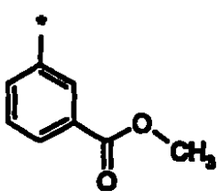
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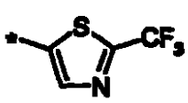
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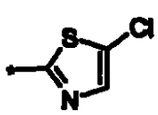
(1.8.37)



(1.8.38)



(1.8.39)



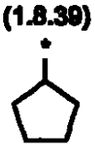
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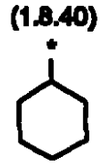
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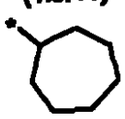
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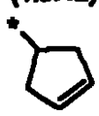
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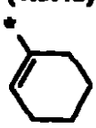
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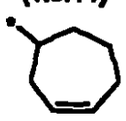
(1.8.45)



(1.8.46)



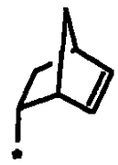
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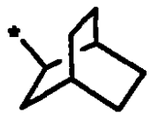
(1.8.48)



(1.8.49)



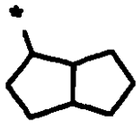
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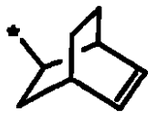
(1.8.51)



(1.8.52)



(1.8.53)



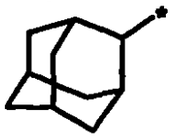
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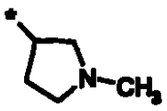
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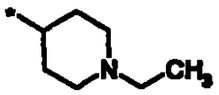
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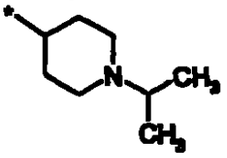
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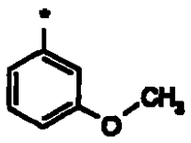
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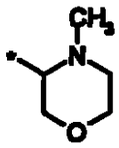
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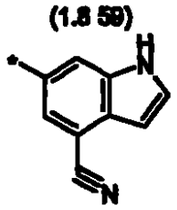
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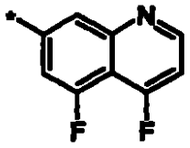
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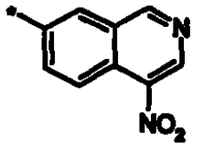
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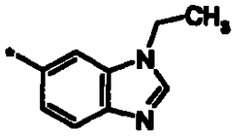
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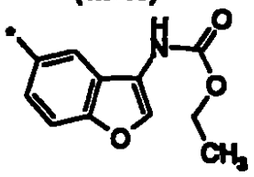
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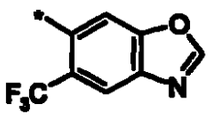
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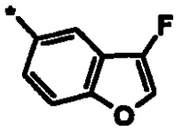
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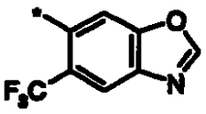
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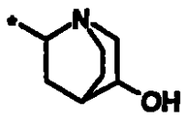
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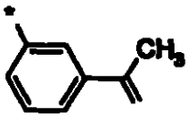
(1.8.69)



(1.8.70)



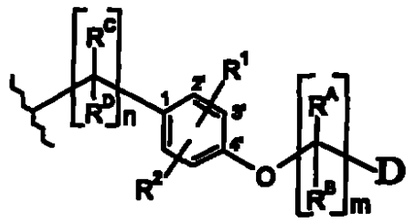
(1.8.71)



(1.8.72)

The character of the nicotinamide nucleus with an ether, thioether or sulfonyl linkage to a substituted phenyl group, which forms the left-hand-side of the compound of Formula (1.0.0), has been discussed above. The right-hand-side of the compound of Formula (1.0.0) comprises, in preferred embodiments where J^2 has the preferred meaning of phenyl a benzyl group which is substituted by substituents R^1 and R^2. Preferably, only a single substituent, R^1 or R^2 is present, the single substituent R^1 or R^2 is in the 2'-position, and the benzyl group is substituted in the 4-position by the moiety containing the substituents R^A, R^B,

and D This preferred right-hand-side of the compound of Formula (1.0 0) may be represented by Formula (1 0.4):



(1.0.4)

5,4.0 J^2 is Phenyl Substituted by R^1 and R^2

The R^1 and R^2 substituents are each a member independently selected from the group consisting of –H; –F, –Cl, (C_1 -C_3)alkyl; fluorinated– and/or chlorinated–(C_1 -C_3) alkyl; fluorinated– and/or chlorinated–(C_1 -C_3)alkoxy; (C_2 –C_4)alkynyl, -CN, $–NO_2$, $–OR^{18}$; and -C(=O)NH_2. Where R^1 and/or R^2 is –H there will be no substituent at any position, especially the 2-position of the phenyl group, attached to the remainder of the left-hand side of the molecule of Formula (1 0.0) Such embodiments are not as preferred as those compounds of the present invention which have a substituent, especially one at the 2-position of the phenyl group. Thus, in some preferred embodiments of the compounds of the present invention, the meaning of R^1 and R^2 is defined as –H; –Cl, –F, chlorinated– and/or fluorinated–(C_1-C_3) alkyl; chlorinated– and/or fluorinated–(C_1 -C_3) alkoxy; or (C_2 –C_4)alkynyl

Where a 6-membered carbon ring system is involved, *e g.*, as in the case of cyclohexyl, phenyl, or pyridyl, it is preferred in particular that such a moiety defining J^2 be attached at its 1- and 4-positions, *i.e* , that the points of attachment of said moiety be in *para* relationship to each other However, other configurations of such a 6-membered carbon ring system defining J^2 are within the scope of the compounds of Formula (1.0.0), e g., where the points of attachment are at the 1- and 2-positions, or at the 1- and 3-positions of said 6-membered carbon ring system

It is preferred to have a halogen group at the point of the molecule occupied by the R^1 or R^2 substituent, since it usually results in improved performance It is contemplated to be within the scope of the present invention that R^1 or R^2 is a small lipophilic group comprising -Cl or –F, chlorinated– and/or fluorinated–(C_1-C_3) alkyl, or chlorinated– and/or fluorinated-(C_1 -C_3) alkoxy Thus, the meaning of the R^1 or R^2 substituent, as well as of any other substituent of a compound of Formula (1 0 0) that includes the definitions –Cl or –F; chlorinated– and/or fluorinated–(C_1-C_3) alkyl, or chlorinated– and/or fluorinated-(C_1-C_3) alkoxy, is selected from the group consisting of the following

—F —CH_2F —CHF_2 —CF_3 —CH_2CHF_2

—CH_2CHCF_2 —CH_2CF_3 -$CHFCH_2F$ -$CHFCHF_2$ —$CHFCF_3$

—$CF_2CF_2CF_3$ —O—CH_2F —O—CHF_2 —O—CF_3 —O—CH_2CH_2F

—O—CH_2CHF_2 —O—CH_2CF_3 —O—$CHFCH_2F$ —O—$CHFCHF_2$ —O—$CHFCF_3$

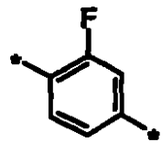
—O—CF_2CH_2F —O—CF_2CHF_2 —O—CF_2CF_3

The selectivity of the overall molecule which is achieved by utilizing a moiety of this type as the R^1 and R^2 substituent may be due to the conformational alignment of the lipophilic moiety with a corresponding lipophilic zone in the PDE4 or PDE4D enzyme substrate, or it may be due to the change in the lipophilicity of the overall molecule which results. Whatever the actual mechanism by which such selectivity is achieved, all such embodiments are contemplated to be within the scope of the present invention.

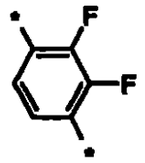
5.4.1 J^2 is Other Than Phenyl

The present invention has also been defined above as being concerned with a compound of Formula (1 0 0) wherein J^2 has the meaning defined above as a moiety comprising a saturated or unsaturated carbon ring system that is 3- to 7-membered monocyclic, or that is 7- to 12-membered, fused or discontinuous, polycyclic; wherein optionally one carbon atom thereof may be replaced by a heteroatom selected from N, O, or S, and where N is selected, optionally a second carbon atom thereof may be replaced by a heteroatom selected from N, O, or S The present invention is further concerned with a compound of Formula (1.0.0) wherein J^2 comprises especially a member selected from the group consisting of phenyl; pyrrolyl, pyrrolidinyl, furanyl, thienyl; pyridyl, pyrimidinyl, piperidinyl; piperazinyl; imidazolyl, imidazolidinyl; oxazolyl, isoxazolyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl; morpholinyl, quinuclidinyl, and azabicyclo[3.3 0]octanyl, a monocyclic -(C_3-C_7) cycloalkyl moiety; a monocyclic -(C_5-C_7) cycloalkenyl moiety that is a member selected from the group consisting of cyclopentenyl, cyclohexenyl, and cycloheptenyl, and a bicyclic -(C_7-C_{10}) cycloalkyl or -(C_7-C_{10}) cycloalkenyl moiety that is a member selected from the group consisting of norbornanyl, norbornenyl, bicyclo[2.2.2]octanyl, bicyclo[3.2 1]octanyl, bicyclo[3.3 0]octanyl, bicyclo[2.2.2]oct-5-enyl, bicyclo[2.2.2]oct-7-enyl, bicyclo[3.3 1]nonanyl, cyclodecanyl, and adamantanyl

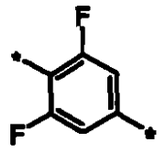
The present invention is also further concerned especially with a compound of Formula (1 0 0) wherein particularly J^2 and the substituents R^1 and R^2 are selected in such a way that this portion of the right-hand terminus of said compound of Formula (1.0 0) is represented by the following partial Formulas (3 0 1) through (3 0.47) set out below



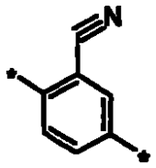
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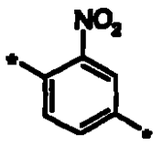
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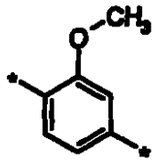
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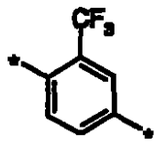
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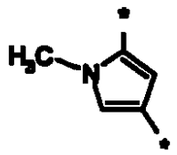
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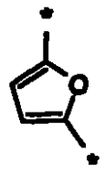
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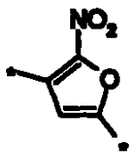
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(3.0.8)



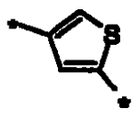
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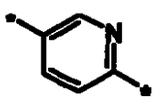
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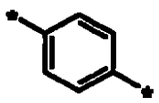
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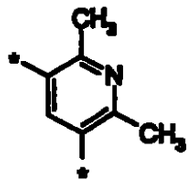
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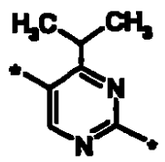
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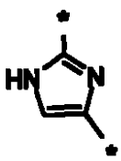
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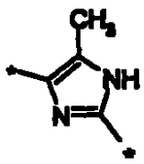
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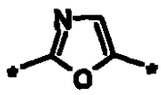
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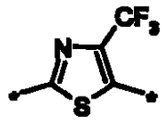
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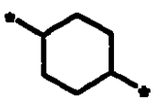
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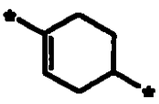
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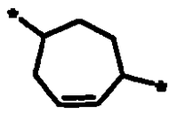
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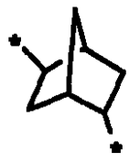
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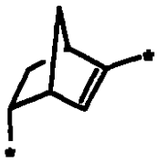
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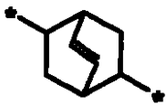
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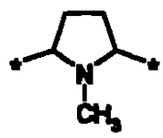
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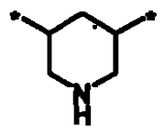
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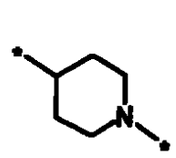
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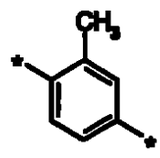
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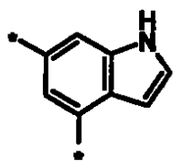
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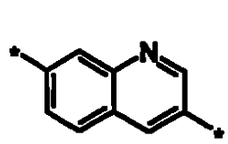
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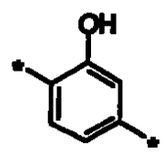
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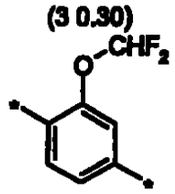
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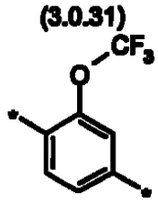
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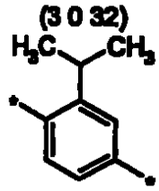
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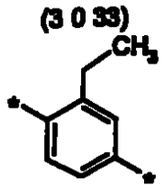
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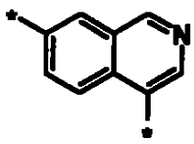
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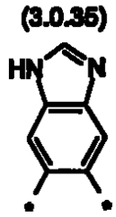
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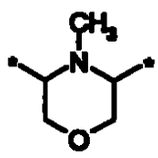
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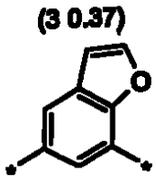
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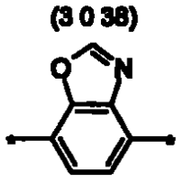
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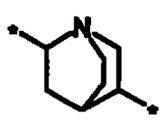
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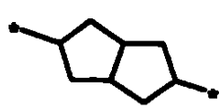
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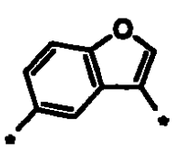
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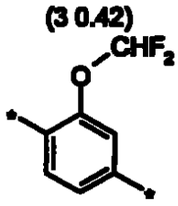
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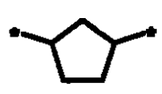
(3.0.44)



(3 0.45)



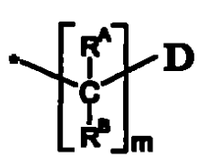
(3 0.46)



(3 0.47)

5.5 The R^A and R^B Substituents

The group of partial Formula (1.0.4) above is substituted in the 4-position by a moiety containing the substituents D, R^A, and R^B, which may be represented by partial Formula (1 1.8):

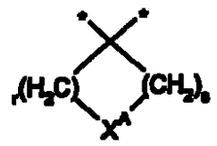


(1 1.8)

where m is 1, 2, or 3 In the more preferred embodiments of the compounds of the present invention, m has the meaning of 0 or 1 When m is 1 the moiety $-[R^A-C-R^B]_m-$ is present,

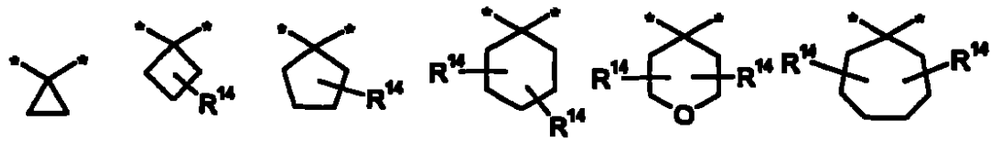
and R^A and R^B are preferably each a member independently selected from the group consisting of -H and (C_1-C_4) alkyl, more preferably –H and –CH_3.

In other preferred embodiments of the present invention R^A and R^B may be taken together, but only in the case where m is 1, to form a spiro moiety of Formula (1.2.0):

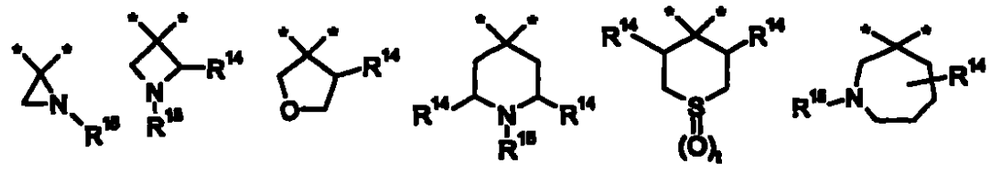


(1.2.0)

where r and s are independently 0 to 4 provided that the sum of r + s is at least 1, but not greater than 5, X^A is –CH_2–, –CHR^{11}–, or –$C(R^{11})_2$– where each R^{11} is selected independently of the other and each R^{11} has the same meaning as defined herein; –NR^{15}– where R^{15} has the same meaning as defined herein, –O–; or –$S(=O)_t$–, where t is 0, 1, or 2; and said spiro moiety is substituted as to any one or more carbon atoms thereof by 0 to 3 substituents R^{14}, as to a nitrogen atom thereof by 0 or 1 substituent R^{15}, and as to a sulfur atom thereof by 0 or 2 oxygen atoms. Accordingly, there results, *inter alia*, the moieties illustrated by partial Formulas (1.2 1) through (1.2 12):



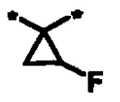
(1.2.1) (1.2.2) (1.2.3) (1.2.4) (1.2.5) (1.2.6)

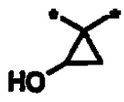


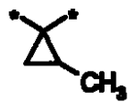
(1.2.7) (1.2.8) (1.2.9) (1.2 10) (1.2 11) (1.2.12)

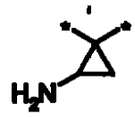
where t is 0, 1, or 2; and R^{14} and R^{15} have the same meaning as defined herein.

Preferred meanings of the R^{14} substituent include –F; –Cl, =O; –OH, –CH_3, –OCH_3, -C(=O)OH; –$C(=O)NH_2$, –NH_2, –$NHCH(CH_3)_2$, –$NHC(=O)CH_3$, –$NHC(=O)OCH_2CH_3$, -$NHS(=O)_2CH_3$, and –$S(=O)_2NH_2$, resulting in moieties such as those of partial Formulas (3 1 1) through (3 1.34)

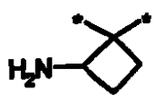

(3 1 1)


(3 1.2)

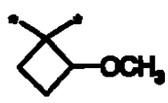

(3.1.3)


(3 1.4)

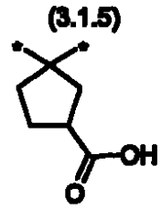

(3.1.5)

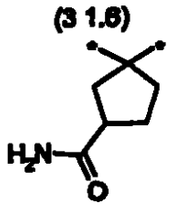

(3 1.6)

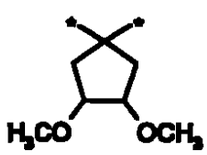

(3 1 7)

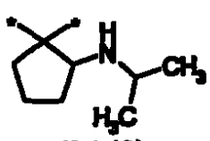

(3 1.8)


(3 1.9)

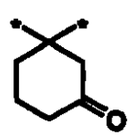

(3 1 10)

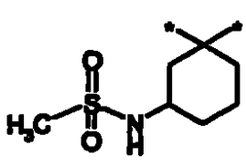

(3 1 11)

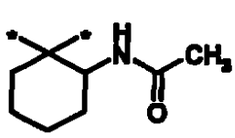

(3 1 12)

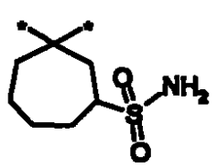

(3 1 13)

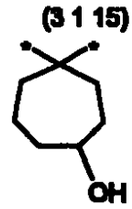

(3.1 14)

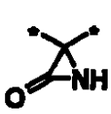

(3 1 15)

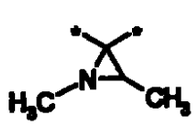

(3 1 16)


(3.1 17)

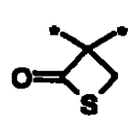

(3 1 18)


(3.1 19)

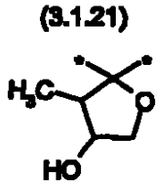

(3 1.20)

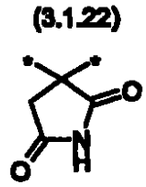

(3.1.21)


(3.1.22)

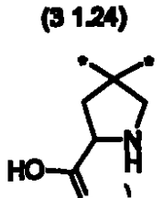

(3.1.23)

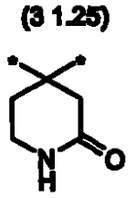

(3 1.24)

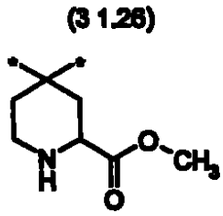

(3 1.25)

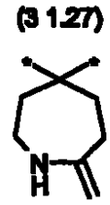

(3 1.26)

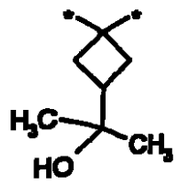

(3 1.27)

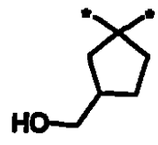

(3 1.28)

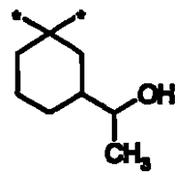

(3 1.29)


(3 1.30)


(3.1.31)


(3 1.32)


(3 1.33)


(3.1.34)

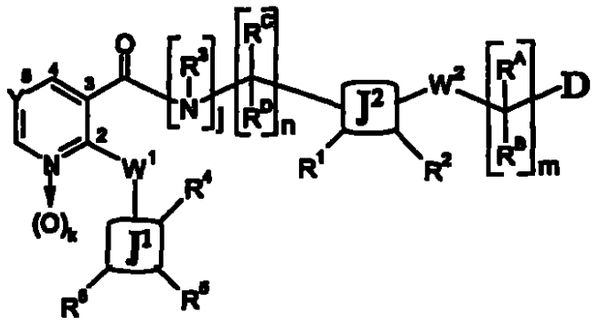
5.6 The R^C and R^D Substituents

As already described, R^C and R^D have the same meaning as defined above for R^A and R^B, except that one of them must be –H, and they are selected independently of each other and of R^A and R^B. Accordingly, all of the particular and preferred embodiments of the compounds of Formula (1 0 0) detailed above with regard to the R^A and R^B substituents, are for the most part also particular and preferred embodiments of the compounds of Formula (1 0 0) with regard to the R^C and R^D substituents.

5.7 The Moiety —$[N(R^3)]_j$—

The subscript j has the meaning of 0 or 1. Where j has the meaning of 1, which is the preferred meaning, the moiety —$N(R^3)$— is present and the compounds of Formula (1 0.0) are essentially nicotinamides in structure with respect to the left-hand side of the core nucleus. The nitrogen atom substituent R^3 is preferably selected from –H, –(C_1-C_2) alkyl, and –(C_1-C_2) alkoxy; and is more preferably –H; $-CH_3$, or $-OCH_3$. In the most preferred embodiments of the compounds of Formula (1 0 0), R^3 has the meaning of –H.

Where J^1 and J^2 both have the prefered meaning of phenyl, and j has the meaning of 0, which is a less preferred meaning than where j is 1, the moiety —$N(R^3)$— is absent and the compounds of Formula (1.0 0) are essentially nicotinoyl moieties, *i.e.*, ketones in structure with respect to the left-hand side of the core nucleus. Such a ketone structure in the left-hand side of the core nucleus, together with benzyl as a preferred meaning of the J moiety, is represented by Formula (1.0 7):



(1.0 7)

where all of the substituents and components thereof, *i.e.*, D, W, Y; k, m, and n; R^1, R^2, R^4, R^5, and R^6; and R^A, R^B, R^C, and R^D, have, for the most part, the same particular and preferred meanings described in detail herein as in the case where j is 1 and the left-hand side of the core nucleus of the compounds is a nicotinamide in structure

5.8 Preferred Subgenus and Species Embodiments of Formula (1.0.0)

In the above description various preferred aspects of the compounds of Formula (1.0.0) have been set forth. As a further demonstration of the scope and the content of the present invention, subgeneric embodiments of the compounds of Formula (1.0.0) are presented. Such preferred embodiments include, but are not limited to, those recited in the following paragraphs (i) through (viii):

(i) A compound according to Formula (1.0.0) wherein where m is 1 or 2, and n is 1, ♦ R^A and R^B are –H, $-CF_3$, or $-(C_1-C_6)$ alkyl substituted by 0 or 1 of –F, -Cl, $-CF_3$, –CN, $-NH_2$, or $-C(=O)NH_2$, or both taken together are spiro $-(C_3-C_6)$ cycloalkyl– substituted by 0 or 1 of –F, -Cl, $-CF_3$, or –CN, ♦ one of R^C and R^D is -H, and the other is –H, $-(C_1-C_4)$ alkyl, or phenyl, each substituted by 0 or 1 of -F, -Cl, or –CN, ♦ W^1 is –O– or –S–; ♦ W^2 is –O–; ♦ Y is $=C(R^1{}_a)-$ where $R^1{}_a$ is -H, –F, –Cl, -CN, $-CH_3$, or $-OCH_3$, ♦ R^1 and R^2 are -H, –F, –Cl, -CN, $-NO_2$, -OH, $-CH_3$, $-OCH_3$, $-OCHF_2$, or $-OCF_2$, ♦ R^3 is -H or $-CH_3$, ♦ R^4 is –H, –F, –CN, $-NO_2$, -OH, $-CH_3$, or $-OCH_3$, ♦ J^1 is phenyl; ♦ R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1) where R^{20} and R^{21} are –H or $-CH_3$, or a moiety of partial Formula (1.3.11), (1.3.12), or (1.3.15) where R^{23} and R^{24} are absent or are –H, or $-CH_3$, ♦ J^2 is phenyl, norbornanyl, furanyl, thienyl, pyrimidinyl, or cyclohexyl, ♦ and D is $-C(=O)OR^7$ where R^7 is -H or $-CH_3$, $-C(=O)NH_2$, or tetrazol-5-yl,

(ii) A compound according to paragraph (i) wherein R^A and R^B are both $-CH_3$, or one is $-CH_3$ and the other is $-CH(CH_3)_2$ or $-C(CH_3)_3$, or one is –H and the other is $-CH_3$ or $-CF_3$, or both taken together are spiro cyclopropyl or spiro cyclobutyl, ♦ one of R^C and R^D is -H and the other is –H or $-CH_3$, W^1 is –O–; ♦ Y is $=C(R^1{}_a)-$ where $R^1{}_a$ is –H, –F, or -Cl, ♦ R^1 and R^2 are –H, -F, or Cl, ♦ R^3 is –H, ♦ R^4 is –H, ♦ R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1) or (1.3.11) where R^{23} and R^{24} are both absent; ♦ J^2 is phenyl, thienyl, or cyclohexyl, ♦ and D is $-C(=O)OR^7$ where R^7 is –H or $-CH_3$, $-C(=O)NH_2$, or tetrazol-5-yl;

(iii) A compound according to paragraph (ii) wherein R^A and R^B are both $-CH_3$, or both taken together are spiro cyclopropyl, ◆ one of R^C and R^D is -H and the other is –H or $-CH_3$, ◆ Y is $=C(R^1_a)-$ where R^1_a is –H, –F, or –Cl; ◆ R^1 and R^2 are –H, -F, or Cl, ◆ R^3 is -H, ◆ R^4 is –H, ◆ R^5 and R^6 are taken together to form a moiety of partial Formula (1.3 11) where R^{23} and R^{24} are both absent; ◆ J^2 is phenyl, ◆ and D is $-C(=O)OR^7$ where R^7 is –H or $-CH_3$, $-C(=O)NH_2$, or tetrazol-5-yl,

(iv) A compound according to paragraph (iii) wherein R^A and R^B are both $-CH_3$, ◆ R^C and R^D are both –H, ◆ Y is $=C(R^1_a)-$ where R^1_a is –H, ◆ and one of R^1 and R^2 is –H and the other is –F,

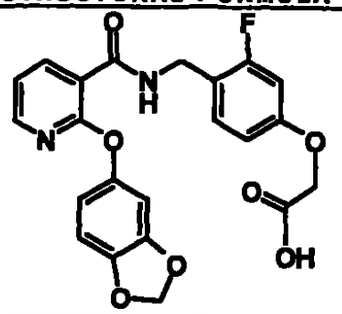
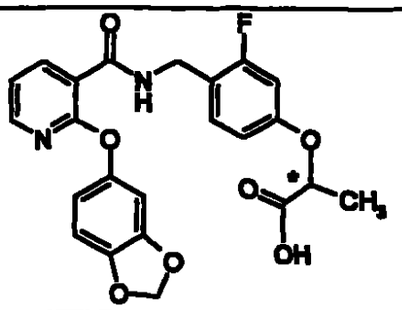
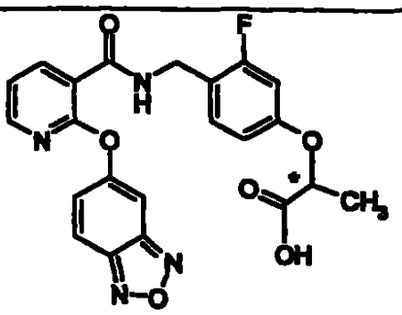
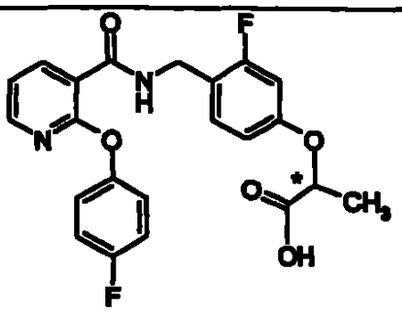
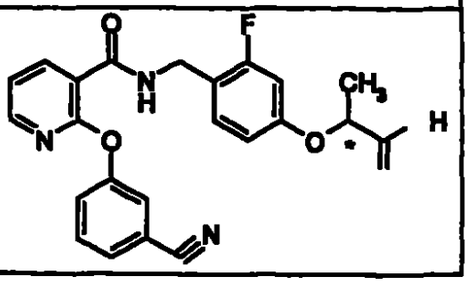
(v) A compound according to paragraph (iii) wherein Y is $=C(R^1_a)-$ where R^1_a is –F, ◆ and R^1 and R^2 are both –H,

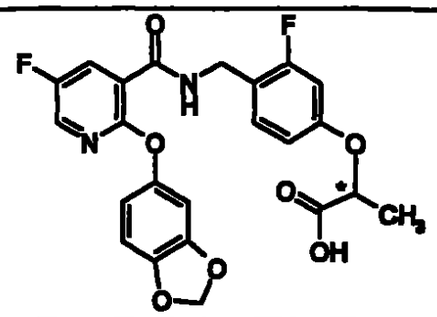
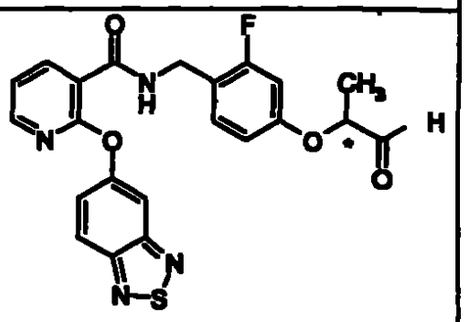
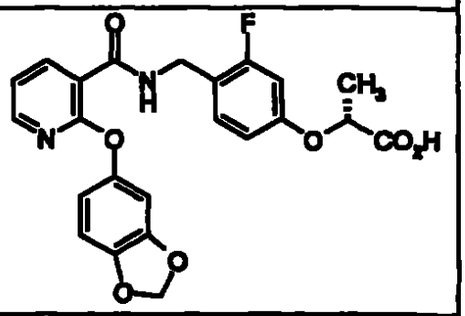
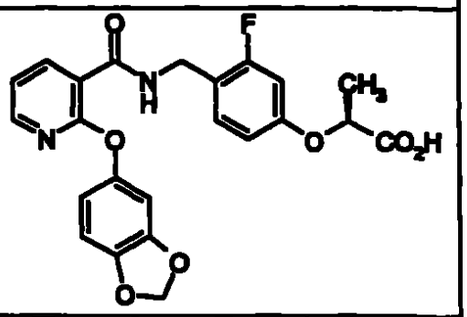
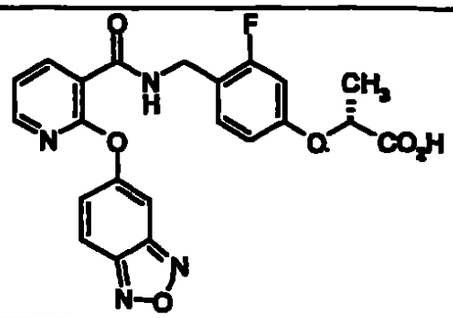
(vi) A compound according to paragraph (ii) wherein R^A and R^B are both $-CH_3$, or both taken together are spiro cyclopropyl, ◆ one of R^C and R^D is -H and the other is –H or $-CH_3$, ◆ Y is $=C(R^1_a)-$ where R^1_a is –H, –F, or –Cl, ◆ R^1 and R^2 are –H, -F, or Cl, ◆ R^3 is -H, ◆ R^4 is –H, R^5 and R^6 are taken together to form a moiety of partial Formula (1.3 1) where R^{20} and R^{21} are both –H, ◆ J^2 is phenyl, ◆ and D is $-C(=O)OR^7$ where R^7 is –H or $-CH_3$, $-C(=O)NH_2$, or tetrazol-5-yl;

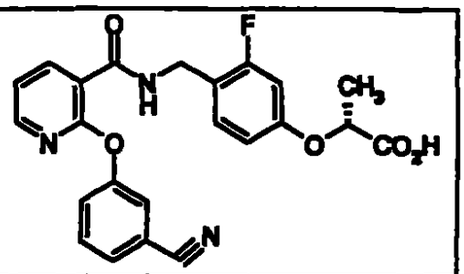
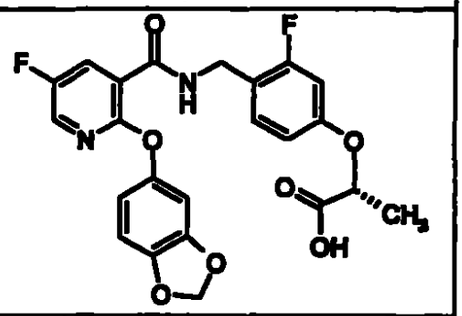
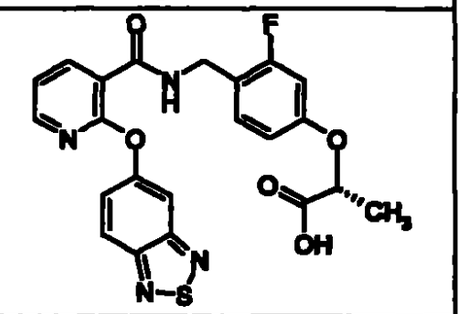
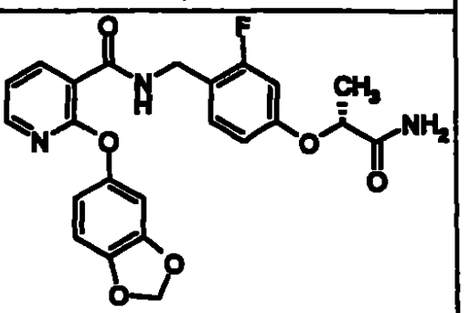
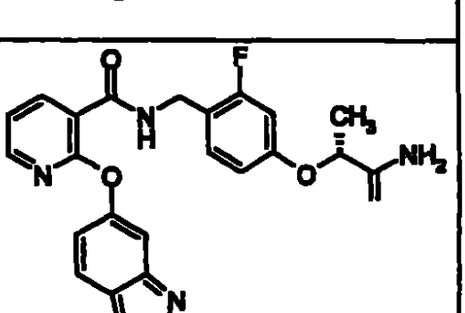
(vii) A compound according to paragraph (vi) wherein R^A and R^B are both $-CH_3$, ◆ R^C and R^D are both –H, ◆ Y is $=C(R^1_a)-$ where R^1_a is –H, ◆ and one of R^1 and R^2 is –H and the other is –F, and

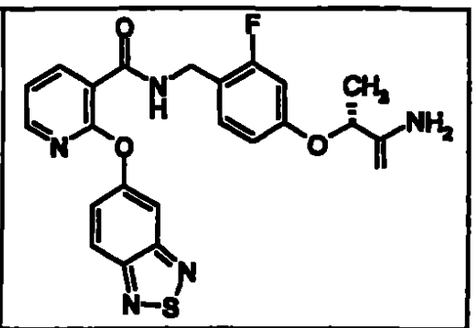
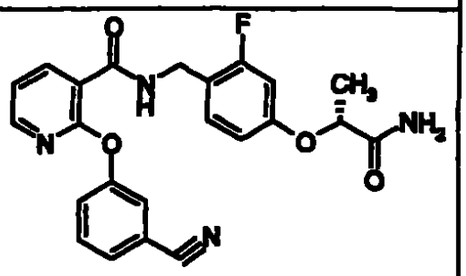
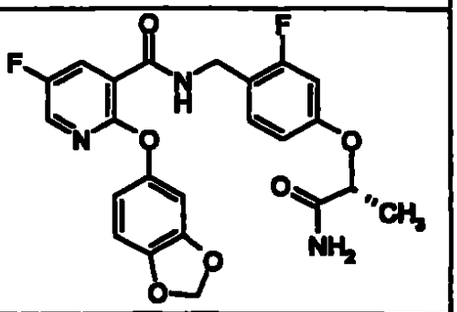
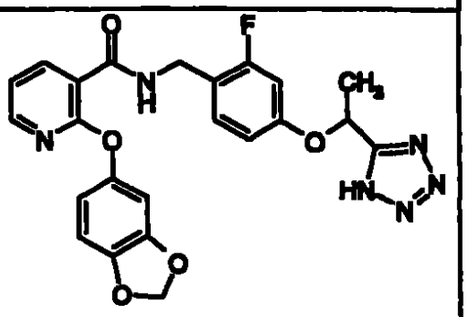
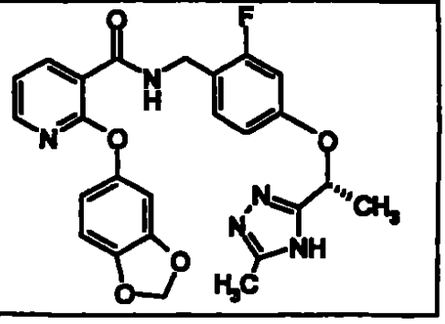
(viii) A compound according to paragraph (vii) wherein Y is $=C(R^1_a)-$ where R^1_a is –F, ◆ and R^1 and R^2 are both –H

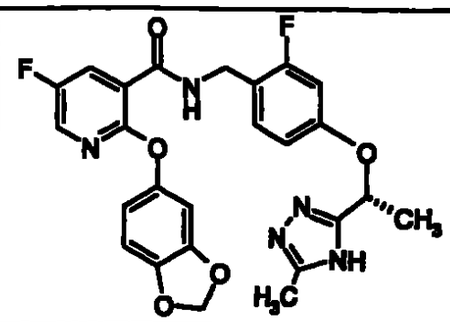
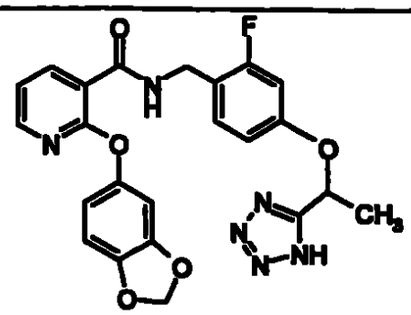
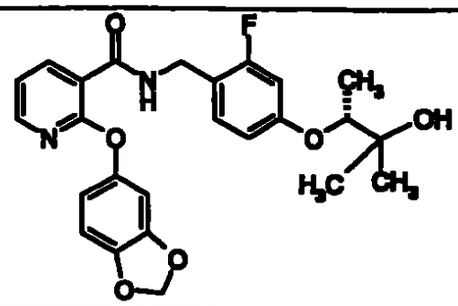
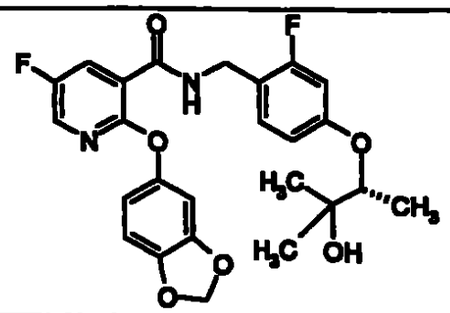
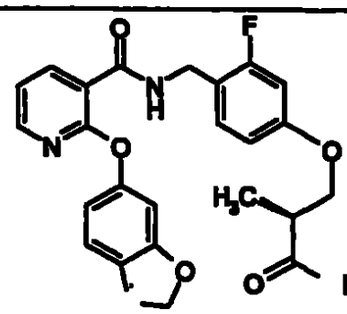
The above description various preferred aspects of the compounds of Formula (1.0 0) have been set forth As a further demonstration of the scope and the content of the present invention, specific compounds comprising embodiments of the compounds of Formula (1 0 0) are presented Such species of Formula (1 0.0) include, but are not limited to the following compounds of Formulas (5.5 1) through (5 5 106)

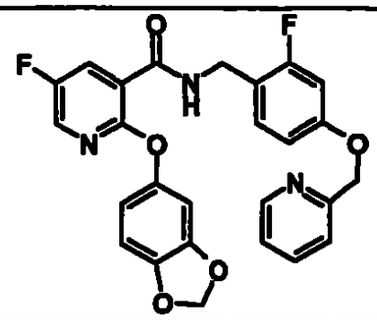
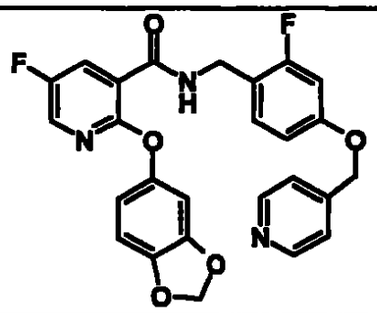
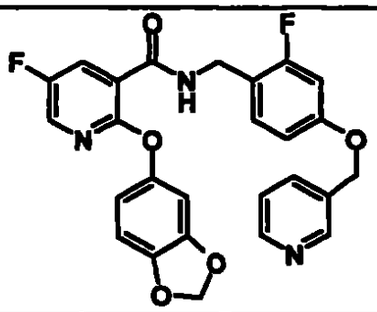
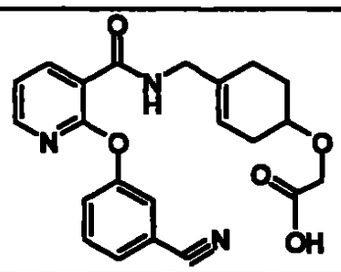
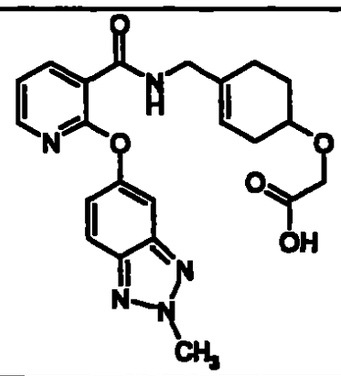
NOMENCLATURE	STRUCTURAL FORMULA
[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid of Formula (5.5.1);	
(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.2);	
(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.3);	
(±)-2-[3-Fluoro-4-({[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.4);	
(±)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.5);	

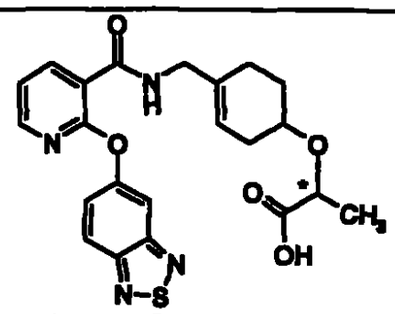
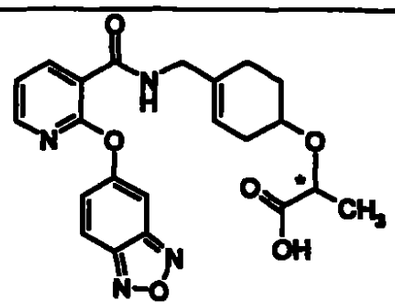
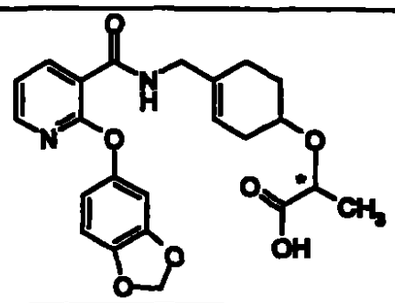
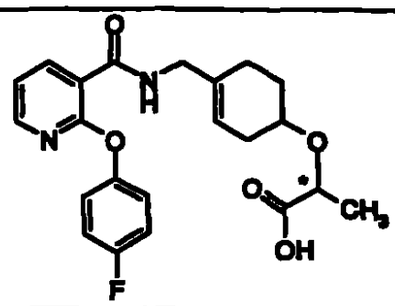
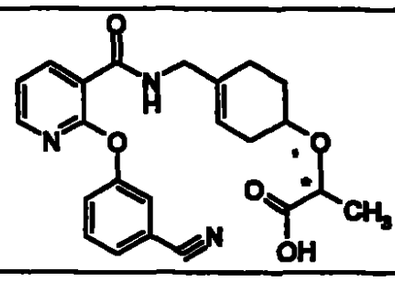
(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.6);	
(±)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.7);	
(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.8);	
(S)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.9);	
(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5.10);	

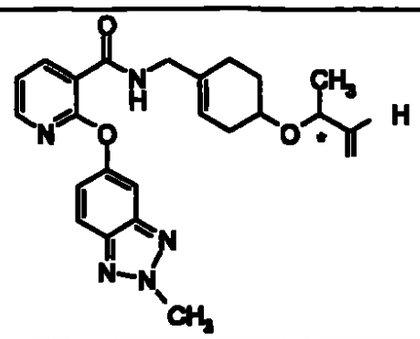
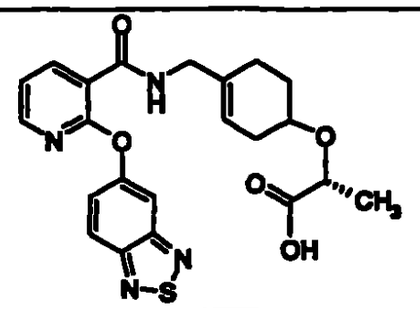
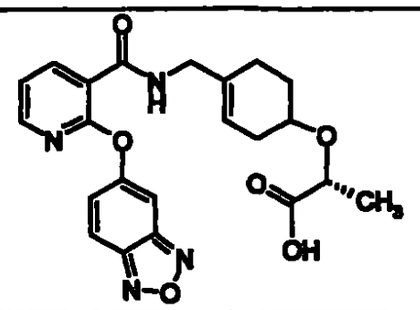
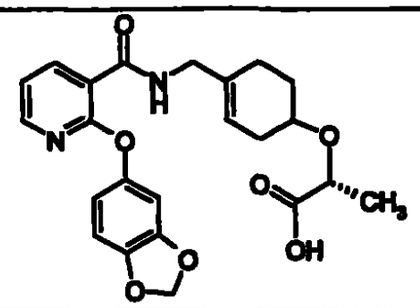
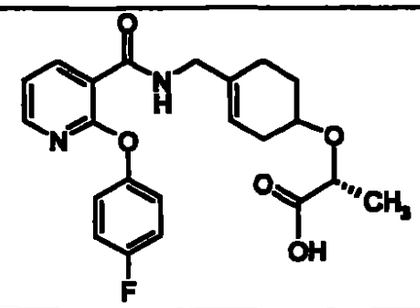
(R)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.11);	
(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5 12);	
(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.13);	
(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5.14);	
(R)-2-(Benzo[2,1,3]oxadiazol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5.15);	

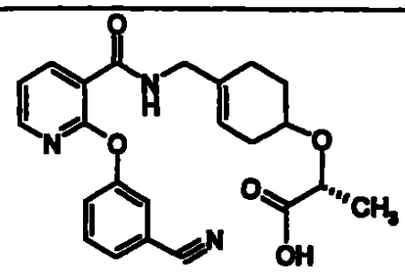
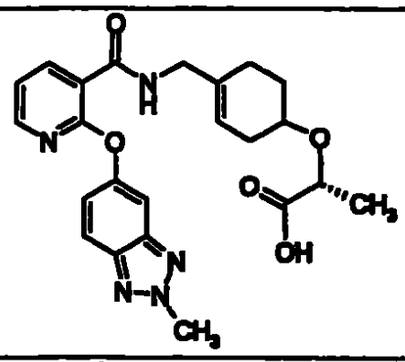
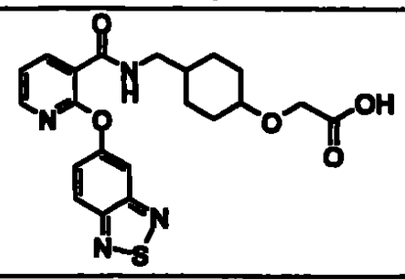
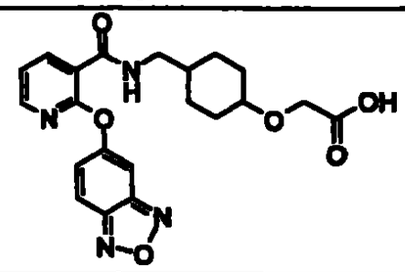
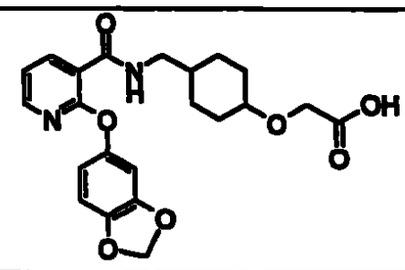
(R)-2-(Benzo[2,1,3]thiadiazol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5.16);	
(R)-N-[4-(1-Carbamoyl-ethoxy)-2-fluoro-benzyl]-2-(3-cyano-phenoxy)-nicotinamide of Formula (5.5.17);	
(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-5-fluoro-nicotinamide of Formula (5.5.18);	
(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5 19);	
(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.20);	

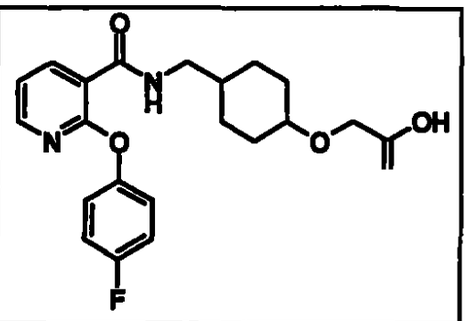
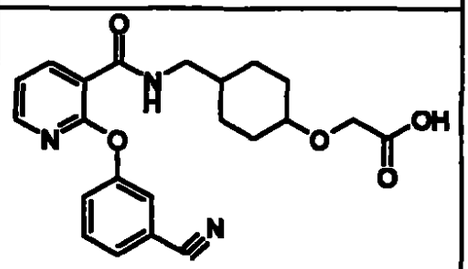
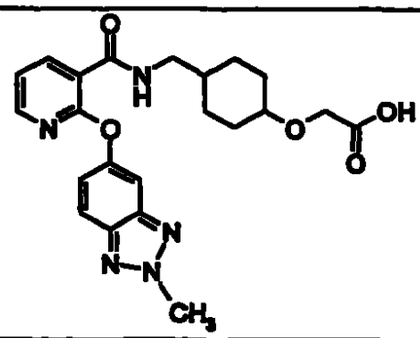
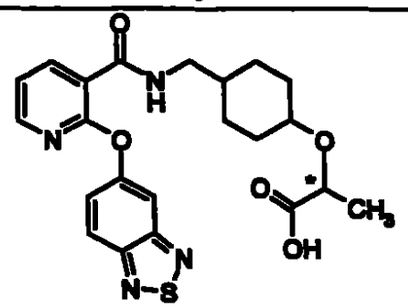
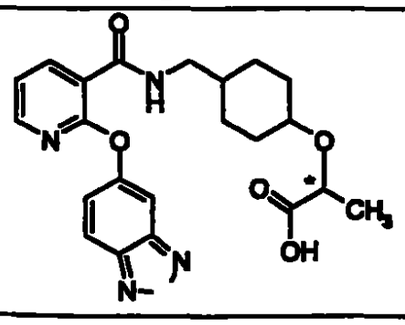
(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.21);	
(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.22);	
(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-(2-hydroxy-1,2-dimethyl-propoxy)-benzyl]-nicotinamide of Formula (5.5.23);	
(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(2-hydroxy-1,2-dimethyl-propoxy)-benzyl]-nicotinamide of Formula (5 5.24);	
(S)-3-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.25);	

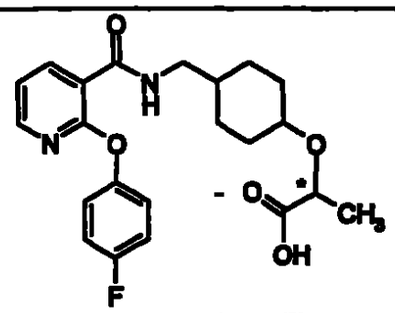
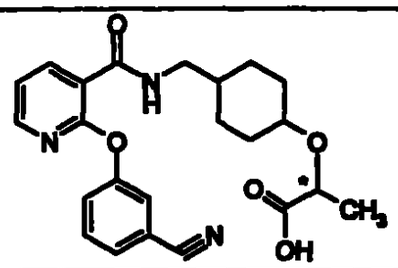
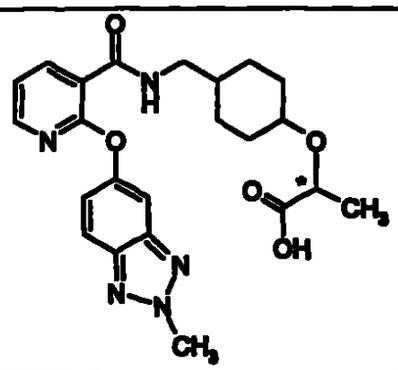
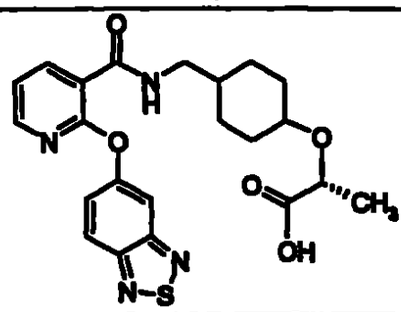
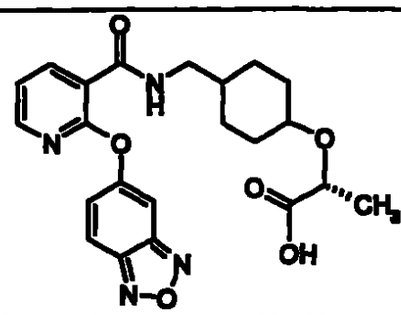
2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-2-ylmethoxy)-benzyl]-nicotinamide of Formula (5.5.26);	
2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-4-ylmethoxy)-benzyl]-nicotinamide of Formula (5.5.27);	
2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-3-ylmethoxy)-benzyl]-nicotinamide of Formula (5.5.28),	
[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.29);	
[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.30);	

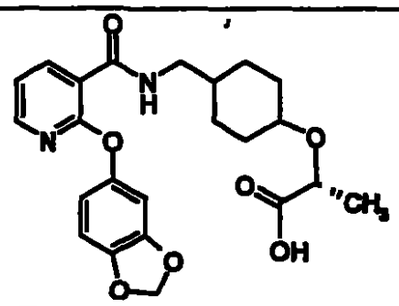
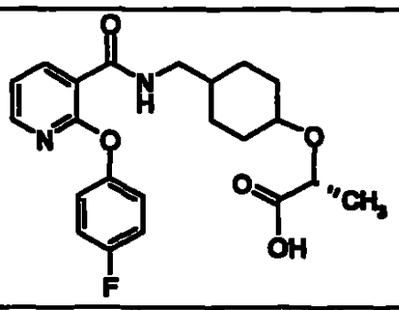
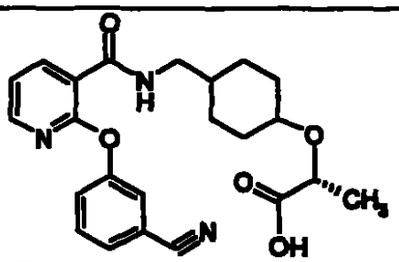
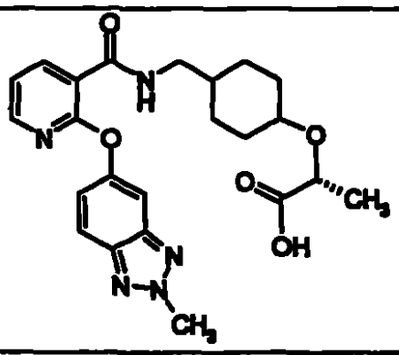
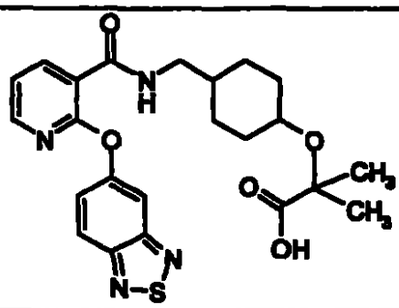
(±)-2-[4-([2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.31);	
(±)-2-[4-([2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5 32);	
(±)-2-[4-([2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.33);	
(±)-2-[4-([2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino)-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.34),	
(±)-2-[4-([2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino)-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.35);	

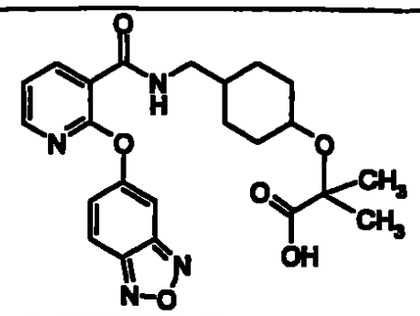
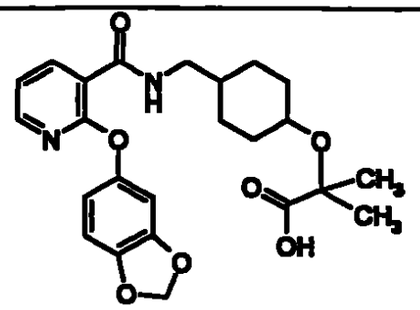
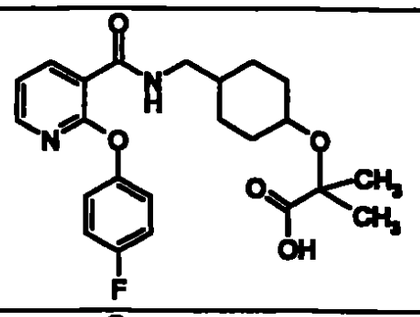
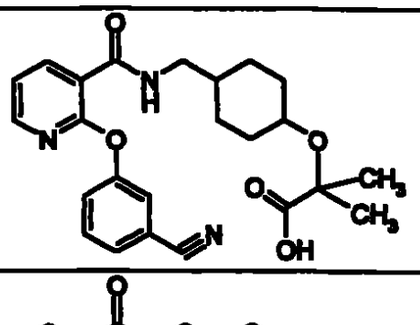
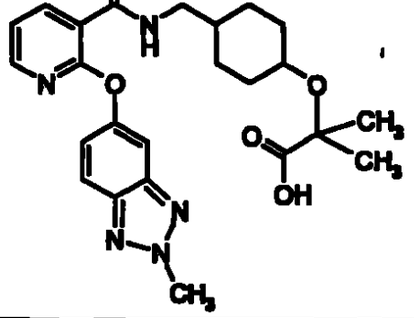
(±)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.36);	
(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.37),	
(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.38);	
(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.39);	
(R)-2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.40),	

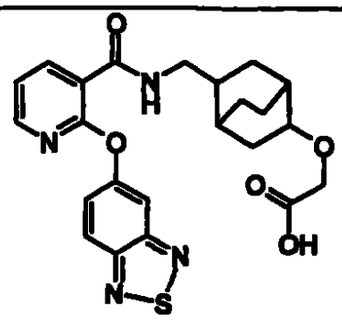
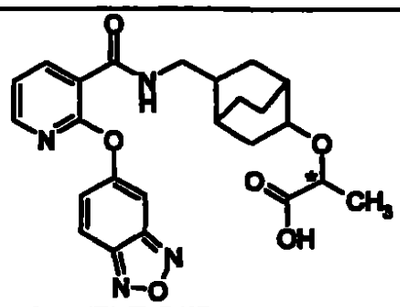
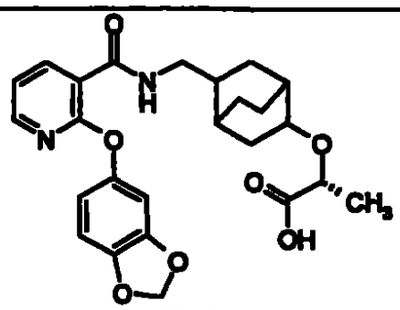
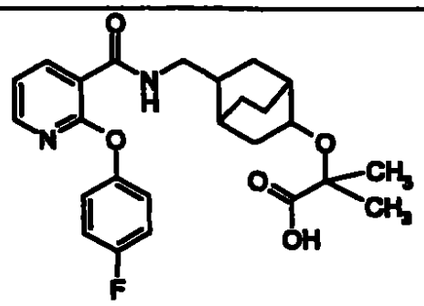
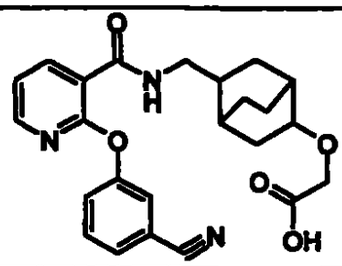
(R)-2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.41);	
(R)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.42);	
[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.43);	
[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.44);	
[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.45);	

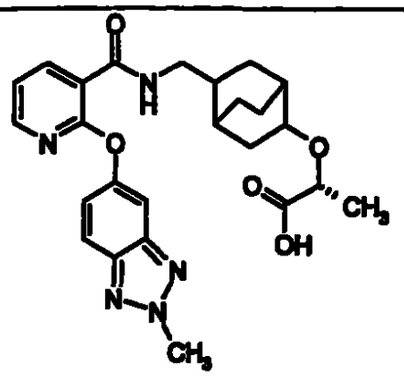
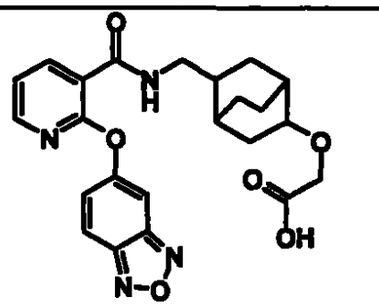
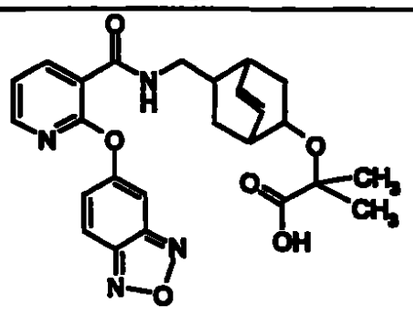
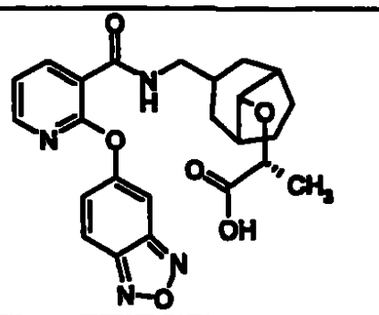
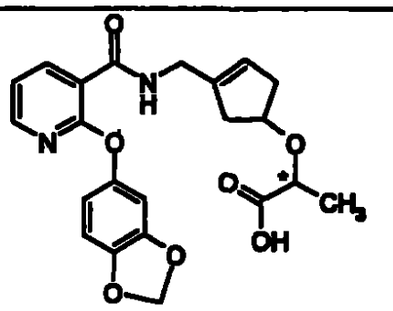
[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.46);	
[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.47);	
[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.48);	
(±)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.49);	
(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.50);	

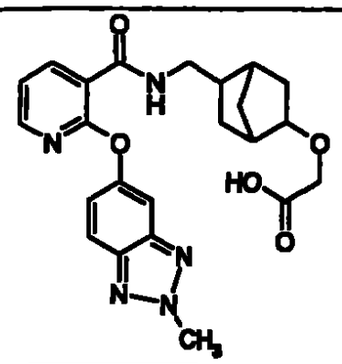
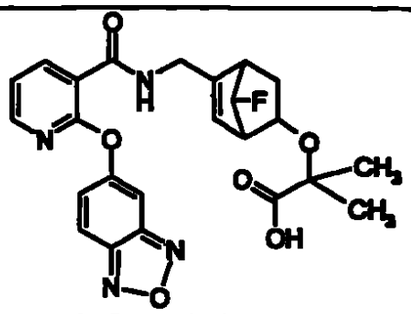
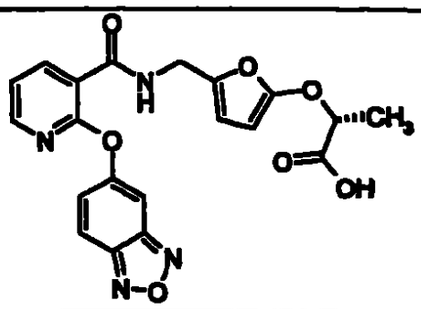
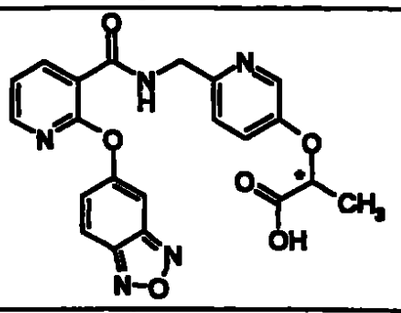
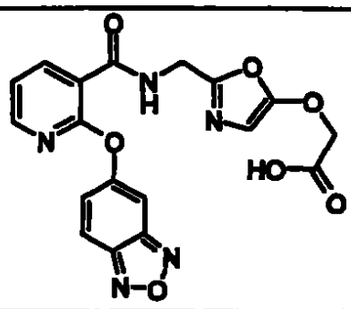
(±)-2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.51);	
(±)-2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.52);	
(±)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.53);	
(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.54);	
(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.55);	

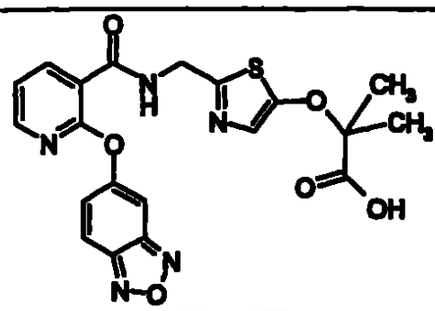
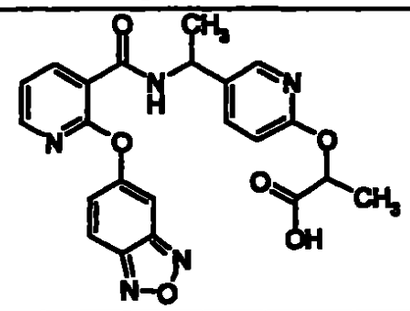
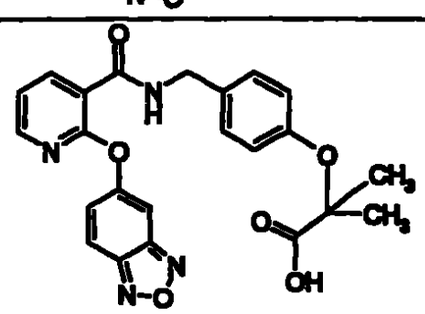
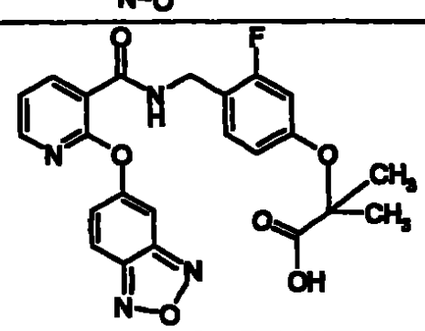
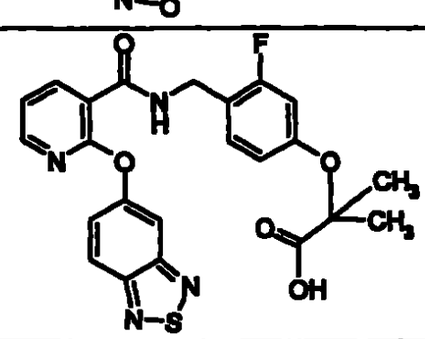
(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5 56);	
(R)-2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5 57);	
(R)-2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.58);	
(R)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.59);	
2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5.60);	

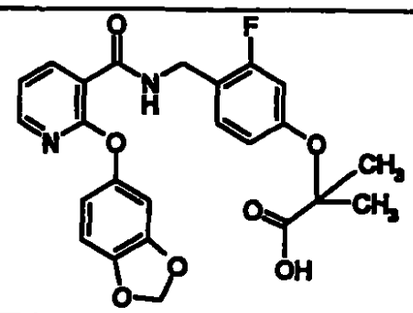
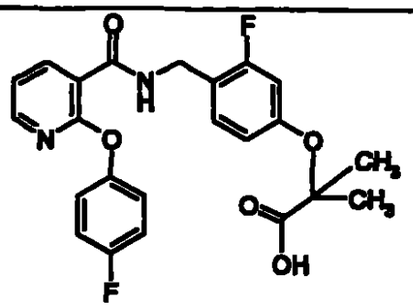
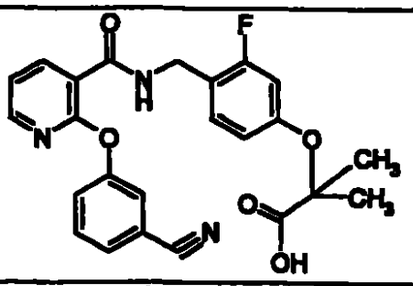
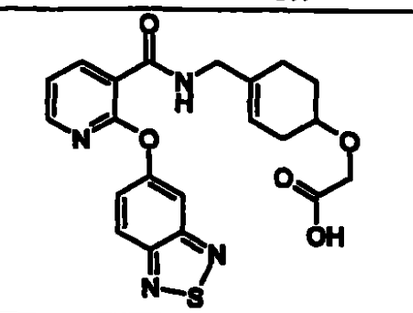
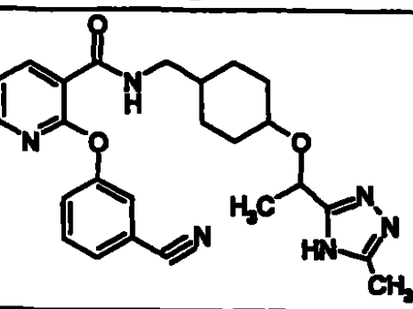
2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5.61);	
2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5.62);	
2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5.63);	
2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5.64);	
2-Methyl-2-[4-({[2-(2-methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.65);	

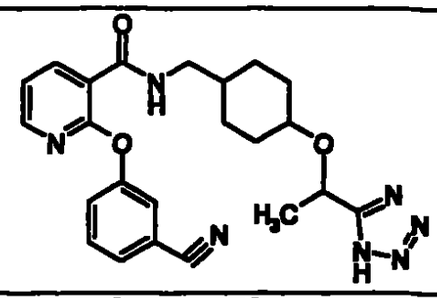
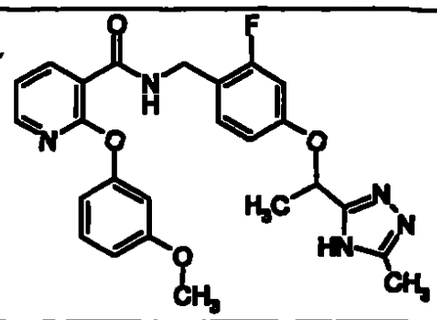
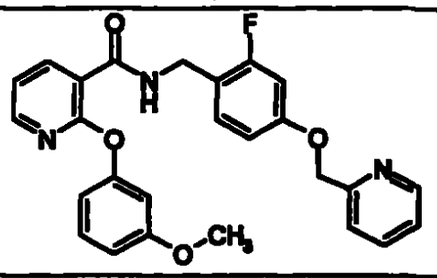
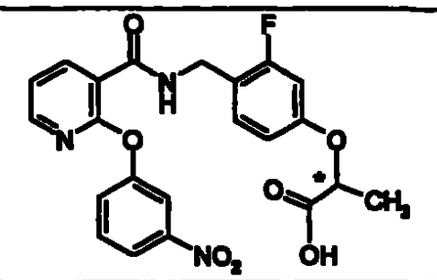
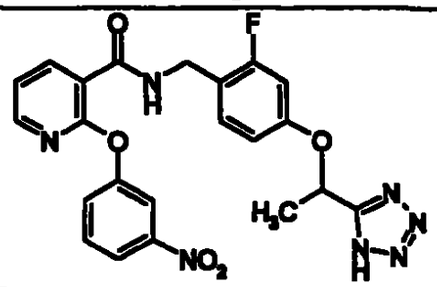
[5-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-acetic acid of Formula (5.5.66);	
(±)-2-[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-propionic acid of Formula (5.5 67);	
(R)-2-[5-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-propionic acid of Formula (5.5.68);	
2-[5-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-2-methyl-propionic acid of Formula (5.5.69);	
2-[5-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-2-methyl-propionic acid of Formula (5.5.70);	

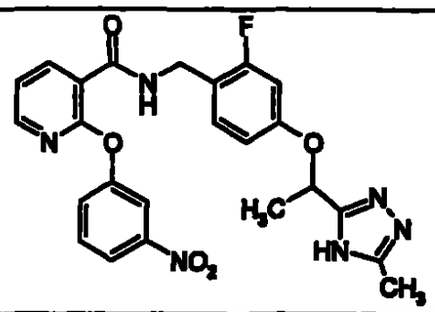
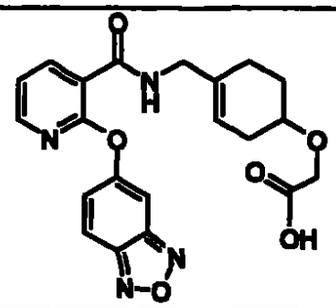
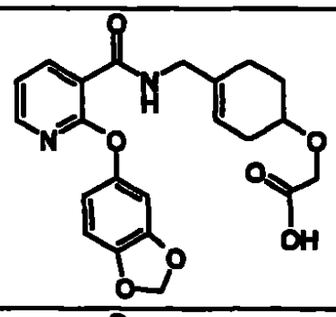
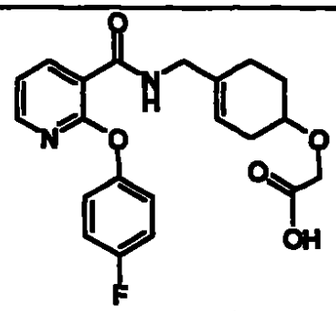
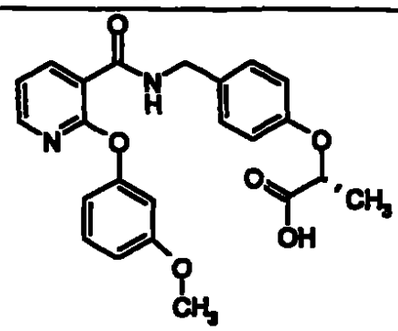
(R)-2-[5-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-propionic acid of Formula (5.5 71);	
[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-acetic acid of Formula (5.5.72);	
2-[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-5-en-2-yloxy]-2-methyl-propionic acid of Formula (5.5 73);	
(R)-2-[3-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[3.2.1]oct-8-yloxy]-propionic acid of Formula (5.5 74);	
2-[3-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclopent-3-enyloxy]-propionic acid of Formula (5.5 75);	

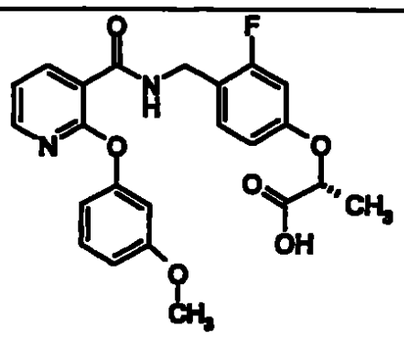
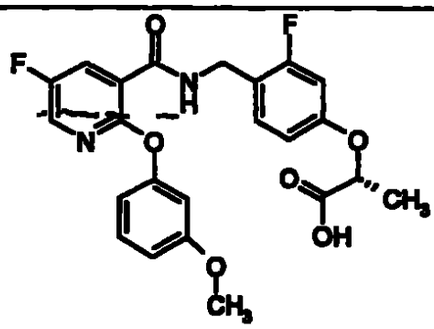
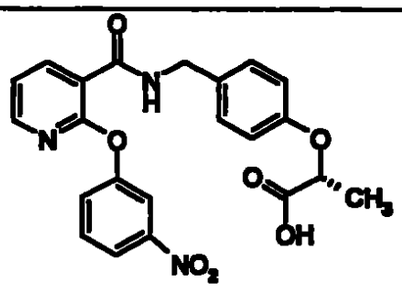
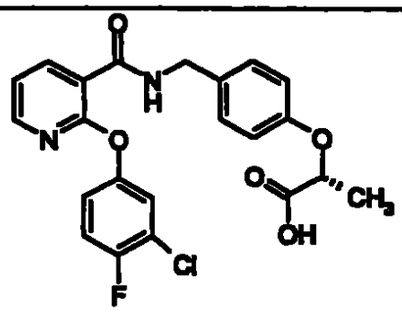
[5-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2 1]hept-2-yloxy]-acetic acid of Formula (5.5.76);	
2-[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-7-fluoro-bicyclo[2.2.1]hept-5-en-2-yloxy]-2-methyl-propionic acid of Formula (5.5 77);	
(R)-2-[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-furan-2-yloxy]-propionic acid of Formula (5.5 78);	
(±)-2-[6-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-pyridin-3-yloxy]-propionic acid of Formula (5.5 79);	
[2-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-oxazol-5-yloxy]-acetic acid of Formula (5 5.80),	

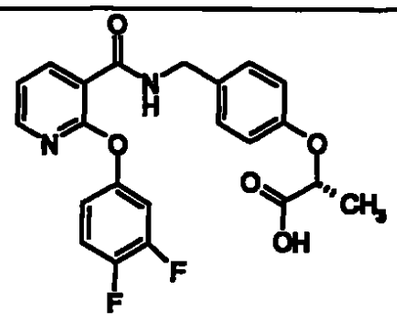
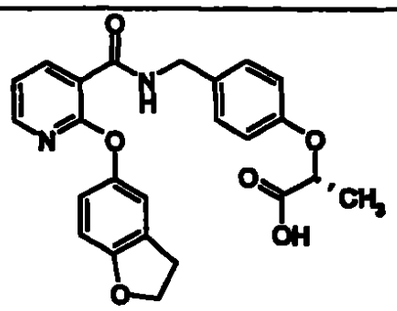
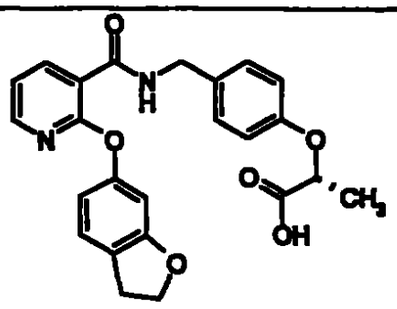
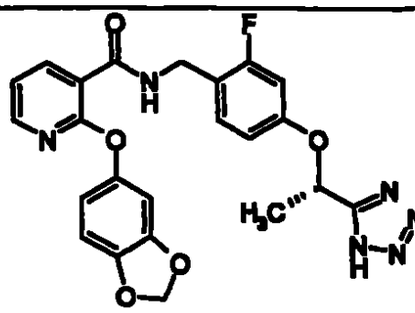
2-[2-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-thiazol-5-yloxy]-2-methyl-propionic acid of Formula (5.5.81);	
(±)-2-[5-(1-[[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-ethyl)-pyridin-2-yloxy]-propionic acid of Formula (5.5.82);	
2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-2-methyl-propionic acid of Formula (5.5.83);	
2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.84);	
2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.85);	

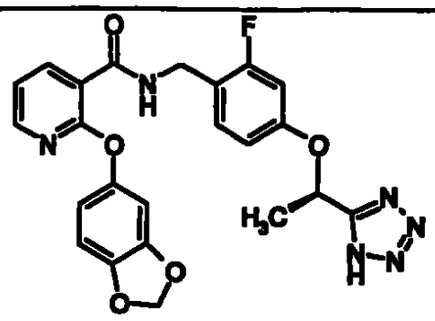
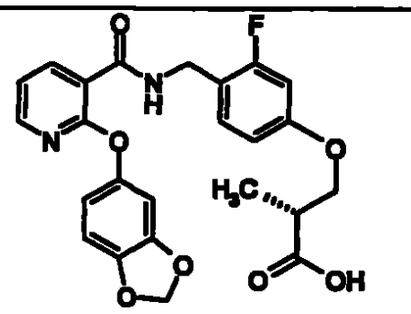
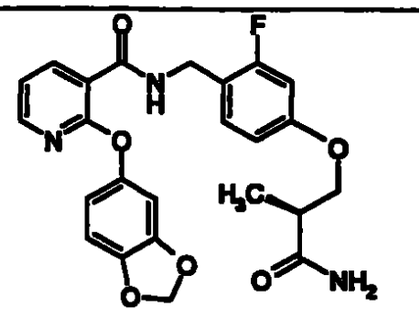
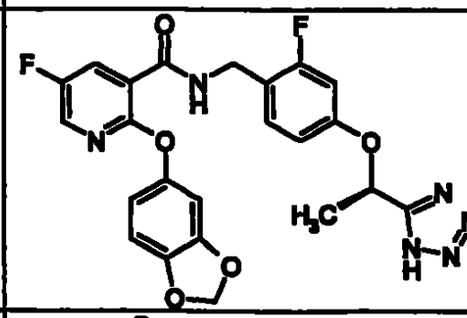
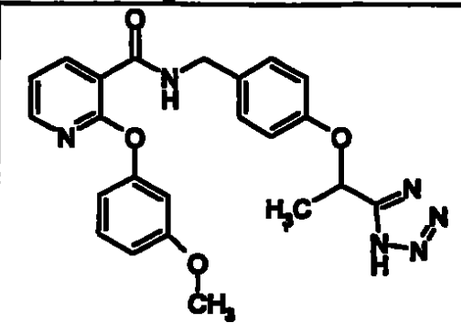
2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.86);	
2-[3-Fluoro-4-({[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-2-methyl-propionic acid of Formula (5 5 87);	
2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.88);	
[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.89);	
(±)-2-(3-Cyano-phenoxy)-N-[4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-cyclohexylmethyl]-nicotinamide of Formula (5.5.90);	

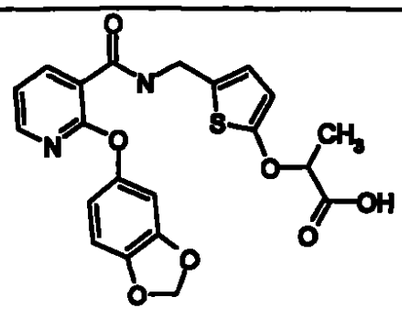
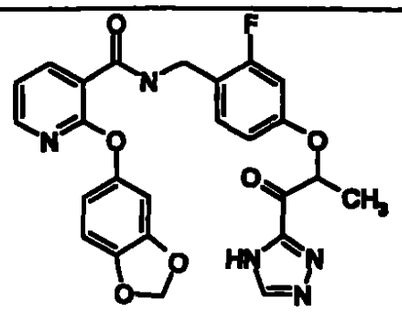
(±)-2-(3-Cyano-phenoxy)-N-[4-[1-(1H-tetrazol-5-yl)-ethoxy]-cyclohexylmethyl]-nicotinamide of Formula (5.5.91);	
(±)-N-[2-Fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-2-(3-methoxy-phenoxy)-nicotinamide of Formula (5.5 92);	
N-[2-Fluoro-4-(pyridin-2-ylmethoxy)-benzyl]-2-(3-methoxy-phenoxy)-nicotinamide of Formula (5.5.93);	
(±)-2-[3-Fluoro-4-([2-(3-nitro-phenoxy)-pyridine-3-carbonyl]-amino)-methyl)-phenoxy]-propionic acid of Formula (5.5.94);	
(±)-N-[2-Fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-2-(3-nitro-phenoxy)-nicotinamide of Formula (5.5 95);	

(±)-N-[2-Fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-2-(3-nitro-phenoxy)-nicotinamide of Formula (5.5.96);	
[4-([[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.97);	
[4-([[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.98);	
[4-([[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5 99);	
(R)-2-[4-([[2-(3-Methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.100);	

(R)-2-[3-Fluoro-4-({[2-(3-methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 101);	
(R)-2-[3-Fluoro-4-({[5-fluoro-2-(3-methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.102);	
(R)-2-[4-({[2-(3-Nitro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.103);	
(R)-2-[4-({[2-(3-Chloro-4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5 5 104);	

(R)-2-[4-({[2-(3,4-Difluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.105);	
(R)-2-[4-({[2-(2,3-Dihydro-benzofuran-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.106);	
(R)-2-[4-({[2-(2,3-Dihydro-benzofuran-6-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 107);	
(S)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.108);	

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5 109);	
(R)-3-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5 110);	
(S)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(2-carbamoyl-propoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5.111);	
(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5 112);	
(±)-2-(3-Methoxy-phenoxy)-N-[4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5 113);	

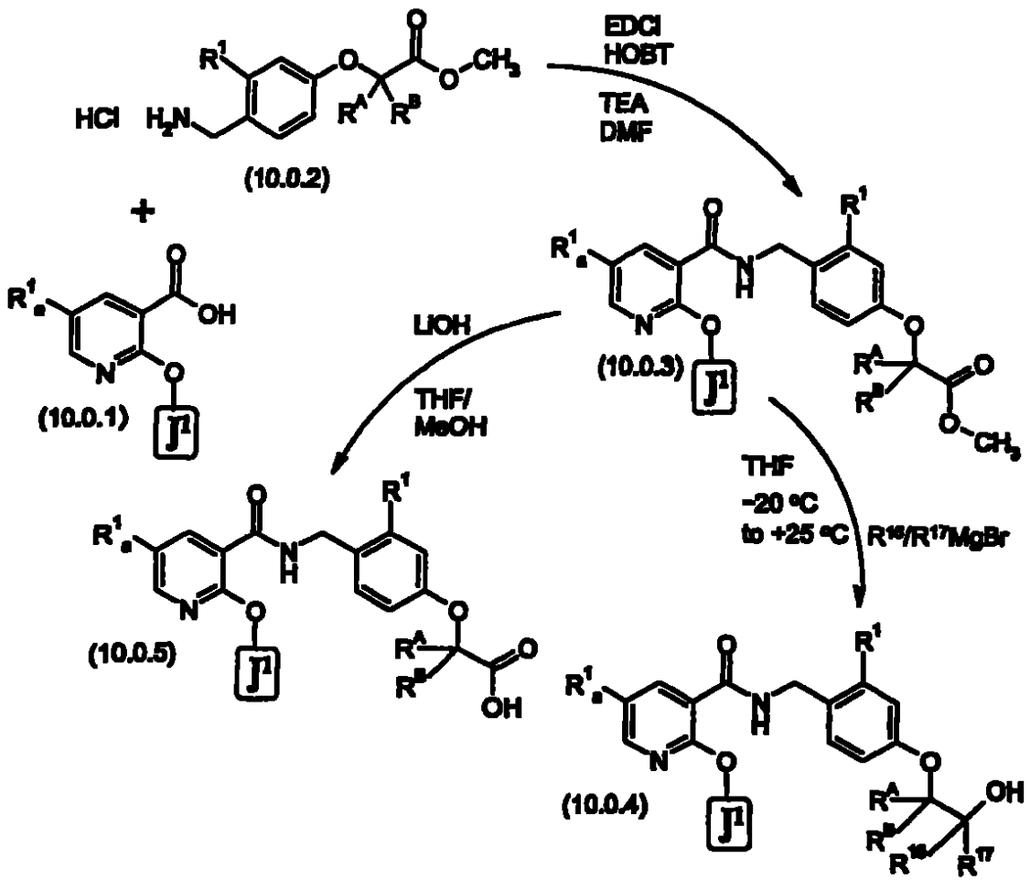
2-[5-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-thiophen-2-yloxy]-propionic acid of Formula (5.5.114);	
(±)-2-(Benzo[1,3]dioxol-5-yloxy)-*N*-[2-fluoro-4-[1-methyl-2-oxo-2-(4*H*-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.115)	

DETAILED DESCRIPTION OF THE INVENTION

6.0 Processes for Making the Compounds of Formula (1.0.0)

A suitable method for preparing a compound of Formula (1 0.0) that belongs to the class of ether acids, where W^1 and W^2 are both –O–, J^2 is phenyl, and D is a moiety of partial Formula (1 1 1), is illustrated in Synthesis Scheme (10.0 0) below

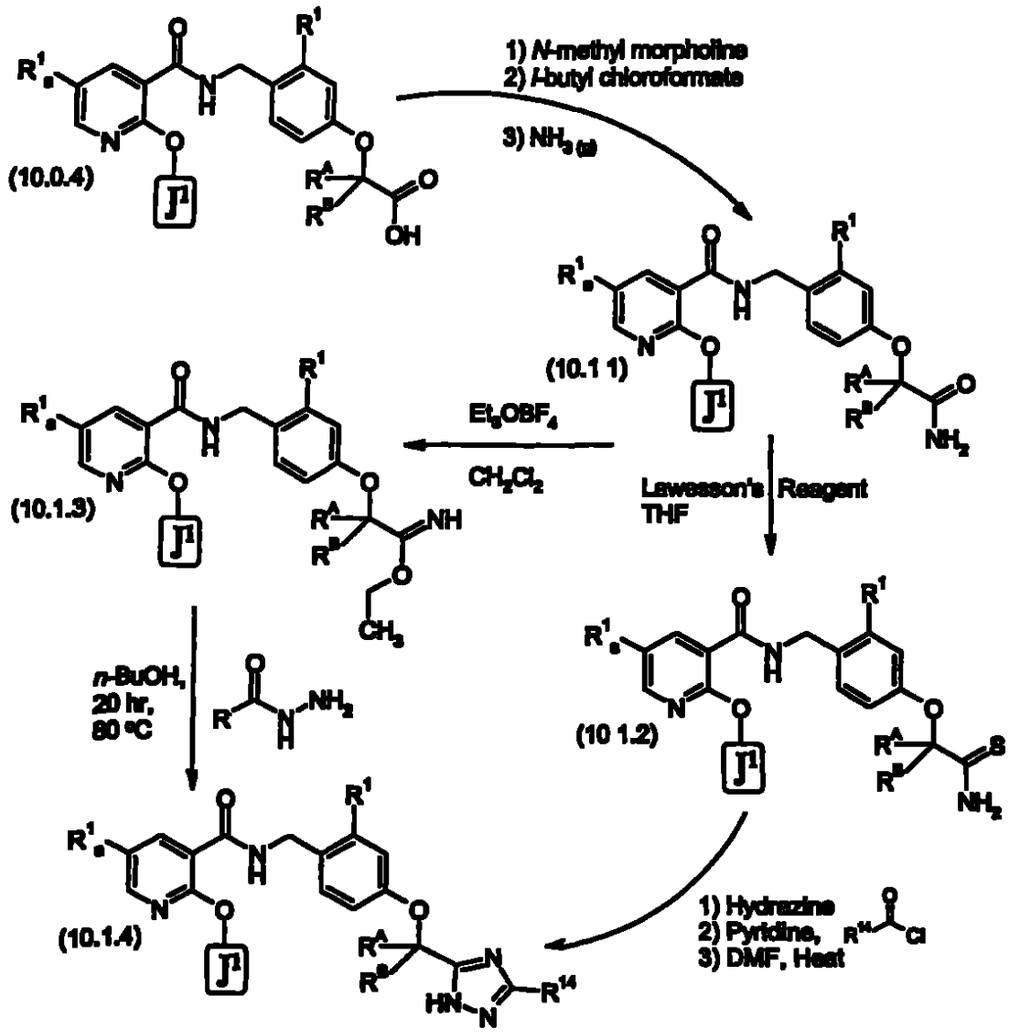
SYNTHESIS SCHEME (10.0.0)



where R^1 is –H or –F, R^A and R^B are –H or (C_1-C_4) alkyl, R^1_a and J^1 have the same meanings as defined above; and R^{16} and R^{17} must have the same meaning.

A suitable method for preparing a compound of Formula (1.0.0) that belongs to the class of triazoles, where W^1 and W^2 are both –O–, J^2 is phenyl, and D is a moiety of partial Formula (1 1.4) where v is 0 and R^5 is triazole, is illustrated in Synthesis Scheme (10.1.0) below The first step of Synthesis Scheme (10 1 0) illustrates the preparation of ether amides of Formula (1.0.0)

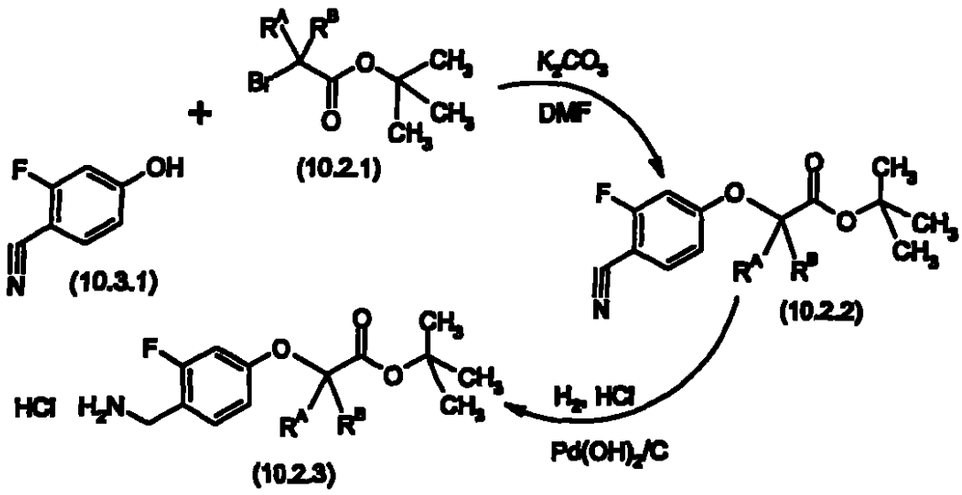
SYNTHESIS SCHEME (10.1.0)



where R^1 is –H or –F, R^A and R^B are –H or (C_1-C_4) alkyl, $R^1{}_a$ and J^1 have the same meanings as defined above; and R^{14} has the same meaning as above, and is preferably methyl, phenyl, or *iso*-propyl.

A suitable method for preparing racemic amino ether ester compounds of Formula (1 0.0) where W^1 and W^2 are both –O–, J^2 is phenyl, and D is a moiety of partial Formula (1 1 1), is illustrated in Synthesis Scheme (10.2 0) below

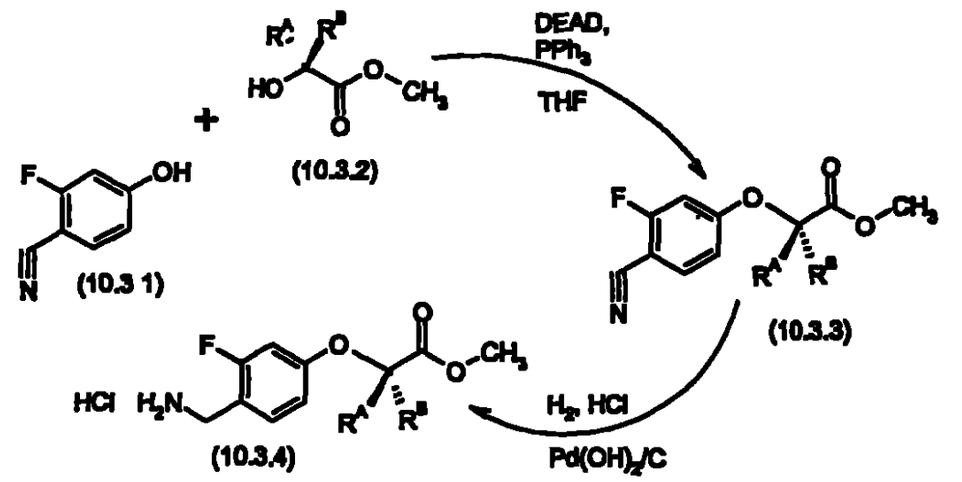
SYNTHESIS SCHEME (10.2.0)



where R^A and R^B have the same meanings as defined above.

A suitable method for preparing enantiomeric amino ether ester compounds of Formula (1.0.0) where W^1 and W^2 are both –O–, J^2 is phenyl, and D is a moiety of partial Formula (1 1 1), is illustrated in Synthesis Scheme (10.3.0) below

SYNTHESIS SCHEME (10.3.0)

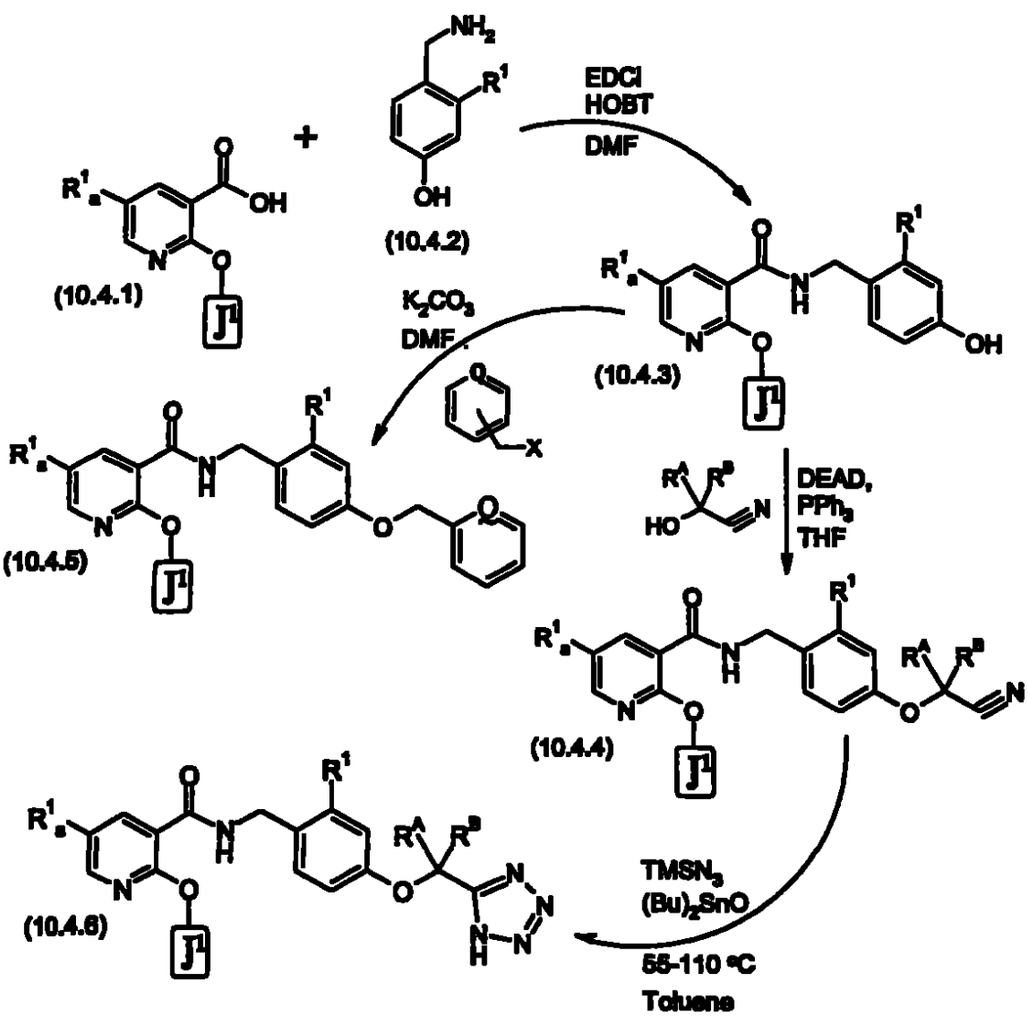


where R^A and R^B have the same meanings as defined above

Other suitable methods for preparing phenyl, pyridyl, and tetrazolyl ether compounds of Formula (1.0 0) where W^1 and W^2 are both –O–, J^2 is phenyl, and D is a moiety of partial

Formula (1 1.4), where v is 0 and R^B is pyridyl or tetrazolyl, are illustrated in Synthesis Scheme (10.4.0) below

SYNTHESIS SCHEME (10.4.0)



where R^1 is –H or –F, R^A and R^B are –H or (C_1-C_4) alkyl, Q is CH or N, X is halo; and R^1_a and J^1 have the same meanings as defined above

DETAILED DESCRIPTION OF THE INVENTION

7.0 Pharmaceutical Salts and Other Forms

The above-described compounds of the present invention may be utilized in the form of acids, esters, or other chemical classes of compounds to which the compounds described belong It is also within the scope of the present invention to utilize those compounds in the

form of their pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures well known in the art.

Pharmaceutically acceptable salt forms of the compounds of Formula (1.0.0) are prepared for the most part by conventional means Where the compound of Formula (1.0.0) contains a carboxylic acid group, a suitable salt thereof may be formed by reacting the compound with an appropriate base to provide the corresponding base addition salt. Examples of such bases are alkali metal hydroxides including potassium hydroxide, sodium hydroxide, and lithium hydroxide, alkaline earth metal hydroxides such as barium hydroxide and calcium hydroxide; alkali metal alkoxides, *e.g.*, potassium ethanolate and sodium propanolate; and various organic bases such as piperidine, diethanolamine, and *N*-methylglutamine. Also included are the aluminum salts of the compounds of Formula (1.0.0).

For certain compounds of Formula (1 0.0) acid addition salts may be formed by treating said compounds with pharmaceutically acceptable organic and inorganic acids, *e.g.*, hydrohalides such as hydrochloride, hydrobromide, hydrolodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, *etc.*, and alkyl- and mono-arylsulfonates such as ethanesulfonate, toluenesulfonate, and benzenesulfonate; and other organic acids and their corresponding salts such as acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate, *etc.*

Accordingly, the pharmaceutically acceptable acid addition salts of the compounds of Formula (1 0.0) include, but are not limited to acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerpphosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydrolodide, 2-hydroxyethanesulfonate, lodide, isethionate, *iso*-butyrate, lactate, lactobionate, malate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate, phthalate,

Further, base salts of the compounds of the present invention include, but are not limited to aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, and zinc salts. Preferred among the above-recited salts are ammonium, the alkali metal salts sodium and potassium, and the alkaline earth metal salts calcium and magnesium Salts of the compounds of Formula (1 0.0) derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to salts

of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, *e.g.*, arginine, betaine, caffeine, chloroprocaine, choline, *N,N'*-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, *iso*-propylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine, and tris-(hydroxymethyl)-methylamine (tromethamine).

Compounds of the present invention which comprise basic nitrogen-containing groups may be quaternized with such agents as (C_1-C_4) alkyl halides, *e.g.*, methyl, ethyl, *iso*-propyl and *tert*-butyl chlorides, bromides and iodides, di(C_1-C_4) alkyl sulfate, *e.g.*, dimethyl, diethyl and diamyl sulfates, (C_{10}-C_{18}) alkyl halides, *e.g.*, decyl, dodecyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, and aryl-(C_1-C_4) alkyl halides, *e.g.*, benzyl chloride and phenethyl bromide. Such salts permit the preparation of both water-soluble and oil-soluble compounds of the present invention

Among the above-recited pharmaceutical salts those which are preferred include, but are not limited to acetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate, and tromethamine.

The acid addition salts of basic compounds of Formula (1.0.0) are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner The free base may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base forms for purposes of the present invention

As indicated, the pharmaceutically acceptable base addition salts of the compounds of Formula (1.0 0) are formed with metals or amines, such as alkali metals and alkaline earth metals, or organic amines. Preferred metals are sodium, potassium, magnesium, and calcium Preferred organic amines are *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, *N*-methyl-D-glucamine, and procaine

The base addition salts of acidic compounds of the present invention are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner The free acid form may be regenerated by contacting the salt

form with an acid and isolating the free acid form in the conventional manner The free acid forms differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid forms for purposes of the present invention

Multiple salts forms are included within the scope of the present invention where a compound of the present invention contains more than one group capable of forming such pharmaceutically acceptable salts Examples of typical multiple salt forms include, but are not limited to bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium, and trihydrochloride.

In light of the above, it can be seen that the expression "pharmaceutically acceptable salt" as used herein is intended to mean an active ingredient comprising a compound of Formula (1 0.0) utilized in the form of a salt thereof, especially where said salt form confers on said active ingredient improved pharmacokinetic properties as compared to the free form of said active ingredient or some other salt form of said active ingredient utilized previously The pharmaceutically acceptable salt form of said active ingredient may also initially confer a desirable pharmacokinetic property on said active ingredient which it did not previously possess, and may even positively affect the pharmacodynamics of said active ingredient with respect to its therapeutic activity in the body

The pharmacokinetic properties of said active ingredient which may be favorably affected include, *e g.*, the manner in which said active ingredient is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation and excretion of said active ingredient. While the route of administration of the pharmaceutical composition is important, and various anatomical, physiological and pathological factors can critically affect bioavailability, the solubility of said active ingredient is usually dependent upon the character of the particular salt form thereof which it utilized Further, as the artisan will appreciate, an aqueous solution of said active ingredient will provide the most rapid absorption of said active ingredient into the body of a patient being treated, while lipid solutions and suspensions, as well as solid dosage forms, will result in less rapid absorption of said active ingredient.

Oral ingestion of an active ingredient of Formula (1.0.0) is the most preferred route of administration for reasons of safety, convenience, and economy, but absorption of such an oral dosage form can be adversely affected by physical characteristics such as polarity, emesis caused by irritation of the gastrointestinal mucosa, destruction by digestive enzymes and low pH, irregular absorption or propulsion in the presence of food or other drugs, and metabolism by enzymes of the mucosa, the intestinal flora, or the liver Formulation of said active ingredient into different pharmaceutically acceptable salt forms may be effective in

overcoming or alleviating one or more of the above-recited problems encountered with absorption of oral dosage forms

A compound of Formula (1 0 0) prepared in accordance with the methods described herein can be separated from the reaction mixture in which it is finally produced by any ordinary means known to the chemist skilled in the preparation of organic compounds Once separated said compound can be purified by known methods. Various methods and techniques can be used as the means for separation and purification, and include, *e.g.*, distillation, recrystallization, column chromatography; ion-exchange chromatography; gel chromatography; affinity chromatography; preparative thin-layer chromatography; and solvent extraction

7.1 Stereoisomers

A compound within the scope of Formula (1.0.0) may be such that its constituent atoms are capable of being arranged in space in two or more different ways, despite having identical connectivities As a consequence, said compound exists in the form of stereoisomers. *Syn-trans* isomerism is but one type of stereoisomerism Where the stereoisomers are nonsuperimposable mirror images of each other, they are enantiomers which have chirality or handedness, because of the presence of one or more asymmetric carbon atoms in their constituent structure. Enantiomers are optically active and therefore distinguishable because they rotate the plane of polarized light by equal amounts, but in opposite directions.

Where two or more asymmetric carbon atoms are present in a compound of Formula (1.0.0), there are two possible configurations at each said carbon atom Where two asymmetric carbon atoms are present, for example, there are four possible stereoisomers. Further, these four possible stereoisomers may be arranged into six possible pairs of stereoisomers that are different from each other In order for a pair of molecules with more than one asymmetric carbon to be enantiomers, they must have different configurations at every asymmetric carbon. Those pairs that are not related as enantiomers have a different stereochemical relationship referred to as a diastereomeric relationship Stereoisomers that are not enantiomers are called diastereoisomers, or more commonly, diastereomers

All of these well known aspects of the stereochemistry of the compounds of Formula (1.0.0) are contemplated to be a part of the present invention Within the scope of the present invention there is thus included compounds of Formula (1.0 0) that are stereoisomers, and where these are enantiomers, the individual enantiomers, racemic mixtures of said enantiomers, and artificial, *i.e.*, manufactured mixtures containing proportions of said enantiomers that are different from the proportions of said enantiomers found in a racemic mixture. Where a compound of Formula (1 0 0) comprises stereoisomers that are

diastereomers, there is included within the scope of said compound the individual diastereomers as well as mixtures of any two or more of said diastereomers in any proportions thereof

By way of illustration, in the case where there is a single asymmetric carbon atom in a compound of Formula (1.0 0), resulting in the (-)(*R*) and (+)(*S*) enantiomers thereof; there is included within the scope of said compound all pharmaceutically acceptable salt forms, prodrugs and metabolites thereof which are therapeutically active and useful in treating or preventing the diseases and conditions described further herein. Where a compound of Formula (1 0 0) exists in the form of (-)(*R*) and (+)(*S*) enantiomers, there is also included within the scope of said compound the (+)(*S*) enantiomer alone, or the (-)(*R*) enantiomer alone, in the case where all, substantially all, or a predominant share of the therapeutic activity resides in only one of said enantiomers, and/or unwanted side effects reside in only one of said enantiomers. In the case where there is substantially no difference between the biological activities of both enantiomers, there is further included within the scope of said compound of Formula (1.0.0) the (+)(*S*) enantiomer and the (-)(*R*) enantiomer present together as a racemic mixture or as a non-racemic mixture in any ratio of proportionate amounts thereof

For example, the particular biological activities and/or physical and chemical properties of a pair or set of enantiomers of a compound of Formula (1.0 0) where such exist, may suggest use of said enantiomers in certain ratios to constitute a final therapeutic product. By way of illustration, in the case where there is a pair of enantiomers, they may be employed in ratios such as 90% (R) – 10% (S), 80% (R) - 20% (S); 70% (R) - 30% (S); 60% (R) - 40% (S); 50% (R) - 50% (S); 40% (R) - 60% (S); 30% (R) - 70% (S); 20% (R) - 80% (S); and 10% (R) - 90% (S). After evaluating the properties of the various enantiomers of a compound of Formula (1.0.0) where such exist, the proportionate amount of one or more of said enantiomers with certain desired properties that will constitute the final therapeutic product can be determined in a straightforward manner

7.2 Isotopes

There is further contemplated to be included within the scope of a compound of Formula (1.0 0) isotopically-labelled forms thereof An isotopically-labelled form of a compound of Formula (1 0 0) is identical to said compound but for the fact that one or more atoms of said compound have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature Examples of isotopes which are readily available commercially and which can be incorporated into a compound of Formula (1.0 0) in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17} , ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl,

respectively A compound of Formula (1.0 0), a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention

An isotopically-labelled compound of Formula (1.0 0) may be used in a number of beneficial ways. For example, an isotopically-labelled compound of Formula (1.0 0), *e.g* , one in which a radioactive isotope such as ^{3}H or ^{14}C has been incorporated, will be useful in drug and/or substrate tissue distribution assays These radioactive isotopes, *i.e.*, tritium, ^{3}H, and carbon-14, ^{14}C, are especially preferred for their ease of preparation and eminent detectability Incorporation of heavier isotopes, *e.g.*, deuterium, ^{2}H, into a compound of Formula (1.0 0) will provide therapeutic advantages based on the greater metabolic stability of said isotopically-labelled compound Greater metabolic stability translates directly into increased *in vivo* half-life or reduced dosage requirements, which under most circumstances would constitute a preferred embodiment of the present invention An isotopically-labelled compound of Formula (1 0.0) can usually be prepared by carrying out the procedures disclosed in the Synthesis Schemes and related description, Examples, and Preparations herein, substituting a readily available isotopically-labelled reagent for its corresponding non-isotopically-labelled reagent.

Deuterium, ^{2}H, can also be incorporated into a compound of Formula (1 0.0) for the purpose of manipulating the oxidative metabolism of said compound by way of the primary kinetic isotope effect. The primary kinetic isotope effect is a change of rate for a chemical reaction that results from substitution of isotopic nuclei, which in turn is caused by the change in ground state energies required for covalent bond formation subsequent to said isotopic substitution Substitution of a heavier isotope will usually result in a lowering of the ground state energy for a chemical bond, thereby causing a reduction in rate for a rate-limiting bond breaking step If the bond-breaking event occurs on or near a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially By way of illustration, when deuterium is bound to a carbon atom at a non-exchangeable site, rate differences of $k_H/k_D = 2\text{-}7$ are typical This difference in rate, applied successfully to an oxidatively labile compound of Formula (1.0.0), can dramatically affect the profile of said compound *in vivo* and result in improved pharmacokinetic properties

In discovering and developing therapeutic agents, the skilled artisan seeks to optimize pharmacokinetic parameters while retaining desirable *in vitro* properties. It is a reasonable surmise that many compounds with poor pharmacokinetic profiles suffer from a lability to oxidative metabolism *In vitro* liver microsomal assays now available provide valuable information about the course of this oxidative metabolism, which in turn permits the rational design of deuterated compounds of Formula (1 0 0) with improved stability through

resistance to such oxidative metabolism Significant improvements in the pharmacokinetic profiles of compounds of Formula (1 0.0) are thereby obtained, and can be expressed quantitatively in terms of increases in *in vivo* half-life (t/2), concentration at maximum therapeutic effect (C_{max}), area under the dose response curve (AUC), and F; and in terms of decreases in clearance, dose, and cost-of-goods.

By way of illustration of the above, a compound of Formula (1.0.0) which has multiple potential sites for oxidative metabolism, e.g., benzylic hydrogen atoms and hydrogen atoms α to a nitrogen atom, is prepared as a series of analogs in which various combinations of hydrogen atoms are replaced by deuterium atoms so that some, most or all of said hydrogen atoms are replaced with deuterium atoms. Half-life determinations provide an expedient and accurate determination of the extent of improvement in resistance to oxidative metabolism In this manner it is determined that the half-life of the parent compound can be extended by as much as 100% as the result of such deuterium-for-hydrogen substitution

Deuterium-for-hydrogen substitution in a compound of Formula (1.0.0) can also be used to achieve a favorable alteration in the metabolite profile of the parent compound as a way of diminishing or eliminating unwanted toxic metabolites. For example, where a toxic metabolite arises through an oxidative carbon-hydrogen, C–H, bond scission, the deuterated analog is reasonably expected to greatly diminish or eliminate production of the unwanted metabolite, even in the case where the particular oxidation is not a rate-determining step.

Further information concerning the state of the art with respect to deuterium-for-hydrogen substitution may be found, *e g.*, in Hanzlik *et al.*, *J Org. Chem.* 55 3992-3997, 1990, Reider *et al.*, *J Org. Chem.* 52 3326-3334, 1987, Foster, *Adv Drug Res.* 14 1-40, 1985, Gillette *et al.* , *Biochemistry* 33(10) 2927-2937, 1994, and Jarman *et al.* , *Carcinogenesis* 16(4) 683-688, 1993.

DETAILED DESCRIPTION OF THE INVENTION

8.0 Therapeutic Applications and Clinical Endpoints

The description which follows concerns the therapeutic applications to which the compounds of Formula (1.0 0) may be put, and where applicable an explanation of the clinical endpoints associated with such therapeutic applications There is also set forth a disclosure of various *in vitro* assays and animal model experiments, which are capable of providing data sufficient to define and demonstrate the therapeutic utility of the compounds of Formula (1.0.0).

The therapeutic utility of the compounds of Formula (1.0 0) is applicable to a patient or subject afflicted with a disease or condition as herein set forth and therefore in need of such treatment. The beneficial results are therapeutic whether administered to animals or

humans As used herein the terms "animal" and "animals" is used merely for the purpose of pointing out human beings as opposed to other members of the animal kingdom The compounds of Formula (1.0.0) have therapeutic applicability in the treatment of mammals, and in particular of humans. All of the major subdivisions of the class of mammals (*Mammalia*) are included within the scope of the present invention with regard to being recipients of therapeutic treatment as described herein Mammals have value as pets to humans and are therefore likely to be subjects of treatment. This applies especially to the canine and feline groups of mammals. Other mammals are valued as domesticated animals and their treatment in accordance with the present invention is likely in view of the adverse economic impact of not treating the diseases and conditions described herein. This applies especially to the equine, bovine, porcine, and ovine groups of mammals

The compounds of Formula (1 0 0) inhibit the PDE4 isozyme and thereby have a wide range of therapeutic applications, as described further below, because of the essential role which the PDE4 family of isozymes plays in the physiology of all mammals The enzymatic role performed by the PDE4 isozymes is the intracellular hydrolysis of adenosine 3',5'-monophosphate (cAMP) within pro-inflammatory leukocytes cAMP, in turn, is responsible for mediating the effects of numerous hormones in the body, and as a consequence, PDE4 inhibition plays a significant role in a variety of physiological processes. There is extensive literature in the art describing the effects of PDE inhibitors on various inflammatory cell responses, which in addition to cAMP elevation, include inhibition of superoxide production, degranulation, chemotaxis and tumor necrosis factor (TNF) release in eosinophils, neutrophils and monocytes

PDE4 was first identified in 1985, Nemoz *et al. Biochem. Pharmacol.* 34 2997-3000, 1985, and the PDE4 inhibitors rolipram and denbufylline were studied early on in clinical trials for CNS indications such as depression. Subsequently, it was established that PDE4 is the principal phosphodiesterase in inflammatory leukocytes. The four subtypes of PDE4, *i.e.*, PDE4A, PDE4B, PDE4C, and PDE4D, are widely distributed in human tissues, as determined by the presence of their mRNAs PDE4D is expressed in kidney, thymus, small intestine, and colon tissues, and is strongly expressed in brain, lung, skeletal muscle, prostate, and peripheral blood leukocyte (PBL) tissues. It is only weakly expressed in heart, placenta, liver, pancreas, spleen, testes, and ovary tissues PDE4A and PDE4B are also strongly expressed in brain and skeletal muscle tissues, and only weakly expressed in placenta, liver, and ovary tissues PDE4C is strongly expressed in skeletal muscle tissue as well, and is also weakly expressed in ovary tissue PDE4C is usually not detectable in the majority of the above-mentioned tissues.

The PDE4 family of isozymes is the predominant form of phosphodiesterase found in cell types implicated in chronic inflammatory diseases, and among bone-marrow derived cell types, only platelets do not express PDE PDE4 is the major cAMP-metabolizing enzyme in immune and inflammatory cells, and is one of two major cAMP-metabolizing enzymes in airway smooth muscle PDE4 is exclusively present in neutrophils, eosinophils, basophils, and monocytes, while in macrophages PDE3 and PDE1 activity, and in T lymphocytes PDE7 activity has also been demonstrated The beneficial anti-inflammatory effects of inhibitors of PDE have been demonstrated heretofore using *in vitro* experiments, which have established that such compounds inhibit superoxide generation in human monocytes, eosinophils, and neutrophils, mediator release in basophils, macrophages, and neutrophils, and TNFα release in monocytes and macrophages. PDE inhibitors also inhibit mediator release of inflammatory cells like monocytes and monocyte-derived macrophages, lung mast cells, T lymphocytes, B lymphocytes, alveolar macrophages, and eosinophils.

Beneficial anti-inflammatory effects have also been observed *in vivo* heretofore, including inhibition of microvascular leakage into the lungs of sensitized guinea pigs, and reduction of bronchial hyper-reactivity and eosinophilia in cynomolgus monkeys following repeated antigen challenge It has also been demonstrated heretofore that PDE4 inhibitors potently suppress TNFα release from mononuclear phagocytes.

8.1 Asthma

One of the most important respiratory diseases treatable with PDE4, especially PDE4D inhibitors of the type within the scope of the compounds of Formula (1.0.0) is asthma, a chronic, increasingly common disorder encountered worldwide and characterized by intermittent reversible airway obstruction, airway hyper-responsiveness and inflammation. The cause of asthma has yet to be determined, but the most common pathological expression of asthma is inflammation of the airways, which may be significant even in the airways of patients with mild asthma. Based on bronchial biopsy and lavage studies it has been clearly shown that asthma involves infiltration by mast cells, eosinophils, and T-lymphocytes into a patient's airways. Bronchoalveolar lavage (BAL) in atopic asthmatics shows activation of interleukin (IL)-3, IL-4, IL-5 and granulocyte/macrophage-colony stimulating factor (GM-CSF) that suggests the presence of a T-helper 2 (Th-2)-like T-cell population

Compounds of Formula (1 0.0) inhibit PDE4 in human eosinophils and are therefore useful in the treatment of atopic and non-atopic asthma. The term "atopy" refers to a genetic predisposition toward the development of type I (immediate) hypersensitivity reactions against common environmental antigens. The most common clinical manifestation is allergic rhinitis, while bronchial asthma, atopic dermatitis, and food allergy occur less frequently Accordingly, the expression "atopic asthma" as used herein is intended to be synonymous with "allergic asthma", *i.e* , bronchial asthma which is an allergic manifestation in a sensitized person The

term "non-atopic asthma" as used herein is intended to refer to all other asthmas, especially essential or "true" asthma, which is provoked by a variety of factors, including vigorous exercise, irritant particles, psychologic stresses, etc.

The use of the compounds of Formula (1.0 0) to treat atopic asthma or non-atopic asthma is established and demonstrated by the models of PDE inhibition, inhibition of eosinophil activation, and the cell infiltration models described below

Pulmonary Inflammation in Allergic Cynomolgus Monkeys -- The ability of the combinations of therapeutic agents of the present invention to inhibit *Ascaris* antigen induced increases in the inflammatory cell content of bronchial alveolar lavage fluid from cynomolgus monkey subjects is evaluated in this method Using a cross-over design, 8-10 Ascaris-sensitive cynomolgus monkeys are treated with vehicle or drug At appropriate pretreatment time, each monkey is anesthetized (ketamine 10 m/kg + xylazine 1 mg/kg, Lm) and intubated with a cuffed endotracheal tube. Bronchoalveolar lavage (BAL) is performed using one 15 ml wash of phosphate buffered saline (PBS) delivered through a pediatric fiberoptic bronchoscope inserted through the endotracheal tube and wedged into a third to fifth generation bronchus Lavage fluid is gently aspirated and collected in a syringe. After BAL is complete, each animal receives a 2 min exposure to a concentration of Ascaris suum aerosol which doubles respiratory system resistance determined in previous experiments. Each monkey is returned to its cage and 24 hr later a second lavage is performed, using 15 ml PBS, on the opposite side of the lung One week after the first trial, control and treated monkeys are reversed and the experiment repeated To determine the percent composition of each leukocyte type, two slides from each monkey BAL sample is obtained by centrifuging 2 x 150 ul lavage fluid for 2 min @ 500 rpm in Cytospin centrifuge Slides are stained in Diff-Quick for differential cell count and cells identified by standard morphological criteria. Total leukocyte numbers per milliliter of BAL fluid are determined by diluting 20 ul of sample in 20 ml Isoton, adding 3 drops of Zapoglobin to lyse erythrocytes and reading the sample using a Coulter Counter Comparisons are made between the ratio of increase in bronchial alveolar lavage eosinophil, cytokine or mediator levels, pre-antigen challenge versus 24 hours post antigen challenge, with and without drug treatment.

In the above test model the combinations of therapeutic agents of the present invention exhibit anti-inflammatory activity at dosages in the range of from 0 001 to 0 1 mg/kg *i.v* or 0.01 to 10.0 mg/kg *p.o.* or 0 001 to 0 1 mg/kg *i.t.*

Another useful assay, based on the use of primates, is that described in Turner *et al*, "Characterization of a primate model of asthma using anti-allergy/anti-asthma agents," *Inflammation Research* 45 239-245, 1996

Anti-Inflammatory Activity – The anti-inflammatory activity of the combinations of therapeutic agents of the present invention is demonstrated by the inhibition of eosinophil activation as measured by sephadex bead stimulated LTE4 production in whole human blood. Whole Blood Assay for LTE4 using Sephadex Beads as Stimulant. On the day before the assay, siliconize glass tubes with Sigmacote (Sigma, Cat# SL-2). Before Drawing the blood, dilute compounds in DMSO 1000X , add 1µl of either DMSO or compound to each respective tube, and place rack of tubes in 37°C water bath Have Blood drawn into heparinized Vacutainer tube #6480 (143USP units sodium heparin, 10ml), 10 tubes =100ml blood Pool Blood tubes in two 50 ml conical tubes Add 1 ml of whole blood to each siliconized tube containing DMSO or compound VORTEX and then incubate at 37°C for 15 minutes. To prepare the Sephadex G-15 beads (Pharmacia, Cat# 17-0020-01) suspension, add 3.3 g. of Sephadex G-15, mix with 20 mls of PBS in a 100 ml beaker then mix with a magnetic stir bar After 15 minutes, add 100µl of Sephadex G-15 beads to each tube except the Sephadex tubes which will provide the baseline value for LTE4 release. Vortex and incubate for 90 minutes at 37°C At the end of 90 minutes incubation, add 20µl of 15% EDTA, VORTEX and centrifuge for 5 minutes at 1000 rpm Then remove and save the plasma sample for analysis. LTE4 levels are determined by Cayman's Cysteinyl-LT ELISA kit (Cat # 520501). Percent inhibition is calculated as 100 X 1 – (LTE4 concentration in the drug treated sample divided by the LTE4 concentration in the non-drug treated control samples).

Compounds of Formula (1.0.0) are active in the above test method at concentrations in the range of from 0.0001µM to 20 0 µM, with preferred embodiments being active at concentrations in the range of from 0.5 nM to 1000 nM

From the above it may be seen that compounds of Formula (1.0.0) are useful for the treatment of inflammatory or obstructive airways diseases or other conditions involving airways obstruction In particular they are useful for the treatment of bronchial asthma.

In view of their anti-inflammatory activity, their influence on airways hyper-reactivity, and their profile in relation to PDE isoenzyme inhibition, in particular as selective PDE4 inhibitors, the compounds of Formula (1.0.0) are useful for the treatment, in particular prophylactic treatment, of obstructive or inflammatory airways diseases Thus, by continued and regular administration over prolonged periods of time the compounds of Formula (1.0.0) are useful in providing advance protection against the recurrence of bronchoconstriction or other symptomatic attack consequential to obstructive or inflammatory airways diseases. The compounds of Formula (1 0 0) are also useful for the control, amelioration or reversal of the basal status of such diseases.

Having regard to their bronchodilator activity the compounds of Formula (1 0.0) are useful as bronchodilators, e.g., in the treatment of chronic or acute bronchoconstriction, and for the symptomatic treatment of obstructive or inflammatory airways diseases.

The words "treatment" and "treating" as used throughout the present specification and claims in relation to obstructive or inflammatory airways diseases are to be understood, accordingly, as embracing both prophylactic and symptomatic modes of therapy

In light of the above description, it may be seen that the present invention also relates to a method for the treatment of airways hyper-reactivity in mammals; to a method of effecting bronchodilation in mammals, and in particular, to a method of treating obstructive or inflammatory airways diseases, especially asthma, in a mammal subject in need thereof, which method comprises administering to said subject mammal an effective amount of a compound of Formula (1.0.0).

Obstructive or inflammatory airways diseases to which the present invention applies include asthma; pneumoconiosis, chronic eosinophilic pneumonia, chronic obstructive airways or pulmonary disease (COAD or COPD); and adult respiratory distress syndrome (ARDS), as well as exacerbation of airways hyper-reactivity consequent to other drug therapy, e.g., aspirin or β-agonist therapy

The compounds of Formula (1.0 0) are useful in the treatment of asthma of whatever type, etiology, or pathogenesis, including intrinsic asthma attributed to pathophysiologic disturbances, extrinsic asthma caused by some factor in the environment, and essential asthma of unknown or inapparent cause The compounds of Formula (1.0.0) are useful in the treatment of allergic (atopic/bronchial/IgE-mediated) asthma, and they are useful as well in the treatment of non-atopic asthma, including e g. bronchitic, emphysematous, exercise-induced, and occupational asthma, infective asthma that is a sequela to microbial, especially bacterial, fungal, protozoal, or viral infection, and other non-allergic asthmas, e.g., incipient asthma (wheezy infant syndrome).

The compounds of Formula (1.0.0) are further useful in the treatment of pneumoconiosis of whatever type, etiology, or pathogenesis; including, e.g., aluminosis (bauxite workers' disease); anthracosis (miners' asthma); asbestosis (steam-fitters' asthma); chalicosis (flint disease); ptilosis caused by inhaling the dust from ostrich feathers, siderosis caused by the inhalation of iron particles, silicosis (grinders' disease); byssinosis (cotton-dust asthma); and talc pneumoconiosis

8.2 Chronic Obstructive Pulmonary Disease (COPD)

The compounds of Formula (1 0 0) are still further useful in the treatment of COPD or COAD including chronic bronchitis, pulmonary emphysema or dyspnea associated therewith COPD is characterized by irreversible, progressive airways obstruction Chronic bronchitis is

associated with hyperplasia and hypertrophy of the mucus secreting glands of the submucosa in the large cartilaginous airways Goblet cell hyperplasia, mucosal and submucosal inflammatory cell infiltration, edema, fibrosis, mucus plugs and increased smooth muscle are all found in the terminal and respiratory bronchioles. The small airways are known to be a major site of airway obstruction Emphysema is characterized by destruction of the alveolar wall and loss of lung elasticity A number of risk factors have also been identified as linked to the incidence of COPD The link between tobacco smoking and COPD is well established Other risk factors include exposure to coal dust and various genetic factors See Sandford *et al.*, "Genetic risk factors for chronic obstructive pulmonary disease," *Eur Respir J* 10 1380-1391, 1997 The incidence of COPD is increasing and it represents a significant economic burden on the populations of the industrialized nations COPD also presents itself clinically with a wide range of variation from simple chronic bronchitis without disability to patients in a severely disabled state with chronic respiratory failure.

COPD is characterized by inflammation of the airways, as is the case with asthma, but the inflammatory cells that have been found in the bronchoalveolar lavage fluid and sputum of patients neutrophils rather than eosinophils Elevated levels of inflammatory mediators are also found in COPD patients, including IL-8, LTB_4, and TNF-α, and the surface epithelium and sub-epithelium of the bronchi of such patients has been found to be infiltrated by T-lymphocytes and macrophages Symptomatic relief for COPD patients can be provided by the use of β-agonist and anticholinergic bronchodilators, but the progress of the disease remains unaltered COPD has been treated using theophylline, but without much success, even though it reduces neutrophil counts in the sputum of COPD patients. Steroids have also failed to hold out much promise as satisfactory treatment agents in COPD

Accordingly, the use of the compounds of Formula (1 0.0) to treat COPD and its related and included obstructed airways diseases, represents a significant advance in the art. The present invention is not limited to any particular mode of action or any hypothesis as to the way in which the desired therapeutic objectives have been obtained by utilizing the compounds of Formula (1.0.0). However, it is recognized in the art that PDE4 is the predominant PDE in neutrophils and macropheges; Cheng *et al*, "Synthesis and *in vitro* profile of a novel series of catechol benzimidazoles. The discovery of potent, selective phosphodiesterase Type IV inhibitors with greatly attenuated affinity for the [3H]rolipram binding site," *Bioorg. Med. Chem. Lett.* 5 1969-1972, 1995, Wright *et al.* "Differential inhibition of human neutrophil functions role of cyclic AMP-specific, cyclic GMP-insensitive phosphodiesterase," *Biochem. Pharmacol.* 40 699-707, 1990; Schudt *et al.*, "Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca!," *Naunyn Schmiedebergs Arch. Pharmacol.* 344 682-690, 1991, and Tenor *et al.*, "Cyclic

nucleotide phosphodiesterase isoenzyme activities in human alveolar macrophages," *Clin. Exp. Allergy* 25 825-833, 1995.

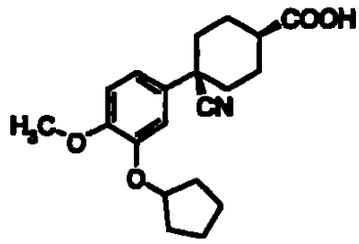
In order to provide a better understanding of the present invention, the inference is made here that the compounds of Formula (1.0 0) inhibit PDE4s in neutrophils, resulting in reduced chemotaxis, activation, adherence, and degranulation, Schudt *et al.*, *Ibid*, Nelson *et al*, "Effect of selective phosphodiesterase inhibitors on the polymorphonuclear leukocyte respiratory burst," *J Allergy Clin. Immunol* 86 801-808, 1990; and Bloeman *et al.*, "Increased cAMP levels in stimulated neutrophils inhibit their adhesion to human bronchial epithelial cells," *Am. J Physiol.* 272 L580-587, 1997

It is also inferred that the compounds of Formula (1.0 0) reduce superoxide anion production mediated by PDE4s in peripheral blood neutrophils, and that they regulate leukotriene synthesis mediated by PDE4s, Wright *et al.*, *Ibid*, Schudt *et al.*, *Ibid*, Bloeman *et al.*, *Ibid.*, Al Essa, *et al.*, "Heterogeneity of circulating and exudated polymorphonuclear leukocytes in superoxide-generating response to cyclic AMP and cyclic AMP-elevating agents: investigation of the underlying mechanism," *Biochem. Pharmacol.* 49 315-322, 1995; Ottonello *et al.*, "Cyclic AMP-elevating agents down-regulate the oxidative burst induced by granulocyte-macrophage colony stimulating factor (GM-CSF) in adherent neutrophils," *Clin. Exp. Immunol.* 101 502-508, 1995, and Ottonello *et al.*, "Tumor necrosis factor alpha-induced oxidative burst in neutrophils adherent to fibronectin effects of cyclic AMP-elevating agents," *Br J Haematol* 91 566-570, 1995.

It is further inferred that the compounds of Formula (1.0.0) inhibit CD11b/CD18 expression, Berends *et al.*, "Inhibition of PAF-induced expression of CD11b and shedding of L-selectin on human neutrophils and eosinophils by the type-IV selective PDE inhibitor, rolipram," *Eur Respir J* 10 1000-1007, 1997; and Derian *et al.*, "Inhibition of chemotactic peptide-induced neutrophil adhesion to vascular endothelium by cAMP modulators," *J. Immunol.* 154 308-317, 1995.

It is still further inferred that the compounds of Formula (1.0.0) inhibit alveolar macrophage PDE4s, thereby reducing the release of chemotactic factors and TNF-α, and that the compounds of Formula (1.0.0) increase synthesis and facilitate release from monocytes of the anti-inflammatory cytokine IL-10, which in turn is capable of decreasing the generation of TNF-α, IL-1β, and GM-CSF by synovial fluid mononuclear cells, thereby augmenting the overall anti-inflammatory profile of the PDE4 inhibitors of Formula (1.0.0); Schudt *et al.*, "PDE isoenzymes as targets for anti-asthma drugs," *Eur Respir J* 8 1179-1183, 1995; and Kambayashi *et al.*, "Cyclic nucleotide phosphodiesterase Type IV participates in the regulation of IL-10 and the subsequent inhibition of TNF-alpha and IL-6 release by endotoxin-stimulated macrophages," *J Immunol.* 155 4909-4916, 1995.

The application of PDE4 inhibitors to the treatment of COPD in human patients has been demonstrated in clinical trials. Treatment with SB-207,499, represented by Formula (0 1.9) above, at a dose of 15 mg twice a day for six weeks has been shown to result in increases in FEV_1 and forced vital capacity (FVC); Brown, W.M., "SB-207499," *Anti-inflamm. Immunomodulatory Invest. Drugs* 1 39-47, 1999. The clinical efficacy of SB-207,499 has also been demonstrated in a four week trial that has provided evidence of improved FEV_1, and in a six week study in COPD patients receiving 15 mg twice a day that has also provided evidence of improved FEV_1, Brown, *ibid.* SB-207,499 has already been described further above and represented by Formula (0 1.9).



SB-207,499 (0 1.9)

8.3 Bronchitis and Bronchiectasis

In accordance with the particular and diverse inhibitory activities described above that are possessed by the compounds of Formula (1.0.0), they are useful in the treatment of bronchitis of whatever type, etiology, or pathogenesis, including, e.g., acute bronchitis which has a short but severe course and is caused by exposure to cold, breathing of irritant substances, or an acute infection, acute laryngotracheal bronchitis which is a form of nondiphtheritic croup; arachidic bronchitis which is caused by the presence of a peanut kernel in a bronchus, catarrhal bronchitis which is a form of acute bronchitis with a profuse mucopurulent discharge, chronic bronchitis which is a long-continued form of bronchitis with a more or less marked tendency to recurrence after stages of quiescence, due to repeated attacks of acute bronchitis or chronic general diseases, characterized by attacks of coughing, by expectoration either scanty or profuse, and by secondary changes in the lung tissue; croupus bronchitis which is characterized by violent cough and paroxysms of dyspnea; dry bronchitis which is characterized by a scanty secretion of tough sputum, infectious asthmatic bronchitis which is a syndrome marked by the development of symptoms of bronchospasm following respiratory tract infections in persons with asthma, productive bronchitis which is bronchitis associated with a productive cough, staphylococcus or streptococcal bronchitis which are caused by staphylococci or streptococci; and vesicular bronchitis in which the inflammation extends into the alveoli, which are sometimes visible under the pleura as whitish-yellow granulations like millet seeds.

Bronchiectasis is a chronic dilatation of the bronchi marked by fetid breath and paroxysmal coughing with the expectoration of mucopurulent matter It may affect the tube uniformly, in which case it is referred to as cylindric bronchiectasis, or it may occur in irregular pockets, in which case it is called sacculated bronchiectasis When the dilated bronchial tubes have terminal bulbous enlargements, the term fusiform bronchiectasis is used In those cases where the condition of dilatation extends to the bronchioles, it is referred to as capillary bronchiectasis If the dilatation of the bronchi is spherical in shape, the condition is referred to as cystic bronchiectasis Dry bronchiectasis occurs where the infection involved is episodic and it may be accompanied by hemoptysis, the expectoration of blood or of blood-stained sputum During quiescent periods of dry bronchiectasis, the coughing which occurs is nonproductive Follicular bronchiectasis is a type of bronchiectasis in which the lymphoid tissue in the affected regions becomes greatly enlarged, and by projection into the bronchial lumen, may seriously distort and partially obstruct the bronchus Accordingly, the compounds of Formula (1.0.0) are useful in the beneficial treatment of the various above-described types of bronchiectasis as a direct result of their inhibition of PDE4 isozymes

The utility of the compounds of Formula (1.0.0) as bronchodilators or bronchospasmolytic agents for treating bronchial asthma, chronic bronchitis and related diseases and disorder described herein, is demonstrable through the use of a number of different *in vivo* animal models known in the art, including those described in the paragraphs below

Bronchospasmolytic Activity *In Vitro* – The ability of the compounds of Formula (1.0.0) to cause relaxation of guinea-pig tracheal smooth muscle is demonstrated in the following test procedure. Guinea-pigs (350-500 g) are killed with sodium pentothal (100 mg/kg I p.). The trachea is dissected and a section 2-3 cm in length is excised. The trachea is transected in the transverse plane at alternate cartilage plates so as to give rings of tissue 3-5 mm in depth. The proximal and distal rings are discarded Individual rings are mounted vertically on stainless steel supports, one of which is fixed at the base of an organ bath, while the other is attached to an isometric transducer The rings are bathed in Krebs solution (composition µM $NaHCO_3$ 25, NaCl 113, KCl 4 7, $MgSO_4$ $7H_2O$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5; glucose 11 7) at 37°C and gassed with O_2/CO_2 (95.5, v/v). Rings prepared in this manner, preloaded to 1 g, generate spontaneous tone and, after a period of equilibration (45-60m), relax consistently on addition of spasmolytic drugs. To ascertain spasmolytic activity, test compounds of Formula (1.0 0) are dissolved in physiological saline and added in increasing quantities to the organ bath at 5m intervals to provide a cumulative concentration-effect curve.

In the above test model, compounds of Formula (1 0.0) produce concentration-related relaxation of guinea-pig tracheal ring preparations at concentrations in the range of from 0.001 to 1.0 µM

The anti-inflammatory activity of the combinations of therapeutic agents of the present invention is demonstrated by the inhibition of TNFα production in human whole blood stimulated with Lipopolysaccharide (LPS) Compounds are analyzed in the presence of beta agonist (10 ng/ml) and Indomethacin (1uM). Prepare 250 ml assay buffer 200 mM HEPES in RPMI 1640 filtered. The following are performed at room temperature at the bench Prepare "IP" cocktail in 50 ml polypropylene tube by adding 0.4 ml of Indomethacin (stock 4 mM) and 0.4 ml of beta agonist (stock 0.04 mg/ml) for f v 40ml with assay buffer Prepare compounds from powder stocks into DMSO to either 200 or 60 mM stock solutions. Make eight-point half-log serial dilutions in glass vials or microtubes Add 0 01 ml of each compound dilution to the 5 ml polypropylene tubes where 0.490 ml assay buffer and 0.50 ml "IP" cocktail is added for f v 1.0 ml. (The compounds' assay f.c. 100-0 1 uM.) Prepare LPS solution such that 0.06 ml LPS (stock 1 mg/ml) is added to 40 ml assay buffer for f.c. 2 ug/ml 6. Prepare a 2% DMSO solution by adding 200 ul DMSO to 9.8 ml assay buffer Add 10 ml of IP cocktail to the 2% DMSO solution. This cocktail is used for control wells such that Indomethacin assay f.c. is 1uM and beta agonist f.c. is 10 ng/ml. The following are performed under the tissue culture hood. Add 0.0125 ml of diluted compound to appropriate well in U-bottom sterile Costar 96-well plate #3790 Add 0.0125 ml LPS to all wells (f.c. 0 1 ug/ml) except negative control wells. Fresh human whole blood is drawn (~22 ml per 96-well plate) usually four green tops per donor into sterile heparin tubes kept at 37oC Add 0.225 ml of whole blood to the plates. Cover, incubate at 37oC, and rock for four hours. Centrifuge the plates at 2000rpm for 10 minutes. Prepare ELISA standards. Remove 100 ul serum into flat bottom plate. Dilute 1:20 by removing 15 ul and adding 285 ul RD6 diluent. Freeze @ -20oC For analysis, thaw and add 200 ul to R & D Systems TNFα ELISA. Process the plates according to R & D Systems protocol Read plate at 450 nm using SoftMax Pro. Analyze and interpret with Java Fitter in order to determine IC50 values. A dose response curve of data expressed as percent control is plotted A minimum of six triplicate points are generated for each compound. The IC50 values are calculated using the Java Fitter curve-fitting program under the "IC50 fix both " parameter

In the above test model, combinations of therapeutic agents of the present invention produce concentration-related inhibition of TNFαproduction at concentrations in the range of from 0.001 to 1 0 µM

8.4 Allergic and Other Types of Rhinitis, Sinusitis

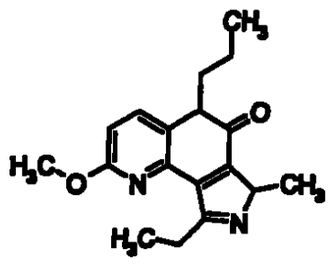
Allergic rhinitis is characterized by nasal obstruction, itching, watery rhinorrhea,

sneezing and occasional anosmia. Allergic rhinitis is divided into two disease categories, seasonal and perennial, in which the former is attributed to pollen or outdoor mould spores, while the latter is attributed to common allergens such as house dust mites, animal danders, and mould spores. Allergic rhinitis generally exhibits an early phase response and a late phase response The early phase response is associated with mast cell degranulation, while the late phase response is characterized by infiltration of eosinophils, basophils, monocytes, and T-lymphocytes. A variety of inflammatory mediators is also released by these cells, all of which may contribute to the inflammation exhibited in the late phase response.

A particularly prevalent form of seasonal allergic rhinitis is hay fever, which is marked by acute conjunctivitis with lacrimation and itching, swelling of the nasal mucosa, nasal catarrh, sudden attacks of sneezing, and often with asthmatic symptoms The compounds of Formula (1.0.0) are especially useful in the beneficial treatment of hay fever

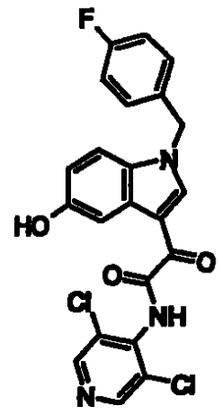
Other types of rhinitis for which the compounds of Formula (1.0.0) may be used as therapeutic agents include acute catarrhal rhinitis which is a cold in the head involving acute congestion of the mucous membrane of the nose, marked by dryness and followed by increased mucous secretion from the membrane, impeded respiration through the nose, and some pain, atrophic rhinitis which is a chronic form marked by wasting of the mucous membrane and the glands; purulent rhinitis which is chronic rhinitis with the formation of pus; and vasomotor rhinitis which is a non-allergic rhinitis in which transient changes in vascular tone and permeability with the same symptoms as allergic rhinitis, are brought on by such stimuli as mild chilling, fatigue, anger, and anxiety

There is a recognized link between allergic rhinitis and asthma. Allergic rhinitis is a frequent accompaniment to asthma, and it has been demonstrated that treating allergic rhinitis will improve asthma Epidemiologic data has also been used to show a link between severe rhinitis and more severe asthma. For example, the compound D-22888, under preclinical development for the treatment of allergic rhinitis, has been shown to exhibit a strong anti-allergic effect and to inhibit rhinorrhea in the antigen-challenged pig See, Marx *et al* "D-22888 - a new PDE4 inhibitor for the treatment of allergic rhinitis and other allergic disorders," *J. Allergy Clin. Immunol.* 99 S444, 1997 Another experimental compound, AWD-12,281 has been shown to be active in a rat model of allergic rhinitis See Poppe *et al* "Effect of AWD 12-281, a new selective PDE-4 inhibitor, loteprednol and beclomethasone in models of allergic rhinitis and airway inflammation in brown norway-rats," *Am. J Respir Crit. Care Med.* A95, 1999 The compounds D-22888 and AWD-12,281 have already been described further above and represented by Formulas (0 0.28) and (0 0.34), respectively



D-22888

(0.0.28)



Lotaprednol (AWD - 12,281)

(0.0.34)

Sinusitis is related to rhinitis in terms of anatomical proximity as well as a shared etiology and pathogenesis in some cases Sinusitis is the inflammation of a sinus and this condition may be purulent or nonpurulent, as well as acute or chronic. Depending upon the sinus where the inflammation is located, the condition is known as ethmoid, frontal, maxillary, or sphenoid sinusitis. The ethmoidal sinus is one type of paranasal sinus, located in the ethmoid bone. The frontal sinus is one of the paired paranasal sinuses located in the frontal bone. The maxillary sinus is one of the paired paranasal sinuses located in the body of the maxilla. Accordingly, the compounds of Formula (1.0.0) are useful in the beneficial treatment of acute or chronic sinusitis, but especially of chronic sinusitis.

8.5 Rheumatoid Arthritis, Osteoarthritis, Pain, Fever, and Gout

Arthritis is defined as inflammation of the joints, and rheumatoid arthritis is a chronic systemic disease primarily of the joints, usually polyarticular, marked by inflammatory changes in the synovial membranes and articular structures, and by muscular atrophy and rarefaction of the bones. Late stages of rheumatoid arthritis are marked by ankylosis and deformity Rheumatoid arthritis is a crippling autoimmune disease of unknown etiology which affects over 1% of the population.

As used herein, the term "rheumatoid arthritis" is intended to include within its scope where applicable related and associated forms of arthritis well known in the art, since these may also be treated with the compounds of Formula (1.0.0). Accordingly, the term "rheumatoid arthritis" includes acute arthritis, which is arthritis marked by pain, heat, redness, and swelling due to inflammation, infection, or trauma, acute gouty arthritis, which is acute arthritis associated with gout; chronic inflammatory arthritis, which is inflammation of the joints in chronic disorders such as rheumatoid arthritis, degenerative arthritis, which is osteoarthritis; infectious arthritis, which is arthritis caused by bacteria, rickettsiae, mycoplasmas, viruses,

fungi, or parasites, Lyme arthritis, which is arthritis of the large joints associated with Lyme disease, proliferative arthritis, which is inflammation of the joints with proliferation of the synovium, seen in rheumatoid arthritis, psoriatic arthritis, which is a syndrome in which psoriasis occurs in association with inflammatory arthritis, and vertebral arthritis, which is inflammation involving the intervertebral disks.

The three major pathological features of rheumatoid arthritis that are responsible for progressive joint destruction are inflammation, abnormal cellular and humoral responses, and synovial hyperplasia The particular cellular pathology of rheumatoid arthritis includes the presence of T-cells and monocytes. The T-cells, which are predominantly memory T-cells, constitute up to 50% of the cells recovered from the synovial tissue of rheumatoid arthritis patients, and of the monocytes found in the same tissue, 30-50% are antigen presenting cells, which is indicative of the autoimmune character of the disease. Pro-inflammatory cytokines, e.g , IL-1, IL-4, IL-5, IL-6, IL-9, IL-13, and TNF-α, are the major contributors to joint tissue damage, inflammation, hyperplasia, pannus formation and bone resorption. See Firestein, G.S and Zvaifler, W.J., "How important are T-cells in chronic rheumatoid synovitis?" *Arth. Rheum.* 33 768-773, 1990 This has been demonstrated, e.g., by the fact that monoclonal antibodies (Mabs) to TNF-α have shown promise in RA clinical trials, Maini *et al*, "Beneficial effects of tumor necrosis factor-alpha (TNF-α blockade in rheumatoid arthritis (RA)," *Clin. Exp. Immunol.* 101 207-212, 1995.

The PDE4 inhibitors of Formula (1 0 0) are useful in the treatment of rheumatoid arthritis as a result of their ability to suppress the activity of a variety of inflammatory cells, including basophils, eosinophils, and mast cells These inhibitory activities of the compounds of Formula (1.0.0) have already been described further above, as has their wide range of *in vitro* anti-inflammatory action *via* the release of reactive oxygen species, prostaglandins, and inflammatory cytokines, e.g., IL-5, IFN-γ, and TNF-α. See further Cohan *et al*, "*In vitro* pharmacology of the novel phosphodiesterase Type IV inhibitor, CP-80,633," *J Pharm. Exp. Ther* 278 1358-1361, 1996, and Barnette *et al*, "SB207499 (Ariflo), a potent and selective second generation phosphodiesterase 4 inhibitor *In vitro* anti-inflammatory actions," J *Pharm. Exp. Ther* 284 420-426, 1998 The PDE4 inhibitors of Formula (1 0.0) are also useful in the treatment of rheumatoid arthritis as a result of their effectiveness in inhibiting T-cell proliferation mediated *via* a number of different agents, including antigens such as house dust mite, which has been demonstrated in the art; Barnette al al, *ibid.* The ability of the compounds of Formula (1.0 0) to facilitate the release of cytokine IL-10 from monocytes, which in turn is capable of decreasing the generation of TNF-α, IL-1, IL-4, IL-5, IL-6, IL-9, IL-13, and GM-CSF by synovial fluid mononuclear cells, further augments the overall anti-inflammatory profile of the PDE4 inhibitors of Formula(1 0.0); Kambayashi *et al, ibid* Further,

the ability of the compounds of Formula (1 0.0) to inhibit TNF-α release from stimulated monocytes can be correlated with animal models of inflammation in which anti-inflammatory effects can be shown to correspond to suppression of TNF-α accumulation. One such animal model involves inhibition of LPS induced TNF-α release in mice by oral administration of a PDE4 inhibitor; Cheng *et al*, "The phosphodiesterase Type 4 (PDE4) inhibitor CP-80,633 *elevates cyclic AMP levels and decreases TNF-α production in mice: effect of* adrenalectomy," *J Pharm. Exp. Ther* 280 621-626, 1997 Another such animal model involves the inhibition of rat paw edema, induced by carageenan, by oral administration of rolipram, Singh *et al*, "Synovial fluid levels of tumor necrosis factor a in the inflamed rat knee: *Modulation by dexamethasone and inhibitors of matrix metalloproteinases* and phosphodiesterases," *Inflamm. Res.* 46(Suppl 2) S153-S154, 1997

Gout refers to a group of disorders of purine metabolism, and fully developed gout is manifested by various combinations of hyperuricemia, recurrent, characteristic acute inflammatory arthritis induced by crystals of monosodium urate monohydrate, tophaceous deposits of said crystals in and around the joints of the extremities, which may lead to joint *destruction and severe crippling, and uric acid urolithiasis. Rheumatic gout is another name* for rheumatoid arthritis. Tophaceous gout is gout in which there are tophi or chalky deposits of sodium urate. Some therapeutic agents are useful in treating both gout and its attendant inflammation, *e.g.*, phenylbutazone and colchicine; while other therapeutic agents possess *only uricosuric properties, e.g., sulfinpyrazone and benzbromarone*

Fever, or pyrexia, may be the result of any one of a large number of different factors, but with regard to the present invention such fever is either that manifested in pharyngoconjunctival fever or rheumatic fever, or that manifested during inflammation A concomitant of inflammation is pain, especially that experienced in the joints and connective tissue of those suffering from rheumatoid arthritis and gout.

Accordingly, the PDE4 inhibitory compounds of Formula (1.0.0) provide beneficial results in the treatment of gout, and fever and pain associated with inflammation.

Animal models of rheumatoid arthritis have also been used in the art for the purpose of demonstrating the correlation between *in vivo* modulation of TNF-α by PDE4 inhibitors and their utility in the treatment of rheumatoid arthritis. The activity of rolipram in animal models of acute inflammation such as the mouse adjuvant arthritis model, has been demonstrated in the art; Sekut *et al*, "Anti-inflammatory activity of phosphodiesterase (PDE) IV inhibitors in acute and chronic models of inflammation," *Clin. Exp. Immunol* 100(1) 126-132, 1995. The ability of rolipram to reduce disease severity in the collagen II induced arthritis (CIA) model after sc. or ip injection has been demonstrated in the art; Nyman *et al*, "Amelioration of collagen II induced arthritis in rats by Type IV phosphodiesterase inhibitor rolipram,' *Clin. Exp. Immunol.*

108 415-419, 1997 In this study the dosing regimen for rolipram was 2 mg/kg twice daily for five days before the onset of arthritis, and it significantly delayed the appearance of arthritic symptoms After the cessation of treatment the test animals developed arthritis and reached the same arthritis top score as the control group In the same study rolipram was also administered at 3 mg/kg twice daily at the time point when arthritis was apparent. This treatment drastically changed the development of the disease whereby progression of severity was halted and even after the cessation of treatment, the arthritis score did not reach the levels observed in untreated animals The investigators were also able to demonstrate a strong down-regulation of TNF-α and IFN-γ mRNA expression in regional lymph nodes, which suggests that the major effect of rolipram is exerted in the effector phase of the inflammatory process Nyman *et al, ibid.*

Inhibition of TNF-α Production by Human Monocytes *In Vitro* - The inhibitory effect of the compounds of Formula (1 0.0) on *in vitro* TNF-α production by human monocytes may be determined in accordance with the protocol described in EP 411 754 (Badger *et al)* and WO 90/15534 (Hanna). The referenced publications also describe two models of endotoxic shock which may be used to determine *in vivo* inhibitory activity of the compounds of Formula (1 0.0). The protocols used in these models are detailed and test compounds demonstrate a positive result by reducing serum levels of TNF-α induced by the injection of endotoxin

Selective PDE4 inhibitors such as RP73401 have been shown to exhibit significant amelioration of disease, especially improvements in joint destruction, synovitis, and fibrosis, in animal models such as those involving streptococcal cell wall (SCW)-induced arthritis; Sounese *et al,* "Potential of phosphodiesterase Type IV inhibitors in the treatment of rheumatoid arthritis," *Drugs* 1 541-553, 1998.

Of particular interest to the treatment of rheumatoid arthritis is the observation that PDE4 inhibitors' have positive effects at the site of action of the disease. For example, RP73401 has been demonstrated to decrease TNF-α mRNA expression at the pannus/cartilage interface of paw joints of collagen II treated mice Sounese *et al, ibid.* RP73401 has also been studied clinically in rheumatoid arthritis patients in a placebo-controlled, double-blind Phase II study of 35 rheumatoid arthritis patients administered 400 pg of the compound t.i.d The compound was able to induce a positive trend towards clinical improvement associated with a reduction in C-reactive protein and IL-6 serum levels. Chikanza *et al,* "The clinical effects of RP73401 phosphodiesterase Type 4 inhibitor in patients with rheumatoid arthritis," *Br J Rheumatol.* 36.Abstr Suppl. I, 186, 1997

Assaying Increased cAMP Accumulation in Intact Tissues Using U-937 cells - Another assay suitable for demonstrating the PDE4 inhibiting activity of the compounds of Formula (1.0 0) is one which utilizes U-937 cells from a human monocyte cell line that has

been shown to contain a large amount of PDE4 In order to assess the inhibition of PDE4 activity in intact cells, non-differentiated U-937 cells at a density of approximately 10^6 cells per reaction tube are incubated with concentrations ranging from 0.01 to 1000 pM of test compound for one minute, and with 1 μM of prostaglandin E2 for an additional four minutes Five minutes after initiating the reaction, cells are lysed by the addition of 17.5% perchloric acid, after which the pH is brought to neutral by the addition of 1 M potassium carbonate The cAMP content of the reaction tube is measured using RIA techniques A detailed protocol for carrying out this assay is described in Brooker *et al*, "Radioimmunoassay of cyclic AMP and cyclic GMP," *Adv Cyclic Nucleotide Res.* 10 1-33, 1979

8.6 Eosinophil-Related Disorders

The ability of the PDE4 inhibitory compounds of Formula (1.0.0) to inhibit eosinophil activation as part of their overall anti-inflammatory activity has been described above. Accordingly, the compounds of Formula (1 0.0) are useful in the therapeutic treatment of eosinophil-related disorders Such disorders include eosinophilia, which is the formation and accumulation of an abnormally large number of eosinophils in the blood The name of the disorder derives from "eosin", a rose-colored stain or dye comprising a bromine derivative of fluorescein which readily stains "eosinophilic leukocytes" in the blood of patients who are thus readily identified A particular eosinophilic disorder that can be treated in accordance with the present invention is pulmonary infiltration eosinophilia, which is characterized by the infiltration of the pulmonary parenchyma by eosinophils This disorder includes especially Loffler's syndrome, which is a condition characterized by transient infiltrations of the lungs, accompanied by cough, fever, dyspnea, and eosinophilia.

Other eosinophilic disorders include chronic eosinophilic pneumonia, which is a chronic interstitial lung disease characterized by cough, dyspnea, malaise, fever, night sweats, weight loss, eosinophilia, and a chest film revealing non-segmental, non-migratory infiltrates in the lung periphery; tropical pulmonary eosinophilia, which is a subacute or chronic form of occult filariasis, usually involving *Brugia malayi, Wuchereria bancrofti,* or filariae that infect animals, occurs in the tropics, and is characterized by episodic nocturnal wheezing and coughing, strikingly elevated eosinophilia, and diffuse reticulonodular infiltrations of the lungs, bronchopneumonic aspergillosis, which is an infection of the bronchi and lungs by *Aspergillus* funga resulting in a diseased condition marked by inflammatory granulomatous lesions in the nasal sinuses and lungs, but also in the skin, ear, orbit, and sometimes in the bones and meninges, and leading to aspergilloma, the most common type of fungus ball formed by colonization of *Aspergillus* in a bronchus or lung cavity

The term "granulomatous" means containing granulomas, and the term "granuloma" refers to any small nodular delimited aggregation of mononuclear inflammatory cells or such a

collection of modified macrophages resembling epithelial cells, usually surrounded by a rim of lymphocytes, with fibrosis commonly seen around the lesion Some granulomas contain eosinophils Granuloma formation represents a chronic inflammatory response initiated by various infectious and noninfectious agents A number of such granulomatous conditions are treatable using a compound of Formula (1.0 0), e g , allergic granulomatous angiitis, also called *Churg-Strauss syndrome, which is a form of systemic necrotizing vasculitis* in which there is prominent lung involvement, generally manifested by eosinophilia, granulomatous reactions, and usually severe asthma A related disorder is polyarteritis nodosa (PAN), which is marked by multiple inflammatory and destructive arterial lesions and is a form of systemic necrotizing vasculitis involving the small and medium-sized arteries with signs and symptoms resulting from infarction and scarring of the affected organ system, in particular the lungs Other eosinophil-related disorders which may be treated in accordance with the present invention are those affecting the airways which are induced or occasioned by a reaction to a therapeutic agent unrelated to any compound of Formula (1 0 0).

8.7 Atopic Dermatitis, Urticaria, Conjunctivitis, and Uveitis

Atopic dermatitis is a chronic inflammatory skin disorder seen in individuals with a hereditary predisposition to a lowered cutaneous threshold to pruritis, that is often accompanied by allergic rhinitis, hay fever, and asthma, and that is principally characterized by extreme itching. Atopic dermatitis is also called allergic dermatitis, and allergic or atopic eczema.

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease in young children, and it affects from 10% to 15% of the population during childhood Atopic dermatitis is frequently associated with asthma and allergies and it has therefore become known as a component of the so-called "atopic triad", since it occurs frequently in individuals with asthma and/or allergic rhinitis See Leung Dym, *Atopic Dermatitis. From Pathogenesis To Treatment*, R.G Landes Co., Austin, Texas, 1-226, 1996 Accordingly, the immune dysfunction associated with atopic dermatitis is treatable with therapeutic agents that are inhibitors of PDE4 For example, rolipram, Ro-201724, and denbufylline have been reported to produce a concentration-related inhibition of the proliferation of human peripheral blood mononuclear cells (HPBM) from normal patients as well as from subjects with atopic dermatitis See, respectively, Torphy *et al., Drugs and the Lung*, Eds. Page and Metzger, Raven Press, New York, 1994, and O'Brien, *Mol Medicine Today*, 369, 1997 These studies also determined that the proliferative response of HPBM from atopic dermatitis patients was more sensitive to PDE4 inhibition than was the proliferation observed in HPBM from normal subjects

Th2 type cytokine secreting T-cells expressing the cutaneous lymphocyte associated antigen play a central role in the induction of local IgE responses and the recruitment of

eosinophils in this disease The chronic inflammation seen in atopic dermatitis is considered to be the result of several interdependent factors, such as repeated or persistent allergen exposure, which can lead to Th2 cell expansion It has been demonstrated that there is an increased frequency of allergen specific T-cells producing increased IL-4, IL-5, and IL-3 levels in the blood of atopic dermatitis patients See Leung Dym *et al.*, "Allergic and immunological skin disorders," *JAMA* 278(22) 1914-1923, 1997 This is significant because IL-4 and IL-3 induce the expression of vascular adhesion molecule-1 (VCAM-1), an adhesion molecule involved in the migration of mononuclear cells and eosinophils into sites of tissue inflammation Further, IL-5 is a key mediator of eosinophil activation, which is a common feature of atopic disease.

Increased concentration of cAMP in lymphocytes and basophils has long been known to be associated with decreased mediator release from those cells, and more recently it has been reported that histamine acting on H2 receptors increases cAMP levels and inhibits IL-4 production in murine Th2 cells It is surmised, accordingly, that there is present in atopic diseases such as atopic dermatitis, impaired β-adrenergic responses or enhanced PDE4 activity of leukocyte inflammatory responses A diminished cAMP response may result from an enhanced PDE4 activity that has a genetic basis or that is an acquired condition

Studies have been carried out which compare different cell types from atopic patients with those from healthy volunteers, and the results have shown that increased cAMP-PDE activity in atopic cells correlates with abnormal inflammatory and immune cell function in atopic dermatitis Further, the PDE4 enzyme from atopic leukocytes is more sensitive to PDE4 inhibitors than the PDE4 enzyme from normal leukocytes, and up to a 14-fold difference has been demonstrated See Chan and Hanifin, "Differential inhibitory effects of cAMP phosphodiesterase isoforms in atopic and normal leukocytes," *J Lab. Clin. Med.*, 121(1) 44-51, 1993 An increased sensitivity can also be seen in the inhibition of proliferation of peripheral blood mononuclear cells from atopic donors on treatment with PDE4 inhibitors For example, rolipram has been found to be more effective at inhibiting PHA stimulated atopic dermatitis PBMC proliferation than at inhibiting PHA stimulated normal PBMC proliferation, with an IC_{50} = 280 nM compared to an IC_{50} = 2600 nM, respectively

Further, it has been shown that a structurally diverse range of selective PDE4 inhibitors are effective in reducing skin eosinophilia in the guinea pig which has been mediated *via* a range of agents such as PAF, arachidonic acid, zymosan activated plasma, and protein of cutaneous anaphylaxis See Beasley *et al*, "Synthesis and evaluation of a novel series of phosphodiesterase 4 inhibitors A potential treatment for asthma," *Bioorg. Med. Chem. Letts.* 8 2629-2634, 1998 Such data shows the utility of PDE4 inhibitors in treating eosinophil driven skin diseases. Such treatment is by means of topical

administration, *e g* , topical atizoram applied bilaterally over eight days to twenty patients in a clinical trial has been found to effectively inhibit all of the inflammatory parameters tested, showing both qualitative and quantitative improvements with no adverse effects See Hanifin *et al.*, "Type 4 phosphodiesterase inhibitors have clinical and *in vitro* anti-inflammatory effects in atopic dermatitis," *J. Invest. Dermatol.* 107 51-56, 1996.

Accordingly, the PDE4 inhibitors of Formula (1 0 0) are useful for the beneficial treatment of atopic dermatitis as described above A related area of therapeutic application for which the compounds of Formula (1 0 0) also produce beneficial results is in the treatment of urticaria Urticaria is a vascular reaction, usually transient, involving the upper dermis, representing localized edema caused by dilatation and increased permeability of the capillaries, and marked by the development of wheals or hives. Many different stimuli are capable of inducing an urticarial reaction, and it may be classified according to precipitating causes, as immune-mediated, complement-mediated which may involve immunologic or nonimmunologic mechanisms, urticariogenic material-induced, physical agent-induced, stress-induced, or idiopathic. The condition may also be designated acute or chronic depending on the duration of an attack. Angioedema is the same response in the deep dermis or subcutaneous or submucosal tissues.

The most common types of urticaria which are treatable with the compounds of Formula (1.0.0) are cholinergic urticaria which is characterized by the presence of distinctive punctate wheals surrounded by areas of erythema, thought to be a nonimmunologic hypersensitivity reaction in which acetylcholine released from parasympathetic or motor nerve terminals induces release of mediators from mast cells, and evoked by conditions of exertion, stress, or increased environmental heat; cold urticaria which is urticaria precipitated by cold air, water, or objects, occurring in two forms In the autosomal dominant form which is associated with fevers, arthralgias, and leukocytosis, the lesions present are erythematous, burning papules and macules, and in the more common acquired form which is usually idiopathic and self-limited, contact urticaria which is a localized or generalized transient wheal-and-flare response elicited by exposure to rapidly absorbable urticariogenic agents; giant urticaria which is angioedema, and papular urticaria which is a persistent cutaneous eruption representing a hypersensitivity reaction to insect bites

Accordingly, the PDE4 inhibitors of Formula (1.0 0) are useful for the beneficial treatment of the various types of urticaria as described above A related area of therapeutic application for which the compounds of Formula (1.0 0) also produce beneficial results is in various ophthalmic uses, in particular in the treatment of conjunctivitis and uveitis

The conjunctiva is a delicate membrane that lines the eyelids and covers the exposed surface of the sclera Conjunctivitis is an inflammation of the conjunctiva that generally

consists of conjunctival hyperemia associated with a discharge The most common types of conjunctivitis, which are treatable with the compounds of Formula (1.0.0), are actinic conjunctivitis produced by ultraviolet light; acute catarrhal conjunctivitis which is an acute, infectious conjunctivitis associated with cold or catarrh and characterized by vivid hyperemia, edema, loss of translucence, and mucous or mucopurulent discharge; acute contagious conjunctivitis which is a mucopurulent, epidemic conjunctivitis caused by *Haemophilus aegyptius* that has the same symptoms as acute catarrhal conjunctivitis and is also called "pinkeye", allergic conjunctivitis which is a component of hay fever; atopic conjunctivitis which is allergic conjunctivitis of the immediate type caused by airborne allergens, *e.g*, pollens, dusts, spores, and animal dander; chronic catarrhal conjunctivitis which is a mild, chronic conjunctivitis with only slight hyperemia and mucous discharge, purulent conjunctivitis which is an acute conjunctivitis caused by bacteria or viruses, particularly gonococci, meningococci, pneumococci, and streptococci, and characterized by severe inflammation of the conjunctiva and copious discharge of pus, and vernal conjunctivitis which is a bilateral conjunctivitis of seasonal occurrence, of unknown cause, affecting children especially boys and characterized by flattened papules and a thick, gelatinous exudate. Accordingly, the PDE4 inhibitors of Formula (1 0 0) are useful for the beneficial treatment of the various types of conjunctivitis as described above. A related area of therapeutic application for which the compounds of Formula (1 0 0) also produce beneficial results is in the treatment of uveitis.

The uvea is the vascular middle coat or tunic of the eye, comprising the iris, ciliary body, and choroid Uveitis is an inflammation of all or part of the uvea and commonly involves the other tunics of the eye, *i.e.*, the sclera and the cornea, and the retina as well The most common types of uveitis, which are treatable with the compounds of Formula (1.0.0), are anterior uveitis which is uveitis involving the structures of the iris and/or ciliary body, including iritis, cyclitis, and iridocyclitis, granulomatous uveitis which is uveitis of any part of the uveal tract but particularly of the posterior portion, characterized by nodular collections of epithelioid cells and giant cells surrounded by lymphocytes, nongranulomatous uveitis which is inflammation of the anterior portion of the uveal tract, *i.e*, the iris and ciliary body; phacoantigenic uveitis which is one of the lens-induced uveitides is a severe anterior uveitis similar to sympathetic ophthalmia, observed weeks or even months after extracapsular lens surgery or other trauma to the capsule, and posterior uveitis which is uveitis involving the posterior segment of the eye, including choroiditis and chorioretinitis. Accordingly, the PDE4 inhibitors of Formula (1 0 0) are useful for the beneficial treatment of the various types of uveitis as described above

8.8 Psoriasis

Psoriasis is a common chronic, squamous dermatosis with polygenic inheritance and a fluctuating course that is characterized by microabscesses and spongiform pustules, as well

as erythematous, dry, scaling patches of various sizes Psoriasis is a common skin disease that affects approximately 2% of the population, and more then 1½ million patients in the US annually consult physicians for treatment. Psoriasis is usually recurrent and in some instances can be very debilitating The etiology of psoriasis is unknown, but it appears to be an autoimmune disease with genetic predisposition.

Psoriasis involves a large T-cell infiltration in the affected regions of the skin, with CD4+ lymphocytes in the dermis and CD8+ lymphocytes in the epidermis These lymphocytes secrete IL-2, IFN-γ, and TNF-α, which alter keratinocyte proliferation and differentiation Further, from 5% to 10% of psoriasis patients develop psoriatic arthritis, the symptoms of which are very similar to those of rheumatoid arthritis The broad spectrum of anti-inflammatory activities displayed by PDE4 inhibitors, already discussed above, enables such inhibitors to be used beneficially in the treatment of psoriasis.

It has been demonstrated that treatment of epidermal basal cells, in primary culture, with the PDE4 inhibitor Ro 20-1724 leads to a three-fold increase in cAMP concentrations It has also been shown that treatment of psoriatic epidermal slices and keratomed psoriatic epidermal slices with Ro 20-1724 results in a very marked elevation of cAMP concentrations over controls Specifically, a 1395% increase in cAMP concentration in keratomed psoriatic epidermis has been observed PDE4 inhibitors have also been shown to inhibit the inflammatory response of a number of mediators *via* either topical or systemic administration For example, rolipram has been shown to inhibit croton oil-induced ear inflammation in the mouse at topical doses as low as 0 03 mg per ear The selective PDE4 inhibitor Ro 20-1724 has also been investigated in two double-blind studies comparing its effectiveness to vehicle, where it has been shown to improve psoriatic lesions without adverse systemic or cutaneous effects.

8.9 Multiple Sclerosis and Other Inflammatory Autoimmune Diseases

A sclerosis is an induration, or hardening, and refers especially to hardening of a part from inflammation, and from increased formation of connective tissue and in diseases of the interstitial substance The term "sclerosis" is used chiefly for such a hardening of the nervous system due to the deposition of connective tissue, or to designate hardening of the blood vessels. Multiple sclerosis (MS) is a disease in which there are foci of demyelination of various sizes throughout the white matter of the central nervous system, sometimes extending into the gray matter, resulting in weakness, incoordination, paresthesias, speech disturbances, and visual complaints Multiple sclerosis is a disease of unknown etiology with a prolonged course involving many remissions and relapses

Multiple sclerosis is an autoimmune disease that in addition to chronic inflammation and demyelination, also results in gliosis within the central nervous system There are

several disease subtypes, including primary progressive multiple sclerosis, and relapsing remitting multiple sclerosis These disease subtypes may be distinguished from each other on the basis of the course of the disease, of the type of inflammation involved, and through the use of magnetic resonance imaging (MRI). It is also possible for the basic disease mechanism to change during the course of multiple sclerosis, with an inflammation-based process being replaced later by one which involves demyelination and axonal damage. See Weilbach and Gold, "Disease modifying treatments for multiple sclerosis. What is on the horizon?" *CNS Drugs* 11 133-157, 1999

In multiple sclerosis inflammatory lesions are localized to, but prevalent throughout the white matter of the central nervous system, although sclerotic plaques characterized by demyelination are a hallmark of the disease The development of demyelination, in turn, is caused by the necrosis of oligodendrocytes, and demyelination is associated with an infiltrate composed mainly of T-cells and macrophages, which together with local cells such as astrocytes, microglia and microvascular brain endothelial cells, express major histocompatibility complex (MHC) class II These cells are thus implicated in antigen presentation and an inflammatory response, and a number of pro-inflammatory cytokines, including TNF-α, TNF-β, IL-1, IL-6 and IFN-γ have been identified in the brain tissue of multiple sclerosis patients and their presence is generally associated with active lesions. TNF-α in particular has been the focus of attention because it mediates myelin and oligodendrocyte damage *in vitro*, induces astrocytes to express surface adhesion molecules, and is associated with disruption of the blood-brain barrier

Animal models have been used to demonstrate the role of TNF-α in multiple sclerosis, *e.g.*, in experimental allergic encephalomyelitis (EAE) administration of anti-TNF antibodies or soluble TNF receptors has been shown to provide a protective effect. See Selmaj *et al.*, "Prevention of chronic relapsing experimental autoimmune encephalomyelitis by soluble tumor necrosis factor," *J Neuroimmunol.* 56 135-141, 1995. A direct correlation between the level of TNF-α mRNA and progression of EAE has also been reported See Reeno *et al.*, "TNF-alpha expression by resident microglia and infiltrating leukocytes in the central nervous system of mice with experimental allergic encephalomyelitis regulation by the Th1 cytokines," *J Immunol* 154 944-953, 1995 Further evidence demonstrating that TNF-α is a mediator of multiple sclerosis is the increased concentration of TNF-α in the cerebrospinal fluid of multiple sclerosis patients during the course of the disease. Further, a transgenic mouse overexpressing TNF-α in the central nervous system has shown signs of spontaneous demyelination, while a transgenic TNF-α knockout mouse has shown a protective effect. See Probert *et al.*, "Spontaneous inflammatory demyelinating disease in transgenic mice showing central nervous system-specific expression of tumor necrosis factor

alpha," *Proc. Natl Acad Sci USA* 92 11294-11298, 1995; and Liu *et al.*, "TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination," *Nature Med* 4 78-83, 1998

Since PDE4 inhibitors also reduce TNF-α, they are beneficial in the treatment of multiple sclerosis because TNF-α plays a key role in mediating multiple sclerosis, as discussed above. For example, in a marmoset model of experimental allergic encephalomyelitis rolipram has been found to suppress the appearance of clinical signs and abolish abnormalities in MRI imaging In another study of the effects of rolipram on chronic relapsing experimental allergic encephalomyelitis in SJL mice, it has been shown that rolipram ameliorates clinical signs and pathological changes in this model See Genain *et al.*, "Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phosphodiesterase," *Proc. Natl. Acad. Sci. USA.* 92 3601-3605, 1995; and Sommer *et al.*, "Therapeutic potential of phosphodiesterase Type 4 inhibition in chronic autoimmune demyelinating disease," *J Neuroimmunol.* 79 54-61, 1997

In addition to inhibiting PDE4 activity and the production of TNF-α, the compounds of Formula (1 0 0) also possess activity as immunosuppressive agents and are especially useful for treating autoimmune diseases in which inflammation is a component part of the autoimmune disease, or in which inflammation is part of the etiology of the autoimmune disease, or in which inflammation is otherwise involved with the autoimmune disease. Alternatively, the compounds of Formula (1 0 0) are anti-inflammatory agents useful in the treatment of inflammatory diseases in which autoimmune reactions are a component part of the inflammatory disease, or in which autoimmune reactions are part of the etiology of the inflammatory disease, or in which autoimmune reactions are otherwise involved with the inflammatory disease Accordingly, the compounds of Formula (1.0 0) are useful in the treatment of multiple sclerosis, as discussed in detail further above.

Other autoimmune/inflammatory diseases that can be treated by therapeutic agents comprising the compounds of Formula (1 0 0) include, but are not limited to, autoimmune hematological disorders such as hemolytic anemia, aplastic anemia, pure red cell anemia, and idiopathic thrombocytopenic purpura, systemic lupus erythematosus, polychondritis, scleroderma, Wegner's granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome; idiopathic sprue; autoimmune inflammatory bowel diseases such as ulcerative colitis and Crohn's disease; endocrin opthamopathy; Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I); anterior uveitis and granulomatous (posterior) uveitis, keratoconjunctivitis sicca and epidemic keratoconjunctivitis, diffuse interstitial pulmonary fibrosis (interstitial lung fibrosis), idiopathic pulmonary fibrosis, cystic fibrosis,

psoriatic arthritis, glomerulonephritis with and without nephrotic syndrome, including acute glomerulonephritis, idiopathic nephrotic syndrome, and minimal change nephropathy; inflammatory/hyperproliferative skin diseases including psoriasis and atopic dermatitis discussed in detail further above, contact dermatitis, allergic contact dermatitis, benign familial pemphigus, pemphigus erythematosus, pemphigus foliaceus, and pemphigus vulgaris

Further, the compounds of Formula (1 0 0) may be used as immunosuppressant agents for the prevention of allogeneic graft rejection following organ transplantation, where such organs typically include tissue from bone marrow, bowel, heart, kidney, liver, lung, pancreas, skin and cornea.

8.10 Inflammatory Bowel Disease

Ulcerative colitis (UC) is a chronic, recurrent ulceration in the colon, chiefly of the mucosa and submucosa, which is of unknown cause, and which is manifested clinically by cramping abdominal pain, rectal bleeding, and loose discharges of blood, pus, and mucus with scanty fecal particles Related diseases of the bowel include collagenous colitis, which is a type of colitis of unknown etiology that is characterized by deposits of collagenous material beneath the epithelium of the colon, and marked by crampy abdominal pain with a conspicuous reduction in fluid and electrolyte absorption that leads to watery diarrhea, colitis polyposa, which is ulcerative colitis associated with the formation of pseudopolyps, *i.e.*, edematous, inflamed islands of mucosa between areas of ulceration; and transmural colitis, which is inflammation of the full thickness of the bowel, rather than mucosal and submucosal disease, usually with the formation of noncaseating granulomas, that clinically resembles ulcerative colitis but in which the ulceration is often longitudinal or deep, the disease is often segmental, stricture formation is common, and fistulas, particularly in the perineum, are a frequent complication

Crohn's disease (CD) is a chronic granulomatous inflammatory disease of unknown etiology involving any part of the gastrointestinal tract, but commonly involving the terminal ileum with scarring and thickening of the bowel wall, frequently leading to intestinal obstruction, and fistula and abscess formation, and having a high rate of recurrence after treatment. Ulcerative colitis, Crohn's disease and the related diseases discussed above are collectively referred to as inflammatory bowel disease (IBD) These diseases are chronic, spontaneously relapsing disorders of unknown cause that are immunologically mediated and whose pathogenesis has been established through the use of animal models and advanced immunological techniques. See Bickston and Caminelli, "Recent developments in the medical therapy of IBD," *Curr Opin. Gastroenterol* 14 6-10, 1998, and Murthy *et al.*, "Inflammatory bowel disease. A new wave of therapy," *Exp. Opin Ther Patents* 8(7) 785-818, 1998 While the incidence of ulcerative colitis has remained relatively stable, the incidence of Crohn's disease has increased significantly

Current therapy for inflammatory bowel disease includes 5-aminosalicylic acid, corticosteroids, and immunomodulators such as azathioprine, 6-mercaptopurine, and methotrexate. These agents have a wide range of adverse side effects and do not modify the disease itself, and there is thus an ongoing need for more effective treatment agents The compounds of Formula (1 0 0) are able to beneficially treat inflammatory bowel diseases as a result of their ability to inhibit the production of TNF-α, because TNF-α causes immune cell activation, proliferation, and mediator release in inflammatory bowel disease See Radford-Smith and Jewell, "Cytokines and inflammatory bowel disease." *Bailliere's Clin. Gasteroenterol.* 10 151-164, 1996 TNF-α has also been detected in the stools and intestinal mucosa of patients with inflammatory bowel disease Further, early clinical studies in Crohn's disease using TNF monoclonal antibodies have shown significant promise.

As already detailed further above, selective PDE4 inhibitors have a marked effect on the inhibition of TNF-α release from peripheral blood mononuclear cells after those cells have been stimulated with a wide range of mediators, both *in vitro* and *in vivo*. The selective PDE4 inhibitor arofylline has been shown to provide beneficial effects when tested in models of colitis in the rat. Further, in a dextran sulfate induced colitis model in the rat, rolipram and the selective PDE4 inhibitor LAS31025 have demonstrated beneficial effects comparable to prednisolone Both test compounds have been shown to ameliorate bleeding and inflammatory markers See Puig *et al.* "Curative effects of phosphodiesterase 4 inhibitors in dextran sulfate sodium induced colitis in the rat," *Gastroenterology* 114(4) A1064, 1998 Other workers have used additional models to demonstrate the ability of selective PDE4 inhibitors to provide gastrointestinal protection For example, it has been shown that lipopolysaccharide induced erythrocyte extravasation in rats and intestinal hypoperfusion in dogs can be attenuated with the selective PDE4 inhibitors rolipram and denbufylline See Cardelus *et al.*, "Inhibiting LPS induced bowel erythrocyte extravasation in rats, and of mesenteric hypoperfusion in dogs, by phosphodiesterase inhibitors," *Eur J Pharmacol.* 299 153-159, 1996, and Cardelus *et al*, "Protective effects of denbufylline against endotoxin induced bowel hyperplasia," *Met. Find Exp. Clin. Pharmacol.* 17(Suppl A) 142, 1995.

§ 11 Septic Shock, Renal Failure, Cachexia, and Infection

Septic shock is shock associated with overwhelming infection, most commonly infection with gram negative-bacteria, although it may be produced by other bacteria, viruses, fungi and protozoa Septic shock is deemed to result from the action of endotoxins or other products of the infectious agent on the vascular system, causing large volumes of blood to be sequestered in the capillaries and veins Activation of the complement and kinin systems and the release of histamine, cytokines, prostaglandins, and other mediators is also involved

It has been shown in a model of endotoxin-induced acute renal failure in rats that the selective PDE4 inhibitor, Ro-201724, given as a post-treatment at 10 µg/kg/min significantly increases urinary cAMP excretion, markedly attenuates endotoxin-induced increases in renal vascular resistance and decreases in renal blood flow and glomerular filtration rate. Ro-201724 has also been shown to improve survival rates for endotoxin-treated rats. See Carcillo *et al.*, *Pharmacol. Exp. Ther* 279 1197, 1996 Pentoxifylline has also been studied in patients suffering from septic shock. In this study twenty-four individuals fulfilling the criteria for septic shock have been selected, twelve of which have received pentoxifylline at 1 mg/kg/hr over a 24-hour period, while the other twelve have served as a control group After 24 hours it has been found that the TNF-α levels in the therapy group have been significantly lowered, while the IL-6 levels have been significantly increased

In another study, it has been shown that pretreatment with pentoxifylline at 5 to 50 mg/kg I.p 3X, or with the selective PDE4 inhibitors rolipram at 10 to 30 mg/kg I.p. 3x, and debufylline at 0 1 to 3 mg/kg I.p 3x, reduces lipopolysaccharide-induced bowel erythrocyte extravasation in rats, and that denbufylline is 100-fold more potent than pentoxifylline in inhibiting lipopolysaccharide-induced mesenteric blood flow fall, without affecting renal blood flow or cardiac index. See Cardelus *et al.*, *Ibid.*, *Eur J Pharmacol*

Renal failure is the inability of the kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake In the acute form, it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema On the basis of the above-described activities of selective PDE4 inhibitors, it has been demonstrated that selective PDE4 inhibitors are useful in the treatment of renal failure, especially acute renal failure See Begany *et al.*, "Inhibition of Type IV phosphodiesterase by Ro-20-1724 attenuates endotoxin-induced acute renal failure," *J Pharmacol. Exp. Ther* 278 37-41, 1996. See also WO 98/00135 assigned to the University of Pittsburgh. Accordingly, the compounds of Formula (1.0.0) are useful in the treatment of renal failure, particularly acute renal failure

Cachexia is a profound and marked state of constitutional disorder characterized by general ill health and malnutrition Cachexia may be the end result of a number of causative factors, *e g*, it may result from infection by any one of a number of different unicellular organisms or microorganisms including bacteria, viruses, fungi, and protozoans Malarial cachexia is representative and comprises a group of signs of a chronic nature that result from antecedent attacks of severe malaria, the principal signs being anemia, sallow skin, yellow sclera, splenomegaly, and hepatomegaly Another cause of cachexia is the deprivation or deterioration of humoral or other organic functions, *e g*, hypophysial cachexia comprises a train of symptoms resulting from total deprivation of function of the pituitary gland, including

phthisis, loss of sexual function, atrophy of the pituitary target glands, bradycardia, hypothermia, apathy, and coma. Uremic cachexia is cachexia associated with other systemic symptoms of advanced renal failure Cardiac cachexia comprises the emaciation due to heart disease. Cachexia suprarenalis, or Addison's disease, is a disorder characterized by hypotension, weight loss, anorexia, and weakness, caused by adrenocortical hormone deficiency It is due to tuberculosis- or autoimmune-induced destruction of the adrenal cortex that results in deficiency of aldosterone and cortisol

Cachexia may also be the result of disease states of various types. Cancerous cachexia comprises the weak, emaciated condition seen in cases of malignant tumor Cachexia can also be a consequence of infection by the human immunodeficiency virus (HIV), and comprises the symptoms commonly referred to as acquired immune deficiency syndrome (AIDS). The compounds of Formula (1.0.0) are useful in treating cachexia of the different types described above as a result of their ability to provide down-regulation or inhibition of TNF-α release. The selective PDE4 inhibitors of the present invention have a marked effect on the inhibition of TNF-α release from peripheral blood mononuclear cells after those cells have been stimulated with a wide range of mediators TNF-α release is implicated or plays a mediating role in diseases or conditions whose etiology involves or comprises morbid, *i.e.*, unhealthy, excessive or unregulated TNF-α release.

The PDE4 inhibitory compounds of Formula (1 0.0) are further useful in the treatment of infection, especially infection by viruses wherein such viruses increase the production of TNF-α in their host, or wherein such viruses are sensitive to upregulation of TNF-α in their host so that their replication or other vital activities are adversely impacted Such viruses include, *e g.*, HIV-1, HIV-2, and HIV-3, cytomegalovirus, CMV; influenza, adenoviruses, and Herpes viruses, especially *Herpes zoster* and *Herpes simplex*

The PDE4 inhibitory compounds of Formula (1.0 0) are further useful in the treatment of yeast and fungus infections wherein said yeast and fungi are sensitive to upregulation by TNF-α or elicit TNF-α production in their host. A particular disease which is treatable in this way is fungal meningitis The compounds of Formula (1.0 0) also provide beneficial effects when combined with, *i.e*, administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections Such drugs of choice include, but are not limited to polymbins, *e g.*, Polymycin B, Imidazoles, *e g.*, clotrimazole, econazole, miconazole, and ketoconazole, triazoles, *e g.*, fluconazole and itranazole; and amphotericins, *e g.*, Amphotericin B and liposomal Amphotericin B The term "co-administration" as used herein with reference to the compounds of Formula (1.0 0) and drugs of choice for the treatment of systemic yeast and fungus infections, is intended to mean and include *(a)* simultaneous administration of such compound(s) and drug(s) to a subject when

formulated together into a single dosage form, *(b)* substantially simultaneous administration of such compound(s) and drug(s) to a subject when formulated apart from each other into separate dosage forms; and *(c)* sequential administration of such compound(s) and drug(s) to a subject when formulated apart from each other and administered consecutively with some significant time interval between.

8.12 Liver Injury

In addition to the above-described adverse effects of TNF-α, it also causes hepatic failure in humans, a phenomenon which has been shown in a number of animal models For example, in an acute model of T-cell mediated hepatic failure, rolipram administered at 0 1 to 10 mg/kg i.p 30 minutes before challenge with either concanavalin A or staphylococcal enterotoxin B, has been shown to significantly reduce plasma TNF-α and INF-γ concentrations, whereas it also significantly elevates IL-10 levels See Gantner *et al*, *J Pharmacol. Exp. Ther* 280 53, 1997 In this same study, rolipram has also been shown to suppress concanavalin A-induced IL-4 release The plasma activities of the liver specific enzymes ALT, AST, and SDH have also been assessed in this study, since any increase in their levels would indicate massive liver cell destruction It has been found that in pretreatment of naïve mice receiving concanavalin A, or galactosamine-sensitized mice receiving galactosamine/staphylococcal enterotoxin B, with rolipram at 0 1 to 10 mg/kg i.p , that rolipram has dose-dependently inhibited the above-mentioned plasma enzyme activities Accordingly, the compounds of Formula (1 0 0) are useful in the treatment of T-cell disorders such as liver failure.

8.13 Pulmonary Hypertension

It is known that the activity of phosphodiesterases, which hydrolyze the vasodilatory second messengers cAMP and cGMP, may be increased by hypoxia-induced pulmonary hypertension (HPH). Hypoxia is a reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood The resulting pulmonary hypertension is characterized by increased pressure, *i e* , above 30 mm Hg systolic and above 12 mm Hg diastolic, within the pulmonary arterial circulation Using a model which utilizes isolated pulmonary artery rings from normal rats and from rats with hypoxia-induced pulmonary hypertension, it has been shown that the selective PDE4 inhibitor rolipram potentiates the relaxant activities of isoproterenol and forskolin The same effect has been observed with milrinone, which is a selective PDE3 inhibitor, thereby supporting inhibition of both PDE3 and PDE4 in order to significantly improve pulmonary artery relaxation in hypoxia-induced pulmonary hypertension See Wagner *et al*, *J Pharmacol. Exp. Ther* 282 1650, 1997 Accordingly, the compounds of Formula (1.0 0) are useful in the treatment of pulmonary hypertension, especially hypoxia-induced pulmonary hypertension

8.14 Bone Loss Disease

Bone loss disease, more commonly referred to as osteoporosis, is a condition of low bone mass and microarchitectural disruption that results in fractures with minimal trauma. Secondary osteoporosis is due to systemic illness or medications such as glucocorticoids Primary osteoporosis, it has been contended, should be viewed as comprising two conditions: Type I osteoporosis which is loss of trabecular bone due to estrogen deficiency at menopause, and Type II osteoporosis which is loss of cortical and trabecular bone due to long-term remodeling inefficiency, dietary inadequacy, and activation of the parathyroid axis with age The primary regulators of adult bone mass include physical activity, reproductive endocrine status, and calcium intake, and optimal maintenance of bone requires sufficiency in all three areas.

It has been demonstrated that selective PDE4 inhibitors are useful in the beneficial treatment of bone loss disease, particularly osteoporosis The effect of denbufylline on bone loss in Walker 256/S-bearing rats and on mineralized nodule formation and osteoclast-like cell formation has been studied in bone marrow culture systems It has been discovered that serial oral administrations of denbufylline inhibit the decrease in the bone mineral density of femurs from Walker 256/S-bearing rats, and restore the bone mass and the number of osteoclasts and osteoblasts per trabecular surface in the femur metaphysis The administration of denbufylline has also been found to result in an increase in the number of mineralized nodules and a decrease in the number of osteoclast-like cells in the *in vitro* bone marrow culture system These beneficial effects are specific for PDE4 inhibition and are mimicked by dibutyryl cAMP, demonstrating that the PDE4 isozyme plays an important role in bone turnover through cAMP See Miyamoto *et al.*, *Biochem. Pharmacol* 54 613, 1997; Weld *et al.*, "Effects of XT-44, a phosphodiesterase 4 inhibitor, in osteoblastgenesis and osteoclastgenesis in culture and its therapeutic effects in rat osteopenia models," *Jpn. J Pharmacol* 79 477-483, 1999, and JP 9169685 assigned to Miyamoto (1997). Consequently, the selective PDE4 inhibitors of Formula (1.0 0) are useful in the treatment of diseases involving bone loss, especially osteoporosis

8.15 CNS disorders

The PDE4 selective inhibitor rolipram was initially developed as an antidepressant and continues to be studied in clinical trials for that indication Further, it has been demonstrated that selective PDE4 inhibitors provide beneficial effects in other central nervous system disorders, including Parkinson's disease, Hulley *et al.*, "Inhibitors of Type IV phosphodiesterases reduce the toxicity of MPTP in substantia nigra neurons *in vivo*," *Eur J Neurosci.* 7 2431-2440, 1995, as well as learning and memory impairment, Egawa *et al.*, "Rolipram and its optical isomers, phosphodiesterase 4 inhibitors, attenuate the scopolamine-induced impairments of learning and memory in rats," *Jpn. J Pharmacol.* 75 275-281, 1997,

Imanishi *et al.*, "Ameliorating effects of rolipram on experimentally induced impairments of learning and memory in rodents," *Eur J Pharmacol.* 321 273-278, 1997, and Barad *et al.*, "Rolipram, a Type IV-specific phosphodiesterase inhibitor, facilitates the establishment of long-lasting long-term potentiation and improves memory," *Proc. Natl. Acad. Sci. USA* 95 15020-15025, 1998.

The use of PDE4 inhibitors to treat tardive dyskinesia and drug dependence has also been disclosed in the art, WO 95/28177 and JP 92221423 (1997), both assigned to Meiji Seika Kaisha Ltd The PDE4 isozyme has been found to play a major role in controlling dopamine biosynthesis in mesencephalic neurons, accordingly PDE4 inhibitors are useful in the treatment of disorders and diseases which are associated with or mediated by dopamine within and around mesencephalic neurons, Yamashita *et al.*, "Rolipram, a selective inhibitor of phosphodiesterase Type 4, pronouncedly enhances the forskolin-induced promotion of dopamine biosynthesis in primary cultured rat mesencephalic neurons," *Jpn. J. Pharmacol.* 75 91-95, 1997

The PDE4 inhibitory compounds of Formula (1.0.0) are further useful in the treatment of arteriosclerotic dementia and subcortical dementia Arteriosclerotic dementia, also called vascular dementia and multi-infarct dementia, is a dementia with a stepwise deteriorating course in the form of a series of small strokes, and an irregular distribution of neurological deficits caused by cerebrovascular disease Subcortical dementia are caused by lesions affecting subcortical brain structures and are characterized by memory loss with slowness in processing information or making intellectual responses Included are dementias that accompany Huntington's chorea, Wilson's disease, paralysis agitans, and thalamic atrophies.

5.16 Other Therapeutic Applications

It has been demonstrated that PDE4 inhibitors are useful in the treatment of ischemia-reperfusion injury, Block *et al.*, "Delayed treatment with rolipram protects against neuronal damage following global ischemia in rats," *NeuroReport* 8 3829-3832, 1997 and Belayev *et al.* "Protection against blood-brain barrier disruption in focal cerebral ischemia by the Type IV phosphodiesterase inhibitor BBB022 a quantitative study," *Brain Res.* 787 277-285, 1998, in the treatment of autoimmune diabetes, Liang *et al.*, "The phosphodiesterase inhibitors pentoxifylline and rolipram prevent diabetes in NOD mice," *Diabetes* 47 570-575, 1998, in the treatment of retinal autoimmunity, Xu *et al*, "Protective effect of the Type IV phosphodiesterase inhibitor rolipram in EAU protection is independent of the IL-10-inducing activity," *Invest. Ophthalmol. Visual Sci.* 40 942-950, 1999; in the treatment of chronic lymphocytic leukemia, Kim and Lerner, "Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic agent in chronic lymphocytic leukemia," *Blood* 92 2484-2494, 1998, in the treatment of HIV infections, Angel *et al.*, "Rolipram, a specific Type IV phosphodiesterase inhibitor, is a potent inhibitor of HIV-1 replication," *AIDS* 9 1137-1144,

1995 and Navarro *et al.*, "Inhibition of phosphodiesterase Type IV suppresses human immunodeficiency virus Type 1 replication and cytokine production in primary T cells. Involvement of NF-kappaB and NFAT," *J Virol.* 72 4712-4720, 1998, in the treatment of lupus erythematosus, JP 10067682 (1998) assigned to Fujisawa Pharm Co Ltd , in the treatment of kidney and ureter disease, DE 4230755 (1994) assigned to Schering AG , in the treatment of urogenital and gastrointestinal disorders, WO 94/06423 assigned to Schering AG , and in the treatment of prostate diseases, WO 99/02161 assigned to Porsemann and WO 99/02161 assigned to Stief

In accordance with the above descriptions, it will be understood that the compounds of Formula (1.0 0) are useful in the beneficial treatment of any one or more members selected from the group consisting of the following diseases, disorders, and conditions

– asthma of whatever type, etiology, or pathogenesis, or asthma that is a member selected from the group consisting of atopic asthma, non-atopic asthma, allergic asthma, atopic, bronchial, IgE-mediated asthma; bronchial asthma, essential asthma, true asthma, intrinsic asthma caused by pathophysiologic disturbances, extrinsic asthma caused by environmental factors, essential asthma of unknown or inapparent cause; non-atopic asthma; bronchitic asthma, emphysematous asthma, exercise-induced asthma, occupational asthma; infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma; incipient asthma, wheezy infant syndrome;

– chronic or acute bronchoconstriction, chronic bronchitis, small airways obstruction; and emphysema,

– obstructive or inflammatory airways diseases of whatever type, etiology, or pathogenesis, or an obstructive or inflammatory airways disease that is a member selected from the group consisting of asthma, pneumoconiosis, chronic eosinophilic pneumonia, chronic obstructive pulmonary disease (COPD); COPD that includes chronic bronchitis, pulmonary emphysema or dyspnea associated therewith, COPD that is characterized by irreversible, progressive airways obstruction, adult respiratory distress syndrome (ARDS), and exacerbation of airways hyper-reactivity consequent to other drug therapy;

– pneumoconiosis of whatever type, etiology, or pathogenesis, or pneumoconiosis that is a member selected from the group consisting of aluminosis or bauxite workers' disease, anthracosis or miners' asthma, asbestosis or steam-fitters' asthma, chalicosis or flint disease; ptilosis caused by inhaling the dust from ostrich feathers, siderosis caused by the inhalation of iron particles, silicosis or grinders' disease; byssinosis or cotton-dust asthma, and talc pneumoconiosis,

– bronchitis of whatever type, etiology, or pathogenesis, or bronchitis that is a member selected from the group consisting of acute bronchitis, acute laryngotracheal bronchitis, arachidic bronchitis, catarrhal bronchitis, croupus bronchitis, dry bronchitis; infectious asthmatic bronchitis, productive bronchitis, staphylococcus or streptococcal bronchitis, and vesicular bronchitis;

– bronchiectasis of whatever type, etiology, or pathogenesis, or bronchiectasis that is a member selected from the group consisting of cylindric bronchiectasis, sacculated bronchiectasis, fusiform bronchiectasis, capillary bronchiectasis, cystic bronchiectasis, dry bronchiectasis, and follicular bronchiectasis;

– seasonal allergic rhinitis, or perennial allergic rhinitis, or sinusitis of whatever type, etiology, or pathogenesis, or sinusitis that is a member selected from the group consisting of purulent or nonpurulent sinusitis, acute or chronic sinusitis; and ethmoid, frontal, maxillary, or sphenoid sinusitis,

– rheumatoid arthritis of whatever type, etiology, or pathogenesis, or rheumatoid arthritis that is a member selected from the group consisting of acute arthritis, acute gouty arthritis; chronic inflammatory arthritis, degenerative arthritis, infectious arthritis; Lyme arthritis, proliferative arthritis, psoriatic arthritis, and vertebral arthritis,

– gout, and fever and pain associated with inflammation;

– an eosinophil-related disorder of whatever type, etiology, or pathogenesis; or an eosinophil-related disorder that is a member selected from the group consisting of eosinophilia, pulmonary infiltration eosinophilia, Loffler's syndrome, chronic eosinophilic pneumonia, tropical pulmonary eosinophilia, bronchopneumonic aspergillosis, aspergilloma; granulomas containing eosinophils, allergic granulomatous angiitis or Churg-Strauss syndrome; polyarteritis nodosa (PAN); and systemic necrotizing vasculitis;

– atopic dermatitis, or allergic dermatitis; or allergic or atopic eczema;

– urticaria of whatever type, etiology, or pathogenesis, or urticaria that is a member selected from the group consisting of immune-mediated urticaria; complement-mediated urticaria, urticariogenic material-induced urticaria, physical agent-induced urticaria; stress-induced urticaria, idiopathic urticaria, acute urticaria; chronic urticaria; angioedema, cholinergic urticaria, cold urticaria in the autosomal dominant form or in the acquired form, contact urticaria, giant urticaria, and papular urticaria;

– conjunctivitis of whatever type, etiology, or pathogenesis; or conjunctivitis that is a member selected from the group consisting of actinic conjunctivitis; acute catarrhal conjunctivitis, acute contagious conjunctivitis, allergic conjunctivitis, atopic conjunctivitis; chronic catarrhal conjunctivitis, purulent conjunctivitis, and vernal conjunctivitis;

--uveitis of whatever type, etiology, or pathogenesis; or uveitis that is a member selected from the group consisting of inflammation of all or part of the uvea, anterior uveitis, iritis, cyclitis, iridocyclitis, granulomatous uveitis, nongranulomatous uveitis; phacoantigenic uveitis, posterior uveitis, choroiditis, and chorioretinitis,

– psoriasis;

– multiple sclerosis of whatever type, etiology, or pathogenesis, or multiple sclerosis that is a member selected from the group consisting of primary progressive multiple sclerosis, and relapsing remitting multiple sclerosis,

– autoimmune/inflammatory diseases of whatever type, etiology, or pathogenesis, or an autoimmune/inflammatory disease that is a member selected from the group consisting of autoimmune hematological disorders, hemolytic anemia, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, polychondritis, scleroderma, Wegner's granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome; idiopathic sprue; autoimmune inflammatory bowel diseases, ulcerative colitis; Crohn's disease; endocrin opthamopathy; Grave's disease; sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis; juvenile diabetes or diabetes mellitus type I, anterior uveitis, granulomatous or posterior uveitis, keratoconjunctivitis sicca, epidemic keratoconjunctivitis, diffuse interstitial pulmonary fibrosis or interstitial lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis; psoriatic arthritis, glomerulonephritis with and without nephrotic syndrome, acute glomerulonephritis, idiopathic nephrotic syndrome, minimal change nephropathy; inflammatory/hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis; allergic contact dermatitis, benign familial pemphigus, pemphigus erythematosus, pemphigus foliaceus, and pemphigus vulgaris,

– prevention of allogeneic graft rejection following organ transplantation;

– inflammatory bowel disease (IBD) of whatever type, etiology, or pathogenesis, or inflammatory bowel disease that is a member selected from the group consisting of ulcerative colitis (UC); collagenous colitis, colitis polyposa, transmural colitis, and Crohn's disease (CD),

– septic shock of whatever type, etiology, or pathogenesis, or septic shock that is a member selected from the group consisting of renal failure, acute renal failure; cachexia, malarial cachexia, hypophysial cachexia, uremic cachexia, cardiac cachexia; cachexia suprarenalis or Addison's disease, cancerous cachexia, and cachexia as a consequence of infection by the human immunodeficiency virus (HIV),

– liver injury;

– pulmonary hypertension, and hypoxia-induced pulmonary hypertension,

— bone loss diseases, primary osteoporosis, and secondary osteoporosis,

— central nervous system disorders of whatever type, etiology, or pathogenesis; or a central nervous system disorder that is a member selected from the group consisting of depression, Parkinson's disease, learning and memory impairment; tardive dyskinesia, drug dependence; arteriosclerotic dementia; and dementias that accompany Huntington's chorea, Wilson's disease, paralysis agitans, and thalamic atrophies,

— infection, especially infection by viruses wherein such viruses increase the production of TNF-α in their host, or wherein such viruses are sensitive to upregulation of TNF-α in their host so that their replication or other vital activities are adversely impacted, including a virus which is a member selected from the group consisting of HIV-1, HIV-2, and HIV-3, cytomegalovirus, CMV; influenza, adenoviruses, and Herpes viruses, including *Herpes zoster* and *Herpes simplex*;

— yeast and fungus infections wherein said yeast and fungi are sensitive to upregulation by TNF-α or elicit TNF-α production in their host, *e.g.*, fungal meningitis, particularly when administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections, including but are not limited to, polymixins, *e.g.*, Polymycin B, imidazoles, *e.g.*, clotrimazole, econazole, miconazole, and ketoconazole; triazoles, *e.g.*, fluconazole and itranazole, and amphotericins, *e.g.*, Amphotericin B and liposomal Amphotericin B; and

— ischemia-reperfusion injury; autoimmune diabetes, retinal autoimmunity; chronic lymphocytic leukemia, HIV infections, lupus erythematosus, kidney and ureter disease; urogenital and gastrointestinal disorders, and prostate diseases.

DETAILED DESCRIPTION OF THE INVENTION

9.0 Combination with Other Drugs and Therapies

The present invention contemplates embodiments in which a compound of Formula (1 0.0) is the only therapeutic agent which is employed in a method of treatment described herein, whether used alone or more commonly, together with a pharmaceutically acceptable carrier to produce a suitable dosage form for administration to a patient. Other embodiments of the present invention contemplate a combination of a compound of Formula (1 0.0) together with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result. The second, *etc.* therapeutic agent may also be one or more compounds of Formula (1 0 0), or one or more PDE4 inhibitors known in the art and described in detail herein More typically, the second, etc therapeutic agent will be selected from a different class of therapeutic agents These selections are described in detail below

As used herein, the terms "co-administration", "co-administered", and "in combination with", referring to the compounds of Formula (1 0.0) and one or more other therapeutic agents, is intended to mean, and does refer to and include the following: *(a)* simultaneous administration of such combination of compound(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient; *(b)* substantially simultaneous administration of such combination of compound(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are ingested at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient; *(c)* sequential administration of such combination of compound(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are ingested at consecutive times by said patient with a significant time interval between each ingestion, whereupon said components are released at substantially different times to said patient; and *(d)* sequential administration of such combination of compound(s) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlappingly ingested at the same and/or different times by said patient.

9.1 With Leukotriene Biosynthesis Inhibitors 5-Lipoxygenase (5-LO) Inhibitors and 5-Lipoxygenase Activating Protein (FLAP) Antagonists

One or more compounds of Formula (1 0 0) is used in combination with leukotriene biosynthesis inhibitors, *I e* , 5-lipoxygenase inhibitors and/or 5-lipoxygenase activating protein antagonists, to form embodiments of the present invention As already adverted to above, 5-

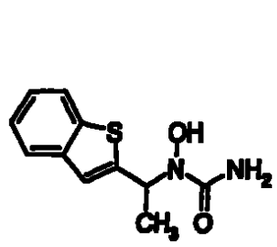
lipoxygenase (5-LO) is one of two groups of enzymes that metabolize arachidonic acid, the other group being the cyclooxygenases, COX-1 and COX-2 The 5-lipoxygenase activating protein is an 18 kDa membrane-bound, arachidonate-binding protein which stimulates the conversion of cellular arachidonic acid by 5-lipoxygenase. The arachidonic acid is converted into 5-hydroperoxyeicosatetraenoic acid (5-HPETE), and this pathway eventually leads to the production of inflammatory leukotrienes; consequently, blocking the 5-lipoxygenase activating protein or the 5-lipoxygenase enzyme itself provides a desirable target for beneficially interfering with that pathway One such 5-lipoxygenase inhibitor is zileuton represented by Formula (0 1 14), which may be found both above and following Among the classes of leukotriene synthesis inhibitors which are useful for forming therapeutic combinations with the compounds of Formula (1.0 0) are the following

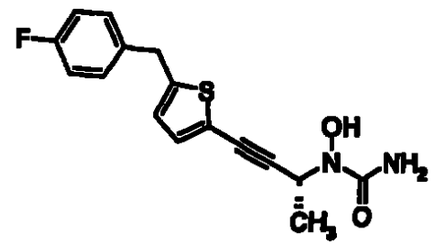
(a) redox-active agents which include *N*-hydroxyureas, *N*-alkylhydroxamic acids; selenite; hydroxybenzofurans, hydroxylamines, and catechols, see Ford-Hutchinson *et al.*, "5-Lipoxygenase," *Ann. Rev Biochem.* 63 383-417, 1994, Weitzel and Wendel, "Selenoenzymes regulate the activity of leukocyte 5-lipoxygenase via the peroxide tone," *J. Biol. Chem.* 268 6288-92, 1993, Björnstedt *et al.* "Selenite incubated with NADPH and mammalian thioredoxin reductase yields selenide, which inhibits lipoxygenase and changes the electron spin resonance spectrum of the active site iron," *Biochemistry* 35 8511-8, 1996, and Stewart *et al.*, "Structure-activity relationships of N-hydroxyurea 5-lipoxygenase inhibitors," *J Med Chem.* 40 1955-68, 1997;

(b) alkylating agents and compounds which react with SH groups have been found to inhibit leukotriene synthesis *in vitro*; see Larsson *et al.*, "Effects of 1-chloro-2,4,6-trinitrobenzene on 5-lipoxygenase activity and cellular leukotriene synthesis," *Biochem. Pharmacol.* 55 863-71, 1998, and

(c) competitive inhibitors of 5-lipoxygenase, based on thiopyranoindole and methoxyalkyl thiazole structures which may act as non-redox inhibitors of 5-lipoxygenase; see Ford-Hutchinson *et al.*, *Ibid.*, and Hamel *et al.*, "Substituted (pyridylmethoxy)naphthalenes as potent and orally active 5-lipoxygenase inhibitors -- synthesis, biological profile, and pharmacokinetics of L-739,010," *J Med. Chem.* 40 2866-75, 1997

The observation that arachidonoyl hydroxyamate inhibits 5-lipoxygenase has led to the discovery of clinically useful selective 5-lipoxygenase inhibitors such as the *N*-hydroxyurea derivatives zileuton and ABT-761, represented by Formulas (0 1 14) and (5.2 1).

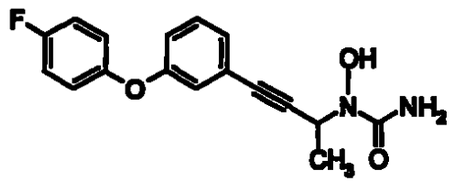




Zileuton ABT-761

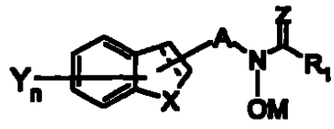
(0 1 14) (5.2.1)

Another *N*-hydroxyurea compound is fenleuton (Abbott-76745) which is represented by Formula (5.2.2):



Fenleuton (5.2.2)

Zileuton is covered by US 4,873,259 (Summers *et al.*) assigned to Abbott Laboratories, which discloses indole, benzofuran, and benzothiophene containing lipoxygenase inhibiting compounds which may be represented by Formula (5.2.3):



(5.2.3)

where R_1 is H, (C_1-C_4) alkyl; (C_2-C_4) alkenyl, or NR_2R^3 where R_2 and R_3 are H; (C_1-C_4) alkyl, or OH, X is O; S, SO_2, or NR_4 where R_4 is H, (C_1-C_8) alkyl, (C_1-C_8) alkanoyl, aroyl, or alkylsulfonyl; A is (C_1-C_8) alkylene, or (C_2-C_8) alkenylene, n is 1-5; and Y is H, halo; OH, CN, halo substituted alkyl; (C_1-C_{12}) alkyl, (C_2-C_{12}) alkenyl, (C_1-C_{12}) alkoxy; (C_3-C_8) cycloalkyl; (C_1-C_8) thioalkyl, aryl, aryloxy; aroyl, (C_1-C_{12}) arylalkyl; (C_2-C_{12}) arylalkenyl, (C_1-C_{12}) arylalkoxy; (C_1-C_{12}) arylthioalkoxy; or substituted derivatives of aryl; aryloxy; aryoyl, (C_1-C_{12}) arylalkyl, (C_2-C_{12}) arylalkenyl, (C_1-C_{12}) arylalkoxy; (C_1-C_{12}) arylthioalkoxy; where said substituent is halo, NO_2, CN, or (C_1-C_{12}) -alkyl –alkoxy and –halosubstitutedalkyl; Z is O or S, and M is H, pharmaceutically acceptable cation, aroyl, or (C_1-C_{12}) alkanoyl

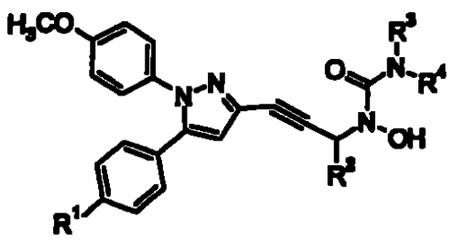
Related compounds are disclosed in US 4,769,387 (Summers *et al.*); US 4,822,811 (Summers); US 4,822,809 (Summers and Stewart), US 4,897,422 (Summers); US 4,992,464

(Summers *et al.*); and US 5,250,565 (Brooks and Summers); each of which is incorporated herein by reference in its entirety as though fully set out herein

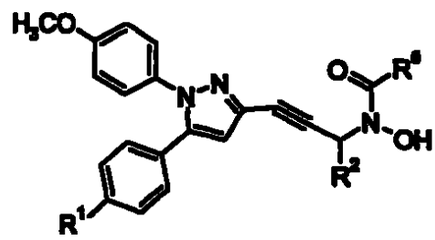
Zileuton or any of the above-described derivatives thereof are combined with the *compounds of Formula (1 0 0)* to form embodiments of the present invention.

Fenleuton is disclosed in US 5,432,194, US 5,446,062, US 5,484,788, US 5,559,144, US 5,616,596; US 5,668,146, US 5,668,150; US 5,843,968; US 5,407,959, US 5,426,111, US 5,446,055, US 5,475,009; US 5,512,581, US 5,516,795, US 5,476,873, US 5,714,488, US 5,783,586, US 5,399,699; US 5,420,282, US 5,459,150, and US 5,506,281, each of which is incorporated herein by reference in its entirety as though fully set out herein Further descriptions of such *N*-hydroxyurea and related inhibitors of 5-lipoxygenase and the synthesis of inflammatory leukotrienes may be found in WO 95/30671, WO 96/02507; WO 97/12885; WO 97/12886, WO 97/12887, WO 98/04555, and WO 98/14429

Tepoxalin is a dual COX/5-LO inhibitor with short-lived *in vivo* activity that has led to the development of two series of hybrid compounds which are *N*-hydroxyureas and hydroxamic acids of Formulas (5.2.4) and (5.2 5), respectively



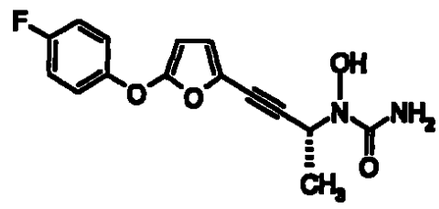
(5.2.4)



(5.2.5)

where R^1 through R^4 are H, Cl, CH_3, ethyl, *iso*-propyl, or *n*-propyl; or R^3 and R^4 together are $(CH_2)_4$ or $(CH_2)_2O(CH_2)_2$, and R^5 is methyl, ethyl, *iso*-propyl, methoxy; trifluoromethyl, chloromethyl, ethyl propionate, phenyl, 2-furyl, 3-pyridyl, or 4-pyridyl See Connolly *et al.*, "N-Hydroxyurea and hydroxamic acid inhibitors of cyclooxygenase and 5-lipoxygenase," *Bioorganic & Medicinal Chemistry Letters* 9 979-984, 1999

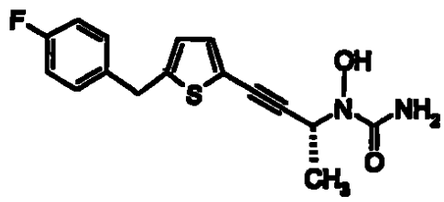
Another *N*-hydroxyurea compound is Abbott-79175 which is represented by Formula (5.2.6):



Abbott-79175 (5.2.6)

Abbott-79175 has a longer duration of action than zileuton, Brooks *et al.*, *J Pharm Exp. Therapeut.* 272 724, 1995.

A still further *N*-hydroxyurea compound is Abbott-85761 which is represented by Formula (5.2 7):

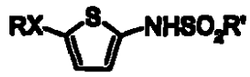


Abbott-85761 (5.2.7)

Abbott-85761 is delivered to the lung by aerosol administration of a homogeneous, physically stable and nearly monodispersed formulation, Gupta *et al.*, "Pulmonary delivery of the 5-lipoxygenase inhibitor, Abbott-85761, in beagle dogs," *International Journal of Pharmaceutics* 147 207-218, 1997

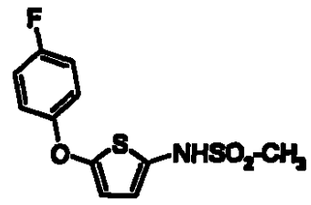
Fenleuton, Abbott-79175, Abbott-85761 or any of the above-described derivatives thereof or of tepoxalin, are combined with the compounds of Formula (1.0.0) to form embodiments of the present invention

Since the elucidation of the 5-LO biosynthetic pathway, there has been an ongoing debate as to whether it is more advantageous to inhibit the 5-lipoxygenase enzyme or to antagonize peptido- or non-peptido leukotriene receptors Inhibitors of 5-lipoxygenase are deemed to be superior to LT-receptor antagonists, since 5-lipoxygenase inhibitors block the action of the full spectrum of 5-LO products, whereas LT-antagonists produce narrower effects. Nevertheless, embodiments of the present invention include combinations of the compounds of Formula (1 0 0) with LT-antagonists as well as 5-LO inhibitors, as described below Inhibitors of 5-lipoxygenase having chemical structures that differ from the classes of *N*-hydroxyureas and hydroxamic acids described above are also used in combination with the compounds of Formula (1 0 0) to form further embodiments of the present invention An example of such a different class is the *N*-(5-substituted)-thiophene-2-alkylsulfonamides of Formula (5.2 8).



(5.2.8)

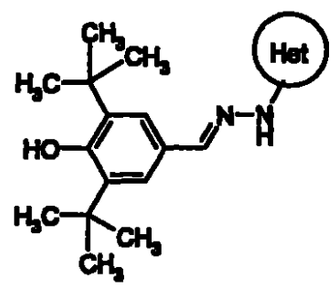
where X is O or S, R' is methyl, *iso*-propyl, *n*-butyl, *n*-octyl, or phenyl, and R is *n*-pentyl, cyclohexyl, phenyl, tetrahydro-1-naphthyl, 1- or 2-naphthyl, or phenyl mono- or di-substituted by Cl, F, Br, CH_3, OCH_3, SCH_3, SO_2CH_3, CF_3, or *iso*-propyl A preferred compound is that of Formula (5.2 9):



(5.2 9)

A further description of these compounds may be found in Beers *et al.*, "*N*-(5-substituted) thiophene-2-alkylsulfonamides as potent inhibitors of 5-lipoxygenase," *Bioorganic & Medicinal Chemistry* 5(4) 779-786, 1997

Another distinct class of 5-lipoxygenase inhibitors is that of the 2,6-di-*tert*-butylphenol hydrazones described in Cuadro *et al.*, "Synthesis and biological evaluation of 2,6-di-*tert*-butylphenol hydrazones as 5-lipoxygenase inhibitors," *Bioorganic & Medicinal Chemistry* 6 173-180, 1998 Compounds of this type are represented by Formula (5.2.10):

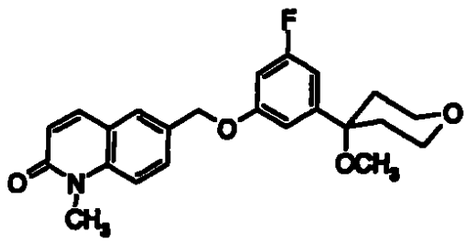


(5.2 10)

where "Het" is benzoxazol-2-yl, benzothiazol-2-yl, pyridin-2-yl, pyrazin-2-yl, pyrimidin-2-yl, 4-phenylpyrimidin-2-yl, 4,6-diphenylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-butylpyrimidin-2-yl; 4,6-dibutylpyrimidin-2-yl, and 4-methyl-6-phenylpyrimidin-2-yl

The *N*-(5-substituted)-thiophene-2-alkylsulfonamides of Formula (5.2.8), or the 2,6-di-*tert*-butylphenol hydrazones of Formula (5.2.10), or any of the above-described derivatives thereof, are combined with the compounds of Formula (1 0 0) to form embodiments of the present invention

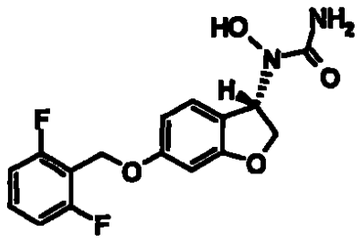
A further distinct class of 5-lipoxygenase inhibitors is that of methoxytetrahydropyrans to which Zeneca ZD-2138 belongs. ZD-2138 is represented by Formula (5.2.11)



(5.2 11)

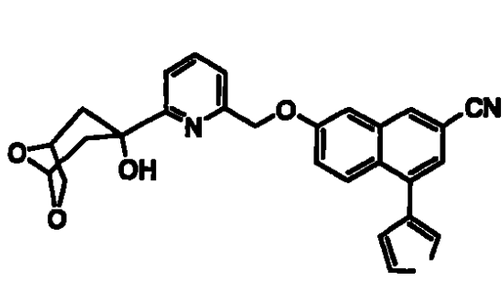
ZD-2138 is highly selective and highly active orally in a number of species and has been evaluated in the treatment of asthma and rheumatoid arthritis by oral administration Further details concerning ZD-2138 and derivatives thereof are disclosed in Crawley *et al.*, *J Med Chem.*, 35 2600, 1992, and Crawley *et al.*, *J Med Chem.* 36 295, 1993.

Another distinct class of 5-lipoxygenase inhibitors is that to which the SmithKline Beecham compound SB-210661 belongs SB-210661 is represented by Formula (5.2.12)

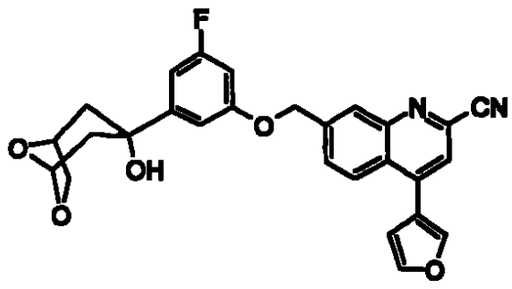


(5.2 12)

Two further distinct and related classes of 5-lipoxygenase inhibitors comprise a series of pyridinyl-substituted 2-cyanonaphthalene compounds and a series of 2-cyanoquinoline compounds discovered by Merck Frosst. These two classes of 5-lipoxygenase inhibitors are exemplified by L-739,010 and L-748,530, represented by Formulas (5.2.13) and (5.2 14) respectively



L-739,010



L-748,530

(5.2 13) (5.2 14)

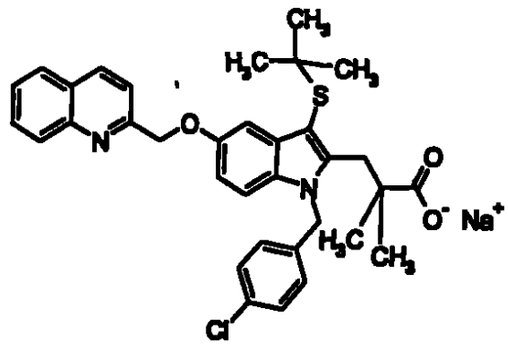
Details concerning L-739,010 and L-746,530 are disclosed in Dubé *et al.*, "Quinolines as potent 5-lipoxygenase inhibitors synthesis and biological profile of L-746,530," *Bioorganic & Medicinal Chemistry* 8 1255-1260, 1998, and in WO 95/03309 (Friesen *et al.*).

The class of methoxytetrahydropyrans including Zeneca ZD-2138 of Formula (5.2 11); or the lead compound SB-210661 of Formula (5.2 12) and the class to which it belongs, or the series of pyridinyl-substituted 2-cyanonaphthalene compounds to which L-739,010 belongs, or the series of 2-cyanoquinoline compounds to which L-746,530 belongs, or any of the above-described derivatives of any of the above-mentioned classes, are combined with the compounds of Formula (1.0 0) to form embodiments of the present invention

In addition to the 5-lipoxygenase enzyme, the other endogenous agent which plays a significant role in the biosynthesis of the leukotrienes is the 5-lipoxygenase activating protein (FLAP) This role is an indirect one, in contrast to the direct role of the 5-lipoxygenase enzyme Nevertheless, antagonists of the 5-lipoxygenase activating protein are employed to inhibit the cellular synthesis of leukotrienes, and as such are also used in combination with the compounds of Formula (1 0 0) to form embodiments of the present invention.

Compounds which bind to the 5-lipoxygenase activating protein and thereby block utilization of the endogenous pool of archidonic acid which is present have been synthesized from indole and quinoline structures, see Ford-Hutchinson *et al., Ibid.*, Rouzer *et al.* "MK-886, a potent and specific leukotriene biosynthesis inhibitor blocks and reverses the membrane association of 5-lipoxygenase in ionophore-challenged leukocytes," *J. Biol. Chem.* 265 1436-42, 1990, and Gorenne *et al.*, "{(R)-2-quinolin-2-yl-methoxy)phenyl)-2-cyclopentyl acetic acid} (BAY x1005), a potent leukotriene synthesis inhibitor effects on anti-IgE challenge in human airways," *J Pharmacol. Exp. Ther* 268 868-72, 1994

MK-591, which has been designated quilfipon sodium, is represented by Formula (5.2.15):



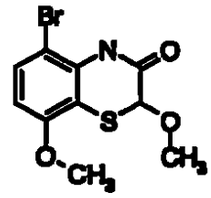
(5.2 15)

The above-mentioned indole and quinoline classes of compounds and the specific compounds MK-591, MK-886, and BAY x 1005 to which they belong, or any of the above-described derivatives of any of the above-mentioned classes, are combined with the compounds of Formula (1.0 0) to form embodiments of the present invention.

9.2 With Receptor Antagonists for Leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4

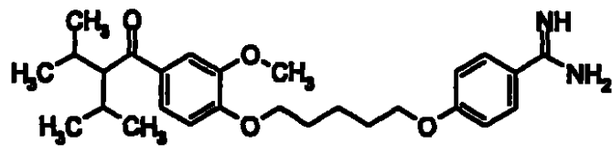
One or more compounds of Formula (1 0 0) is used in combination with receptor antagonists for leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4. The most significant of these leukotrienes in terms of mediating inflammatory response, are LTB_4 and LTD_4. Classes of antagonists for the receptors of these leukotrienes are described in the paragraphs which follow

4-Bromo-2,7-dimethoxy-3*H*-phenothiazin-3-ones, including L-651,392, are potent receptor antagonists for LTB_4 that are described in US 4,939,145 (Guindon *et al.*) and US 4,845,083 (Lau *et al.*). L-651,392 is represented by Formula (5.2 16)



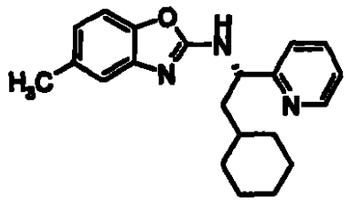
L-651,392 (5.2.16)

A class of amidino compounds that includes CGS-25019c is described in US 5,451,700 (Morrissey and Suh); US 5,488,160 (Morrissey); and US 5,639,788 (Morrissey and Suh). These receptor antagonists for LTB_4 are typified by CGS-25019c, which is represented by Formula (5.2 17)



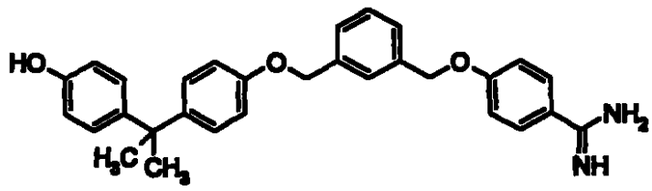
CGS-25019c (5.2.17)

Ontazolast, a member of a class of benzoxazolamines that are receptor antagonists for LTB_4, is described in EP 535 521 (Anderskewitz *et al.*); and is represented by Formula (5.2.18):



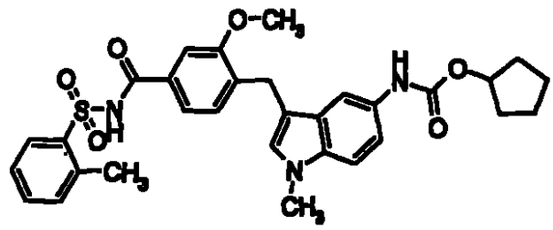
Ontazolast (5.2.18)

The same group of workers has also discovered a class of benzenecarboximidamides which are receptor antagonists for LTB_4, described in WO 97/21670 (Anderskewitz *et al.*), and WO 98/11119 (Anderskewitz *et al.*); and which are typified by BIIL 284/260, represented by Formula (5.2.19)



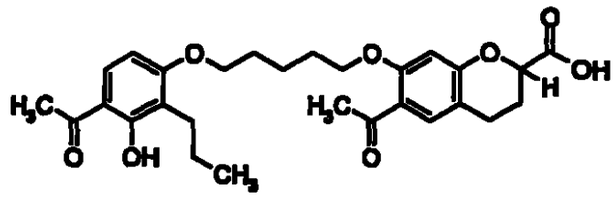
BIIL 284/260 (5.2.19)

Zafirlukast is a receptor antagonist for LTC_4, LTD_4, and LTE_4 which is sold commercially under the name Accolate® It belongs to a class of heterocyclic amide derivatives described in US 4,859,692 (Bernstein *et al.*); US 5,319,097 (Holohan and Edwards); US 5,294,636 (Edwards and Sherwood); US 5,482,963, US 5,583,152 (Bernstein *et al.*); and US 5,612,367 (Timko *et al*). Zafirlukast is represented by Formula (5.2.20)



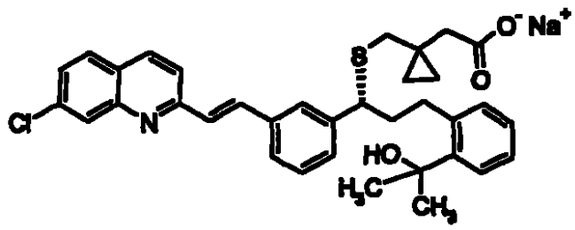
Zafirlukast (5.2.20)

Ablukast is a receptor antagonist for LTD_4 that is designated Ro 23-3544/001, and is represented by Formula (5.2.21):



Ablukast (5.2.21)

Montelukast is a receptor antagonist for LTD_4 which is sold commercially under the name Singulair® and is described in US 5,565,473. Montelukast is represented by Formula (5.2.22):



Montelukast (5.2.22)

Other receptor antagonists for LTD_4 include pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195

The above-mentioned phenothiazin-3-one class of compounds, including L-651,392; the class of amidino compounds that includes CGS-25019c; the class of benzoxazolamines which includes Ontazolast; the class of benzenecarboximidamides which is typified by BIIL 284/260; the heterocyclic amide derivatives including Zafirlukast; Ablukast and Montelukast and the classes of compounds to which they belong, or any of the above-described derivatives of any of the above-mentioned classes, are combined with the compounds of Formula (1.0 0) to form embodiments of the present invention

9.3 With Other Therapeutic Agents to Form Further Combinations

One or more compounds of Formula (1 0 0) are used together with other therapeutic agents as well as non-therapeutic agents to form combinations that are further embodiments of the present invention and that are useful in the treatment of a significant number of different diseases, disorders, and conditions described herein. Said embodiments comprise one or more compounds of Formula (1 0 0) together with one or more of the following

(a) PDE4 inhibitors including inhibitors of the isoform PDE4D;

(b) 5-Lipoxygenase (5-LO) inhibitors, or 5-lipoxygenase activating protein (FLAP) antagonists,

(c) Dual inhibitors of 5-lipoxygenase (5-LO) and antagonists of platelet activating factor (PAF);

(d) Leukotriene antagonists (LTRAs) including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4,

(e) Antihistaminic H_1 receptor antagonists including cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine;

(f) Gastroprotective H_2 receptor antagonists,

(g) α_1– and α_2–adrenoceptor agonist vasoconstrictor sympathomimetic agents administered orally or topically for decongestant use, including propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride;

(h) α_1– and α_2–adrenoceptor agonists in combination with inhibitors of 5-lipoxygenase (5-LO);

(i) Anticholinergic agents including ipratropium bromide;

(j) β_1– to β_4–adrenoceptor agonists including isoprenaline, sibuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol,

(k) Theophylline and aminophylline;

(l) Sodium cromoglycate;

(m) Muscarinic receptor (M1, M2, and M3) antagonists,

(n) COX-1 inhibitors (NSAIDs); COX-2 selective inhibitors including rofecoxib; and nitric oxide NSAIDs,

(o) Insulin-like growth factor type I (IGF-1) mimetics,

(p) Ciclesonide;

(q) Inhaled glucocorticoids with reduced systemic side effects, including flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate;

(r) Tryptase inhibitors,

(s) Platelet activating factor (PAF) antagonists,

(t) Monoclonal antibodies against endogenous inflammatory entities,

(u) IPL 576;

(v) Anti-tumor necrosis factor (TNFα) agents including Etanercept, Infliximab, and D2E7,

(w) DMARDs including Leflunomide;

(x) TCR peptides,

(y) Interleukin converting enzyme (ICE) inhibitors;

(z) IMPDH inhibitors,

(aa) Adhesion molecule inhibitors including VLA-4 antagonists,

(bb) Cathepsins,

(cc) MAP kinase inhibitors,

(dd) Glucose-6 phosphate dehydrogenase inhibitors,

(ee) Kinin-B_1- and B_2-receptor antagonists,

(ff) Gold in the form of an aurothio group together with various hydrophilic groups,

(gg) Immunosuppressive agents, *e g* , cyclosporine, azathioprine, and methotrexate;

(hh) Anti-gout agents, *e.g.*, colchicine,

(ii) Xanthine oxidase inhibitors, *e.g* , allopurinol,

(jj) Uricosuric agents, *e.g.*, probenecid, sulfinpyrazone, and benzbromarone;

(kk) Antineoplastic agents, especially antimitotic drugs including the vinca alkaloids such as vinblastine and vincristine;

(ll) Growth hormone secretagogues,

(mm) Inhibitors of matrix metalloproteases (MMPs), *i.e.*, the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase, especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11),

(nn)Transforming growth factor (TGFβ);

(oo)Platelet-derived growth factor (PDGF);

(pp)Fibroblast growth factor, *e g.*, basic fibroblast growth factor (bFGF);

(qq)Granulocyte macrophage colony stimulating factor (GM-CSF);

(rr) Capsaicin cream,

(ss)Anti-emetic agents including NK-1 receptor antagonists and D-4418, and

(tt) Anti-depressants.

DETAILED DESCRIPTION OF THE INVENTION

10.0 Pharmaceutical Compositions and Formulations

The description which follows concerns the manner in which the compounds of Formula (1.0 0), together with other therapeutic agents or non-therapeutic agents where these are desired, are combined with what are for the most part conventional pharmaceutically acceptable carriers to form dosage forms suitable for the different routes of administration which are utilized for any given patient, as well as appropriate to the disease, disorder, or condition for which any given patient is being treated

The preferred routes of administration for the compounds of Formula (1.0.0) are by way of oral and aerosol formulations prepared and delivered in a conventional fashion Detailed information regarding the preparation of such formulations and the manner in which they are to be given to a patient in need of treatment are discussed further below

The pharmaceutical compositions of the present invention comprise any one or more of the above-described inhibitory compounds of the present invention, or a pharmaceutically acceptable salt thereof as also above-described, together with a pharmaceutically acceptable carrier in accordance with the properties and expected performance of such carriers which are well-known in the pertinent art.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, and the particular mode of administration It should be understood, however, that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated The amount of active ingredient may also depend upon the therapeutic or prophylactic agent, if any, with which the ingredient is co-administered

The above-described compounds of the present invention may be utilized in the form of acids, esters, or other chemical classes of compounds to which the compounds described belong It is also within the scope of the present invention to utilize those compounds in the form of pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures described in detail above and well known in the art. An active ingredient comprising a compound of Formula (1 0.0) is often utilized in the form of a salt thereof, especially where said salt form confers on said active ingredient improved pharmacokinetic properties as compared to the free form of said active ingredient or some other salt form of said active ingredient utilized previously The pharmaceutically acceptable salt form of said active ingredient may also initially confer a desirable pharmacokinetic property on said active ingredient which it did not previously possess, and may even positively affect the pharmacodynamics of said active ingredient with respect to its therapeutic activity in the body

The pharmacokinetic properties of said active ingredient which may be favorably affected include, *e.g.*, the manner in which said active ingredient is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation and excretion of said active ingredient. While the route of administration of the pharmaceutical composition is important, and various anatomical, physiological and pathological factors can critically affect bioavailability, the solubility of said active ingredient is usually dependent upon the character of the particular salt form thereof which it utilized Further, as the artisan understands, an aqueous solution of said active ingredient will provide the most rapid absorption of said active ingredient into the body of a patient being treated, while lipid solutions and suspensions, as well as solid dosage forms, will result in less rapid absorption of said active ingredient. Oral ingestion of said active ingredient is the most preferred route of administration for reasons of safety, convenience, and economy, but absorption of such an oral dosage form can be adversely affected by physical characteristics such as polarity, emesis caused by irritation of the gastrointestinal mucosa, destruction by digestive enzymes and low pH, irregular absorption or propulsion in the presence of food or other drugs, and metabolism by enzymes of the mucosa, the intestinal flora, or the liver Formulation of said active ingredient into different pharmaceutically acceptable salt forms may be effective in overcoming or alleviating one or more of the above-recited problems encountered with absorption of oral dosage forms

Among the pharmaceutical salts recited further above, those which are preferred include, but are not limited to acetate, besylate, citrate, fumarate, gluconate, hemisuccinate, hippurate, hydrochloride, hydrobromide, isethionate, mandelate, meglumine, nitrate, oleate, phosphonate, pivalate, sodium phosphate, stearate, sulfate, sulfosalicylate, tartrate, thiomalate, tosylate, and tromethamine.

Multiple salts forms are included within the scope of the present invention where a compound of the present invention contains more than one group capable of forming such pharmaceutically acceptable salts Examples of typical multiple salt forms include, but are not limited to bitartrate, diacetate, difumarate, dimeglumine, diphosphate, disodium, and trihydrochloride.

The pharmaceutical compositions of the present invention comprise any one or more of the above-described inhibitory compounds of the present invention, or a pharmaceutically acceptable salt thereof as also above-described, together with a pharmaceutically acceptable carrier in accordance with the properties and expected performance of such carriers which are well-known in the pertinent art.

The term "carrier" as used herein includes acceptable diluents, excipients, adjuvants, vehicles, solubilization aids, viscosity modifiers, preservatives and other agents well known to the artisan for providing favorable properties in the final pharmaceutical composition In order to illustrate such carriers, there follows a brief survey of pharmaceutically acceptable carriers that may be used in the pharmaceutical compositions of the present invention, and thereafter a more detailed description of the various types of ingredients. Typical carriers include but are by no means limited to, ion exchange compositions, alumina, aluminum stearate; lecithin, serum proteins, *e g.*, human serum albumin, phosphates, glycine; sorbic acid, potassium sorbate; partial glyceride mixtures of saturated vegetable fatty acids, hydrogenated palm oils, water; salts or electrolytes, *e g.*, prolamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts, colloidal silica, magnesium trisilicate; polyvinyl pyrrolidone; cellulose-based substances, *e g.*, sodium carboxymethylcellulose, polyethylene glycol, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat.

More particularly, the carriers used in the pharmaceutical compositions of the present invention comprise various classes and species of additives which are members independently selected from the groups consisting essentially of those recited in the following paragraphs

Acidifying and alkalizing agents are added to obtain a desired or predetermined pH and comprise acidifying agents, *e g* , acetic acid, glacial acetic acid, malic acid, and propionic acid Stronger acids such as hydrochloric acid, nitric acid and sulfuric acid may be used but are less preferred Alkalizing agents include, *e g* , edetol, potassium carbonate, potassium hydroxide, sodium borate, sodium carbonate, and sodium hydroxide Alkalizing agents which contain active amine groups, such as diethanolamine and trolamine, may also be used

Aerosol propellants are required where the pharmaceutical composition is to be delivered as an aerosol under significant pressure Such propellants include, *e.g.*, acceptable

fluorochlorohydrocarbons such as dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane, nitrogen, or a volatile hydrocarbon such as butane, propane, isobutane or mixtures thereof

Antimicrobial agents including antibacterial, antifungal and antiprotozoal agents are added where the pharmaceutical composition is topically applied to areas of the skin which are likely to have suffered adverse conditions or sustained abrasions or cuts which expose the skin to infection by bacteria, fungi or protozoa Antimicrobial agents include such compounds as benzyl alcohol, chlorobutanol, phenylethyl alcohol, phenylmercuric acetate, potassium sorbate, and sorbic acid Antifungal agents include such compounds as benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, and sodium benzoate.

Antimicrobial preservatives are added to the pharmaceutical compositions of the present invention in order to protect them against the growth of potentially harmful microorganisms, which usually invade the aqueous phase, but in some cases can also grow in the oil phase of a composition Thus, preservatives with both aqueous and lipid solubility are desirable Suitable antimicrobial preservatives include, e g., alkyl esters of *p*-hydroxybenzoic acid, propionate salts, phenoxyethanol, methylparaben sodium, propylparaben sodium, sodium dehydroacetate, benzalkonium chloride, benzethonium chloride, benzyl alcohol, hydantoin derivatives, quaternary ammonium compounds and cationic polymers, imidazolidinyl urea, diazolidinyl urea, and trisodium ethylenediamine tetracetate (EDTA). Preservatives are preferably employed in amounts ranging from about 0.01% to about 2 0% by weight of the total composition

Antioxidants are added to protect all of the ingredients of the pharmaceutical composition from damage or degradation by oxidizing agents present in the composition itself or the use environment, e.g , anoxomer, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, potassium metabisulfite, propyl octyl and dodecyl gallate, sodium metabisulfite, sulfur dioxide, and tocopherols.

Buffering agents are used to maintain a desired pH of a composition once established, from the effects of outside agents and shifting equilibria of components of the composition The buffering may be selected from among those familiar to the artisan skilled in the preparation of pharmaceutical compositions, e g., calcium acetate, potassium metaphosphate, potassium phosphate monobasic, and tartaric acid.

Chelating agents are used to help maintain the ionic strength of the pharmaceutical composition and bind to and effectively remove destructive compounds and metals, and include, e.g., edetate dipotassium, edetate disodium, and edetic acid

Dermatologically active agents are added to the pharmaceutical compositions of the present invention where they are to be applied topically, and include, *e.g.*, wound healing agents such as peptide derivatives, yeast, panthenol, hexylresorcinol, phenol, tetracycline hydrochloride, lamin and kinetin, retinoids for treating skin cancer, *e.g.*, retinol, tretinoin, isotretinoin, etretinate, acitretin, and arotinoid, mild antibacterial agents for treating skin infections, *e.g.*, resorcinol, salicylic acid, benzoyl peroxide, erythromycin-benzoyl peroxide, erythromycin, and clindamycin, antifungal agents for treating tinea corporis, tinea pedis, candidiasis and tinea versicolor, *e g.*, griseofulvin, azoles such as miconazole, econazole, itraconazole, fluconazole, and ketoconazole, and allylamines such as naftifine and terfinafine, antiviral agents for treating cutaneous herpes simplex, herpes zoster, and chickenpox, *e.g.*, acyclovir, famciclovir, and valacyclovir; antihistamines for treating pruritis, atopic and contact dermatitis, *e.g* , diphenhydramine, terfenadine, astemizole, loratadine, cetirizine, acrivastine, and temelastine, topical anesthetics for relieving pain, irritation and itching, *e.g.*, benzocaine, lidocaine, dibucaine, and pramoxine hydrochloride, topical analgesics for relieving pain and inflammation, *e g.*, methyl salicylate, camphor, menthol, and resorcinol; topical antiseptics for preventing infection, *e.g.*, benzalkonium chloride and povidone-iodine; and vitamins and derivatives thereof such as tocopherol, tocopherol acetate, retinoic acid and retinol.

Dispersing and suspending agents are used as aids for the preparation of stable formulations and include, *e.g.*, poligeenan, povidone, and silicon dioxide

Emollients are agents, preferably non-oily and water-soluble, which soften and soothe the skin, especially skin that has become dry because of excessive loss of water Such agents are used with pharmaceutical compositions of the present invention which are intended for topical applications, and include,, *e.g* , hydrocarbon oils and waxes, triglyceride esters, acetylated monoglycerides, methyl and other alkyl esters of C_{10} -C_{20} fatty acids, C_{10} - C_{20} fatty acids, C_{10} -C_{20} fatty alcohols, lanolin and derivatives, polyhydric alcohol esters such as polyethylene glycol (200-600), polyoxyethylene sorbitan fatty acid esters, wax esters, phospholipids, and sterols, emulsifying agents used for preparing oil-in-water emulsions, excipients, *e g.*, laurocapram and polyethylene glycol monomethyl ether; humectants, *e g.*, sorbitol, glycerin and hyaluronic acid, ointment bases, *e g.*, petrolatum, polyethylene glycol, lanolin, and poloxamer; penetration enhancers, *e g* , dimethyl isosorbide, diethyl-glycol-monoethylether, 1-dodecylazacycloheptan-2-one, and dimethylsulfoxide (DMSO); preservatives, *e g.*, benzalkonium chloride, benzethonium chloride, alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, cetylpyridinium chloride, propylparaben, quaternary ammonium compounds such as potassium benzoate, and thimerosal, sequestering agents comprising cyclodextrins, solvents, *e g.*, acetone, alcohol, amylene hydrate, butyl alcohol, corn oil, cottonseed oil, ethyl acetate, glycerin, hexylene glycol, isopropyl alcohol, isostearyl alcohol, methyl alcohol, methylene chloride, mineral oil, peanut

oil, phosphoric acid, polyethylene glycol, polyoxypropylene 15 stearyl ether, propylene glycol, propylene glycol diacetate, sesame oil, and purified water; stabilizers, *e.g.*, calcium saccharate and thymol, surfactants, *e.g*, lapyrium chloride, laureth 4, *i.e.*, α-dodecyl-ω-hydroxy-poly(oxy-1,2-ethanediyl) or polyethylene glycol monododecyl ether

Emulsifying agents, including emulsifying and stiffening agents and emulsion adjuncts, are used for preparing oil-in-water emulsions when these form the basis of the pharmaceutical compositions of the present invention Such emulsifying agents include, *e.g.*, non-ionic emulsifiers such as C_{10} -C_{20} fatty alcohols and said fatty alcohols condensed with from 2 to 20 moles of ethylene oxide or propylene oxide, (C_8 -C_{12})alkyl phenols condensed with from 2 to 20 moles of ethylene oxide, mono- and di- C_{10} -C_{20} fatty acid esters of ethylene glycol, C_{10} -C_{20} fatty acid monoglyceride, diethylene glycol, polyethylene glycols of MW 200-6000, polypropylene glycols of MW 200-3000, and particularly sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan, hydrophilic wax esters, cetostearyl alcohol, oleyl alcohol, lanolin alcohols, cholesterol, mono- and di-glycerides, glyceryl monostearate, polyethylene glycol monostearate, mixed mono- and distearic esters of ethylene glycol and polyoxyethylene glycol, propylene glycol monostearate, and hydroxypropyl cellulose Emulsifying agents which contain active amine groups may also be used and typically include anionic emulsifiers such as fatty acid soaps, *e.g.*, sodium, potassium and triethanolamine soaps of C_{10} -C_{20} fatty acids; alkali metal, ammonium or substituted ammonium (C_{10} -C_{20})alkyl sulfates, (C_{10} -C_{20})alkyl sulfonates, and (C_{10} -C_{20})alkyl ethoxy ether sulfonates Other suitable emulsifying agents include castor oil and hydrogenated castor oil, lecithin, and polymers of 2-propenoic acid together with polymers of acrylic acid, both cross-linked with allyl ethers of sucrose and/or pentaerythritol, having varying viscosities and identified by product names carbomer 910, 934, 934P, 940, 941, and 1342 Cationic emulsifiers having active amine groups may also be used, including those based on quaternary ammonium, morpholinium and pyridinium compounds. Similarly, amphoteric emulsifiers having active amine groups, such as cocobetaines, lauryl dimethylamine oxide and cocoylimidazoline, may be used Useful emulsifying and stiffening agents also include cetyl alcohol and sodium stearate; and emulsion adjuncts such as oleic acid, stearic acid, and stearyl alcohol

Excipients include, *e.g.*, laurocapram and polyethylene glycol monomethyl ether

Where the pharmaceutical composition of the present invention is to be applied topically, penetration enhancers may be used, which include, *e g.*, dimethyl isosorbide, diethyl-glycol-monoethylether, 1-dodecylazacycloheptan-2-one, and dimethylsulfoxide (DMSO) Such compositions will also typically include ointment bases, *e.g*, petrolatum,

polyethylene glycol, lanolin, and poloxamer, which is a block copolymer of polyoxyethylene and polyoxypropylene, which may also serve as a surfactant or emulsifying agent.

Preservatives are used to protect pharmaceutical compositions of the present invention from degradative attack by ambient microorganisms, and include, *e.g.*, benzalkonium chloride, benzethonium chloride, alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, cetylpyridinium chloride, monothioglycerol, phenol, phenoxyethanol, methylparagen, imidazolidinyl urea, sodium dehydroacetate, propylparaben, quaternary ammonium compounds, especially polymers such as polixetonium chloride, potassium benzoate, sodium formaldehyde sulfoxylate, sodium propionate, and thimerosal.

Sequestering agents are used to improve the stability of the pharmaceutical compositions of the present invention and include, *e g* , the cyclodextrins which are a family of natural cyclic oligosaccharides capable of forming inclusion complexes with a variety of materials, and are of varying ring sizes, those having 6-, 7- and 8-glucose residues in a ring being commonly referred to as α-cyclodextrins, β-cyclodextrins, and γ-cyclodextrins, respectively Suitable cyclodextrins include, *e.g.*, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, δ-cyclodextrin and cationized cyclodextrins

Solvents which may be used in preparing the pharmaceutical compositions of the present invention include, *e.g.*, acetone, alcohol, amylene hydrate, butyl alcohol, corn oil, cottonseed oil, ethyl acetate, glycerin, hexylene glycol, isopropyl alcohol, isostearyl alcohol, methyl alcohol, methylene chloride, mineral oil, peanut oil, phosphoric acid, polyethylene glycol, polyoxypropylene 15 stearyl ether, propylene glycol, propylene glycol diacetate, sesame oil, and purified water

Stabilizers which are suitable for use include, *e g* , calcium saccharate and thymol

Stiffening agents are typically used in formulations for topical applications in order to provide desired viscosity and handling characteristics and include, *e.g.*, cetyl esters wax, myristyl alcohol, paraffin, synthetic paraffin, emulsifying wax, microcrystalline wax, white wax and yellow wax.

Sugars are often used to impart a variety of desired characteristics to the pharmaceutical compositions of the present invention and in order to improve the results obtained, and include, *e g.*, monosaccharides, disaccharides and polysaccharides such as glucose, xylose, fructose, reose, ribose, pentose, arabinose, allose, talose, altrose, mannose, galactose, lactose, sucrose, erythrose, glyceraldehyde, or any combination thereof

Surfactants are employed to provide stability for multi-component pharmaceutical compositions of the present invention, enhance existing properties of those compositions, and bestow desirable new characteristics on said compositions Surfactants are used as wetting

agents, antifoam agents, for reducing the surface tension of water, and as emulsifiers, dispersing agents and penetrants, and include, *e g.*, lapyrium chloride; laureth 4, *i.e.*, α-dodecyl-ω-hydroxy-poly(oxy-1,2-ethanediyl) or polyethylene glycol monododecyl ether; laureth 9, *i.e.*, a mixture of polyethylene glycol monododecyl ethers averaging about 9 ethylene oxide groups per molecule; monoethanolamine; nonoxynol 4, 9 and 10, *i.e.*, polyethylene glycol mono(*p*-nonylphenyl) ether; nonoxynol 15, *i.e.*, α-(*p*-nonylphenyl)-ω-hydroxypenta-deca(oxyethylene); nonoxynol 30, *i.e.*, α-(*p*-nonylphenyl)-ω-hydroxytriaconta(oxyethylene); poloxalene, *i.e.*, nonionic polymer of the polyethylene-polypropylene glycol type, MW = approx. 3000, poloxamer, referred to in the discussion of ointment bases further above, polyoxyl 8, 40 and 50 stearate, *i.e.*, poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, octadecanoate; polyoxyl 10 oleyl ether, *i.e.*, poly(oxy-1,2-ethanediyl), α-[(Z)-9-octadecenyl-ω-hydroxy-, polysorbate 20, *i.e.*, sorbitan, monododecanoate, poly(oxy-1,2-ethanediyl), polysorbate 40, *i.e.*, sorbitan, monohexadecanoate, poly(oxy-1,2-ethanediyl); polysorbate 60, *i.e.*, sorbitan, monooctadecanoate, poly(oxy-1,2-ethanediyl); polysorbate 65, *i.e.*, sorbitan, trioctadecanoate, poly(oxy-1,2-ethanediyl); polysorbate 80, *i.e.*, sorbitan, mono-9-monodecenoate, poly(oxy-1,2-ethanediyl); polysorbate 85, *i.e.*, sorbitan, tri-9-octadecenoate, poly(oxy-1,2-ethanediyl), sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate; sorbitan monostearate; sorbitan sesquioleate; sorbitan trioleate, and sorbitan tristearate.

The pharmaceutical compositions of the present invention may be prepared using very straightforward methodology which is well understood by the artisan of ordinary skill Where the pharmaceutical compositions of the present invention are simple aqueous and/or other solvent solutions, the various components of the overall composition are brought together in any practical order, which will be dictated largely by considerations of convenience. Those components having reduced water solubility, but sufficient solubility in the same co-solvent with water, may all be dissolved in said co-solvent, after which the co-solvent solution will be added to the water portion of the carrier whereupon the solutes therein will become dissolved in the water To aid in this dispersion/solution process, a surfactant may be employed

Where the pharmaceutical compositions of the present invention are to be in the form of emulsions, the components of the pharmaceutical composition will be brought together in accordance with the following general procedures The continuous water phase is first heated to a temperature in the range of from about 60° to about 95°C, preferably from about 70° to about 85°C, the choice of which temperature to use being dependent upon the physical and chemical properties of the components which make up the oil-in-water emulsion. Once the continuous water phase has reached its selected temperature, the components of the final

composition to be added at this stage are admixed with the water and dispersed therein under high-speed agitation Next, the temperature of the water is restored to approximately its original level, after which the components of the composition which comprise the next stage are added to the composition mixture under moderate agitation and mixing continues for from about 5 to about 60 minutes, preferably about 10 to about 30 minutes, depending on the components of the first two stages Thereafter, the composition mixture is passively or actively cooled to from about 20° to about 55°C for addition of any components in the remaining stages, after which water is added in sufficient quantity to reach its original predetermined concentration in the overall composition

According to the present invention, the pharmaceutical compositions may be in the form of a sterile injectable preparation, for example a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as do natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as *Rh,* HCIX or similar alcohol

The pharmaceutical compositions of the present invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added For oral administration in a capsule form, useful diluents include lactose and dried corn starch When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the drug Such materials include cocoa butter, beeswax and polyethylene glycols

The pharmaceutical compositions of the present invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation, as described above, or in a suitable enema formulation. Topically active transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate , cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

Pharmaceutical compositions within the scope of the present invention include those wherein the therapeutically effective amount of an active ingredient comprising a compound of the present invention required for treating or preventing diseases, disorders, and conditions mediated by or associated with modulation of PDE4, especially PDE4D activity as described herein, is provided in a dosage form suitable for systemic administration. Such a pharmaceutical composition will contain said active ingredient in suitable liquid form for delivery by: (1) injection or infusion which is intraarterial, intra- or transdermal, subcutaneous, intramuscular, intraspinal, intrathecal, or intravenous, wherein said active ingredient: (a) is contained in solution as a solute, (b) is contained in the discontinuous phase of an emulsion, or the discontinuous phase of an inverse emulsion which inverts upon injection or infusion, said emulsions containing suitable emulsifying agents, or (c) is contained in a suspension as a suspended solid in colloidal or microparticulate form, said suspension containing suitable suspending agents, (2) injection or infusion into suitable body tissues or cavities as a depot, wherein said composition provides storage of said active ingredient and thereafter delayed-, sustained-, and/or controlled-release of said active ingredient for systemic distribution, (3) instillation, inhalation or insufflation into suitable body tissues or cavities of said pharmaceutical composition in suitable solid form, where said active ingredient: (a) is contained in a solid implant composition providing delayed-, sustained-, and/or controlled-release of said active ingredient; (b) is contained in a particulate composition to be inhaled into the lungs, or (c) is contained in a particulate composition to be blown into suitable body

tissues or cavities, where said composition optionally provides delayed-, sustained-, and/or controlled-release of said active ingredient; or (4) ingestion of said pharmaceutical composition in suitable solid or liquid form for peroral delivery of said active ingredient, where said active ingredient is contained in a solid dosage form, or (b) is contained in a liquid dosage form

Particular dosage forms of the above-described pharmaceutical compositions include (1) suppositories as a special type of implant, comprising bases which are solid at room temperature but melt at body temperature, slowly releasing the active ingredient with which they are impregnated into the surrounding tissue of the body, where the active ingredient becomes absorbed and transported to effect systemic administration; (2) solid peroral dosage forms selected from the group consisting of (a) delayed-release oral tablets, capsules, caplets, lozenges, troches, and multiparticulates, (b) enteric-coated tablets and capsules which prevent release and absorption in the stomach to facilitate delivery distal to the stomach of the patient being treated, (c) sustained-release oral tablets, capsules and microparticulates which provide systemic delivery of the active ingredient in a controlled manner up to a 24-hour period, (d) fast-dissolving tablets, (e) encapsulated solutions, (f) an oral paste, (g) a granular form incorporated in or to be incorporated in the food of a patient being treated, and (h) liquid peroral dosage forms selected from the group consisting of solutions, suspensions, emulsions, inverse emulsions, elixirs, extracts, tinctures, and concentrates

Pharmaceutical compositions within the scope of the present invention include those wherein the therapeutically effective amount of an active ingredient comprising a compound of the present invention required for treating or preventing diseases, disorders, and conditions mediated by or associated with modulation of PDE4, especially PDE4D activity as described herein is provided in a dosage form suitable for local administration to a patient being treated, wherein said pharmaceutical composition contains said active ingredient in suitable liquid form for delivering said active ingredient by: (1) injection or infusion into a local site which is intraarterial, intraarticular, intrachondrial, intracostal, intracystic, intra- or transdermal, intrafascicular, intraligamentous, intramedulary, intramuscular, intranasal, intraneural, intraocular, *i.e.*, opthalmic administration, intraosteal, intrapelvic, intrapericardial, intraspinal, intrasternal, intrasynovial, intratarsal, or intrathecal, including components which provide delayed-release, controlled-release, and/or sustained-release of said active ingredient into said local site, where said active ingredient is contained (a) in solution as a solute, (b) in the discontinuous phase of an emulsion, or the discontinuous phase of an inverse emulsion which inverts upon injection or infusion, said emulsions containing suitable emulsifying agents, or (c) in a suspension as a suspended solid in colloidal or microparticulate form, said suspension containing suitable suspending agents, or (2) injection or infusion as a depot for delivering

said active ingredient to said local site, wherein said composition provides storage of said active ingredient and thereafter delayed-, sustained-, and/or controlled-release of said active ingredient into said local site, and wherein said composition also includes components which ensure that said active ingredient has predominantly local activity, with little systemic carryover activity; or wherein said pharmaceutical composition contains said active ingredient in suitable solid form for delivering said inhibitor by (3) instillation, inhalation or insufflation to said local site, where said active ingredient is contained (a) in a solid implant composition which is installed in said local site, said composition optionally providing delayed-, sustained-, and/or controlled-release of said active ingredient to said local site; (b) in a particulate composition which is inhaled into a local site comprising the lungs, or (c) in a particulate composition which is blown into a local site, where said composition includes components which will ensure that said active ingredient has predominantly local activity, with insignificant systemic carryover activity, and optionally provides delayed-, sustained-, and/or controlled-release of said active ingredient to said local site. For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspension in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum

The pharmaceutical compositions of the present invention may also be administered by nasal aerosol or inhalation through the use of a nebulizer, a dry powder inhaler or a metered dose inhaler Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, hydrofluorocarbons, and/or other conventional solubilizing or dispersing agents.

As already mentioned, the active ingredients of Formula (1.0.0) of the present invention may be administered systemically to a patient to be treated as a pharmaceutical composition in suitable liquid form by injection or infusion There are a number of sites and organ systems in the body of the patient which will allow the properly formulated pharmaceutical composition, once injected or infused, to permeate the entire body and all of the organ system of the patient being treated An injection is a single dose of the pharmaceutical composition forced, usually by a syringe, into the tissue involved The most common types of injections are intramuscular, intravenous, and subcutaneous By contrast, an infusion is the gradual introduction of the pharmaceutical composition into the tissue involved The most common type of infusion is intravenous Other types of injection or infusion comprise intraarterial, intra- or transdermal (including subcutaneous), or intraspinal especially intrathecal In these liquid pharmaceutical compositions, the active ingredient may

be contained in solution as the solute This is the most common and most preferred type of such composition, but requires an active ingredient in a salt form that has reasonably good aqueous solubility Water (or saline) is by far the most preferred solvent for such compositions Occasionally supersaturated solutions may be utilized, but these present stability problems that make them impractical for use on an everyday basis.

If it is not possible to obtain a form of some compound of Formula (1.0.0) that has the requisite degree of aqueous solubility, as may sometimes occur, it is within the skill of the artisan to prepare an emulsion, which is a dispersion of small globules of one liquid, the discontinuous or internal phase, throughout a second liquid, the continuous or external phase, with which it is immiscible. The two liquids are maintained in an emulsified state by the use of emulsifiers which are pharmaceutically acceptable Thus, if the active ingredient is a water-insoluble oil, it can be administered in an emulsion of which it is the discontinuous phase. Also where the active ingredient is water-insoluble but can be dissolved in a solvent which is immiscible with water, an emulsion can be used While the active ingredient would most commonly be used as the discontinuous or internal phase of what is referred to as an oil-in-water emulsion, it could also be used as the discontinuous or internal phase of an inverse emulsion, which is commonly referred to as a water-in-oil emulsion. Here the active ingredient is soluble in water and could be administered as a simple aqueous solution However, inverse emulsions invert upon injection or infusion into an aqueous medium such as the blood, and offer the advantage of providing a more rapid and efficient dispersion of the active ingredient into that aqueous medium than can be obtained using an aqueous solution. Inverse emulsions are prepared by using suitable, pharmaceutically acceptable emulsifying agents well known in the art. Where the active ingredient has limited water solubility, it may also be administered as a suspended solid in colloidal or microparticulate form in a suspension prepared using suitable, pharmaceutically acceptable suspending agents. The suspended solids containing the active ingredient may also be formulated as delayed-, sustained-, and/or controlled-release compositions

While systemic administration will most frequently be carried out by injection or infusion of a liquid, there are many situations in which it will be advantageous or even necessary to deliver the active ingredient as a solid Systemic administration of solids is carried out by installation, inhalation or insufflation of a pharmaceutical composition in suitable solid form containing the active ingredient. Installation of the active ingredient may entail installing a solid implant composition into suitable body tissues or cavities. The implant may comprise a matrix of bio-compatible and bio-erodible materials in which particles of a solid active ingredient are dispersed, or in which, possibly, globules or isolated cells of a liquid active ingredient are entrapped Desirably, the matrix will be broken down and completely absorbed by the body The composition of the matrix is also preferably selected to provide

controlled-, sustained-, and/or delayed release of the active ingredient over extended periods of time, even as much as several months.

The term "implant" most often denotes a solid pharmaceutical composition containing the active ingredient, while the term "depot" usually implies a liquid pharmaceutical composition containing the active ingredient, which is deposited in any suitable body tissues or cavities to form a reservoir or pool which slowly migrates to surrounding tissues and organs and eventually becomes systemically distributed However, these distinctions are not always rigidly adhered to in the art, and consequently, it is contemplated that there is included within the scope of the present invention liquid implants and solid depots, and even mixed solid and liquid forms for each. Suppositories may be regarded as a type of implant, since they comprise bases which are solid at room temperature but melt at a patient's body temperature, slowly releasing the active ingredient with which they are impregnated into the surrounding tissue of the patient's body, where the active ingredient becomes absorbed and transported to effect systemic administration.

Systemic administration can also be accomplished by inhalation or insufflation of a powder, *i.e.*, particulate composition containing the active ingredient. For example, the active ingredient in powder form may be inhaled into the lungs using conventional devices for aerosolizing particulate formulations The active ingredient as a particulate formulation may also be administered by insufflation, *i.e.*, blown or otherwise dispersed into suitable body tissues or cavities by simple dusting or using conventional devices for aerosolizing particulate formulations These particulate compositions may also be formulated to provide delayed-, sustained-, and/or controlled-release of the active ingredient in accordance with well understood principles and known materials.

Other means of systemic administration which may utilize the active ingredients of the present invention in either liquid or solid form include transdermal, intranasal, and opthalmic routes In particular, transdermal patches prepared in accordance with well known drug delivery technology may be prepared and applied to the skin of a patient to be treated, whereafter the active agent by reason of its formulated solubility characteristics migrates across the epidermis and into the dermal layers of the patient's skin where it is taken up as part of the general circulation of the patient, ultimately providing systemic distribution of the active ingredient over a desired, extended period of time Also included are implants which are placed beneath the epidermal layer of the skin, *i.e* between the epidermis and the dermis of the skin of the patient being treated Such an implant will be formulated in accordance with well known principles and materials commonly used in this delivery technology, and may be prepared in such a way as to provide controlled-, sustained-, and/or delayed-release of the active ingredient into the systemic circulation of the patient. Such subepidermal (subcuticular)

Implants provide the same facility of installation and delivery efficiency as transdermal patches, but without the limitation of being subject to degradation, damage or accidental removal as a consequence of being exposed on the top layer of the patient's skin.

In the above description of pharmaceutical compositions containing an active ingredient of Formula (1 0 0), the equivalent expressions "administration", "administration of", "administering", and "administering a" have been used with respect to said pharmaceutical compositions. As thus employed, these expressions are intended to mean providing to a patient in need of treatment a pharmaceutical composition of the present invention by any of the routes of administration herein described, wherein the active ingredient is a compound of Formula (1 0 0) or a prodrug, derivative, or metabolite thereof which is useful in treating a disease, disorder, or condition mediated by or associated with modulation of PDE4, especially PDE4D activity in said patient. Accordingly, there is included within the scope of the present invention any other compound which, upon administration to a patient, is capable of directly or indirectly providing a compound of Formula (1.0.0) Such compounds are recognized as prodrugs, and a number of established procedures are available for preparing such prodrug forms of the compounds of Formula (1.0 0).

The dosage and dose rate of the compounds of Formula (1 0 0) effective for treating or preventing a disease, disorder, or condition mediated by or associated with modulation of PDE4, especially PDE4D activity, will depend on a variety of factors, such as the nature of the inhibitor, the size of the patient, the goal of the treatment, the nature of the pathology to be treated, the specific pharmaceutical composition used, and the observations and conclusions of the treating physician.

For example, where the dosage form is oral, *e g* , a tablet or capsule, suitable dosage levels of the compounds of Formula (1.0 0) will be between about 0 1 µg/kg and about 50.0 mg/kg body weight per day, preferably between about 5 0 µg/kg and about 5.0 mg/kg body weight per day, more preferably between about 10 0 µg/kg and about 1.0 mg/kg of body weight per day, and most preferably between about 20 0 µg/kg and about 0.5 mg/kg of body weight per day of the active ingredient.

Where the dosage form is topically administered to the bronchia and lungs, *e g.*, by means of a powder inhaler or nebulizer, suitable dosage levels of the compounds of Formula (1.0 0) will be between about 0 001 µg/kg and about 10.0 mg/kg body weight per day, preferably between about 0 5 µg/kg and about 0.5 mg/kg body weight per day, more preferably between about 1 0 µg/kg and about 0 1 mg/kg of body weight per day, and most preferably between about 2 0 µg/kg and about 0 05 mg/kg of body weight per day of the active ingredient.

Using representative body weights of 10 kg and 100 kg in order to illustrate the range of daily aerosolized topical dosages which might be used as described above, suitable dosage levels of the compounds of Formula (1 0 0) will be between about 1.0 - 10.0 µg and 500.0 - 5000 0 mg per day, preferably between about 5 0 - 50 0 µg and 5 0 - 50 0 mg per day, more preferably between about 100 0 - 1000 0 µg and 10.0 - 100.0 mg per day, and most preferably between about 200.0 - 2000 0 µg and about 5.0 - 50 0 mg per day of the active ingredient comprising a compound of Formula (1.0 0). These ranges of dosage amounts represent total dosage amounts of the active ingredient per day for a given patient. The number of times per day that a dose is administered will depend upon such pharmacological and pharmacokinetic factors as the half-life of the active ingredient, which reflects its rate of catabolism and clearance, as well as the minimal and optimal blood plasma or other body fluid levels of said active ingredient attained in the patient which are required for therapeutic efficacy

Numerous other factors must also be considered in deciding upon the number of doses per day and the amount of active ingredient per dose that will be administered Not the least important of such other factors is the individual response of the patient being treated. Thus, for example, where the active ingredient is used to treat or prevent asthma, and is administered topically *via* aerosol inhalation into the lungs, from one to four doses consisting of acuations of a dispensing device, *i.e* , "puffs" of an inhaler, will be administered each day, each dose containing from about 50 0 µg to about 10.0 mg of active ingredient.

The compounds of Formula (1 0 0) may be administered in a controlled release formulation such as a slow release or a fast (immediate) release formulation Such controlled release formulations of the compounds of Formula (1.0 0) may be prepared using methods well known to those skilled in the art. For example, the formulation of a therapeutic product having up to three or even four dosage forms with different release profiles may be prepared With respect to the immediate release component, in one embodiment, the immediate release dosage form component provides from about 20% to about 50% of the total dosage of therapeutic agent to be delivered by the product. With respect to the delayed release component, the time of release can be controlled by the concentration of the therapeutic agent in the coating and/or the thickness of the coating These remaining dosage forms deliver the remainder of the therapeutic agent. If more than one delayed release dosage form is used, each of the delayed release dosage forms may provide about equal amounts of therapeutic agent, but they may also be formulated to provide different amounts Each of the dosage forms may contain the same therapeutic agent, but each of the dosage forms may also contain more than one, or different therapeutic agent.

The immediate release portion of the controlled release formulation can be a mixture of ingredients that breaks down quickly after administration to release the therapeutic agent. This can take the form of either a discrete pellet or granule that is mixed in with, or compressed with, the other components of the formulation The materials for the immediate release component include, *e.g.*, microcrystalline cellulose, corn starch, pregelatinized starch, potato starch, rice starch, sodium carboxymethyl starch, hydroxypropyl cellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, ethylcellulose, chitosan, hydroxychitosan, hydroxymethylated-chitosan, cross-linked chitosan, cross-linked hydroxymethylchitosan, maltodextrin, mannitol, sorbitol, dextrose, maltose, fructose, glucose, levulose, sucrose, polyvinylpyrrolidone (PVP), acrylic acid derivatives, *e.g.*, Carbopol and Eudragit, polyethylene glycols, *e g* , low molecular weight PEGs PEG2000 –10000, and high molecular weight PEGs, *e.g.*, Polyox, with molecular weights above 20,000 daltons These materials will usually be present in the range of 1 0 to 60% (W/W).

It may be desirable to have other ingredients in the controlled release formulation as an aid in the dissolution of the therapeutic agent, or in the breakdown of some other component after ingestion or administration Such ingredients include surfactants, *e.g.*, sodium lauryl sulfate, sodium monoglycerate, sorbitan monooleate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, glyceryl monostearate, glyceryl monooleate, glyceryl monobutyrate, a non-ionic surfactant, *e g.*, from Pluronic, or other materials with surface active properties. All of these ingredients may be used in combination and will usually be present in the range of 0.05-15% (W/W).

A non-pH-sensitive delayed release component of the controlled release formulations used in the present invention may have the same ingredients as the immediate release component described above, but with additional polymers integrated into the composition, or applied as coatings over the pellet or granule which is formed Materials used to obtain a delay in release suitable for this component are, *e.g.*, polyethylene glycol (PEG) with a molecular weight above 4,000 daltons, *e.g.*, Carbowax and Polyox, waxes, *e g.*, white wax or bees wax, paraffin, acrylic acid derivatives, *e.g.*, Eudragit, propylene glycol, and ethylcellulose Typically, these materials are present in the range of 0.5-25% (W/W) of this component.

A pH-sensitive, *i.e* , enteric release component of the controlled release formulations used in the present invention may have the same ingredients as the immediate release component described above, but with additional polymers integrated into the composition, or applied as coatings over the pellet or granule which is formed The kind of materials useful for this purpose are cellulose acetate pthalate, Eudragit L, and other pthalate salts of cellulose derivatives , which can be present in concentrations from 4-20% (W/W).

A sustained release component of the controlled release formulations used in the present invention may have the same ingredients as the immediate release component described above, but with additional polymers integrated into the composition, or applied as coatings over the pellet or granule which is formed The kind of materials useful for this purpose are ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, methylcellulose, nitrocellulose, Eudragit R, and Eudragit RL, Carbopol, and polyethylene glycols with molecular weights in excess of 8,000 daltons, which may be present in concentrations from 4-20% (W/W).

The particulate units that form the basis for the controlled release formulations used in the present invention may be in the form of discrete pellets or particles contained in a capsule, or in the form of particles embedded in a tablet or suspended in a liquid suspension The controlled release formulation may be administered, *e.g.*, by a sublingual, transmucosal, transdermal, or parenteral route, and preferably is administered orally

In a particular embodiment of the controlled release formulation used in the present invention, the formulation of a compound of Formula (1.0.0) is preferably based on active pellets having a core forming inert component which may comprise non-pareil sugar seeds (sugar spheres, USP XXII) having an average size of from 14 to 35 mesh. The core forming inert component is coated with a formulation which comprises a compound of Formula (1.0.0) and hydroxypropyl methylcellulose. A sufficient amount of the coating is applied to provide the desired dosage of a compound of Formula (1.0 0), *i.e.*, preferably between about 5.0 µg/kg and about 5.0 mg/kg body weight per day

To form a pellet designated A, the active pellet is then coated with a seal coat which may comprise a mixture of hydroxypropyl methylcellulose and polyethylene glycol. The polyethylene glycol may have a number average molecular weight of from 200 to 2000 Generally a ratio of 2.1 to 6 1 of hydroxypropyl methylcellulose to polyethylene glycol may be applied as a 3 to 7 wt % solution in a solvent such as ethanol, isporopyl alcohol, water, and mixtures therof The seal coat is then coated with a release modifying coating which comprises a mixture of an acrylic resin which is soluble in acidic media, and a water insoluble polymer, *e g.*, a cellulosic polymer such as ethylcellulose or cellulose acetate, in a weight ratio of about 1:4, respectively Said release modifying coating is applied from a 3 to 7 wt % solution of isopropyl alcohol, ethanol, acetone, or mixtures therof A useful acrylic resin which is soluble in acidic media is Eudragit E which is a cationic copolymer of dimethylaminoethyl methacrylate and neutral methacrylic acid esters having a mean weight average molecular weight of 150,000

To form a pellet designated B, pellet A is coated with a first coating of hydroxypropyl methylcellulose, after which an enteric coating is applied, where the enteric coating polymer is

shellac, methacrylic acid copolymers (Eudragit S or L), cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, cellulose acetate trimellitate, polyvinyl acetate phthalate, or mixtures thereof, preferably cellulose acetate phthalate. The thickness of the coating is selected to provide the desired release rate, which depends on the thickness and the constituents of the coating

Auxiliary coating aids may be utilized, e.g., 1-5 wt % based on the active core component and the total weight of the final coating, of a plasticizer such as acetyltributyl citrate, triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol (molecular weight of from 380 to 420), propylene glycol and mixtures thereof, in combination with one or more antisticking agents, e g., an alkaline earth metal stearate such as magnesium stearate or calcium stearate, or talc.

The cores are formed by spraying the non-pareil seeds with an aqueous or non-aqueous suspension which contains a compound of Formula (1.0.0) and hydroxypropyl methylcellulose. The suspension medium may comprise any low viscosity solvent, e.g., isopropyl alcohol, ethanol, water, or mixtures thereof It is preferred to dry each coating before applying a second coating Pellets A and pellets B are blended together to obtain a finished product having the following *in vitro* release profile: 50 to 80 wt % released after 2 hours in SGF (pH 1.5); 70 to 95 wt % released after 4 hours in SGF (pH 1.5); and not less than 80 wt % released after 6 hours in SGF (pH 1 5); as determined in a USPXXII Type 2 apparatus, at 37° C and 50 rpm

The pellets may be placed in a gelatin capsule or they may be made into tablets by first adding from 25 to 40 wt % of a solid, pharmaceutically acceptable tablet excipient, e.g., lactose, dextrose, mannitol, calcium phosphate, microcrystalline cellulose, kaolin, powdered sucrose or mixtures thereof, which will form a compressible mixture with pellets A and B, preferably without crushing pellets A or B, and optionally an effective amount of a tablet disintegrating agent, e g., crospovidone, croscarmellose sodium, dry starch, or sodium starch glycolate, and a lubricant.

In another embodiment of a controlled release formulation used in the present invention, crosslinked polyvinyl alcohol (PVA) microspheres containing a compound of Formula (1.0 0) are prepared from an aqueous solution of PVA containing various concentrations of glutaraldehyde dispersed as droplets in liquid paraffin using a suitable sizing agent. Crosslinking of the PVA droplets with glutaraldehyde is induced by an acid catalyst, HCl, which is produced by the addition of small quantities of benzoyl chloride into the dispersion medium Microspheres containing a compound of Formula (1.0.0) are prepared by

carrying out the crosslinking reaction in the presence of said compound of Formula (1.0.0) In another embodiment, polycarbonate microspheres loaded with a compound of Formula (1 0.0) are prepared by a solvent evaporation technique which results in high drug loading of >50%

A further embodiment of the controlled release formulations for use in the present invention comprises controlled-release tablets having an internal drug containing phase and an external phase comprising a polyethylene glycol (PEG) polymer which has a weight average molecular weight of 3000-10000 A compound of Formula (1.0.0) in crystalline form is loaded into a coating pan and spray-coated with a suspension containing Eudragit L30D, acetyl triethylcitrate, talc, and water at 54- 60° C until the coated crystals of said compound of Formula (1 0 0) are formed The coated crystals are mixed with an equal weight of PEG (av, mol wt. 3350) at 50° C to form a molten blend which is formed into tablets

Another sustained release oral solid dosage form embodiment for use in the present invention comprises an effective amount of a compound of Formula (1.0 0) having a solubility of less than about 10 g/l, and a sustained release excipient comprising a gelling agent, an inert pharmaceutical diluent, and an effective amount of a pharmaceutically acceptable cationic crosslinking agent. The ratio of the compound of Formula (1.0 0) to gelling agent is preferably from about 1.3 to about 1.8, and the resulting tablet provides a therapeutically effective blood level of the compound of Formula (1 0 0) for at least about 12 hours, and in preferred embodiments, for about 24 hours Preferably, said gelling agent is a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, and said inert pharmaceutical diluent is granulated with a solution or a dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. The combination of xanthan gum with locust bean gum is a preferred gelling agent.

The cationic cross-linking agent may be monovalent or multivalent metal cations The preferred salts are the inorganic salts, including various alkali metal and/or alkaline earth metal sulfates, chlorides, borates, bromides, citrates, acetates, lactates, etc. Preferred salts are calcium sulfate and sodium chloride The cationic cross-linking agent is added in an amount effective to obtain a desired increase in gel strength, typically in an amount from about 1 to about 20% by weight of the sustained release excipient.

The hydrophobic polymer is selected from an alkylcellulose such as ethylcellulose, other hydrophobic cellulosic materials, polymers or copolymers derived from acrylic or methacrylic acid esters, copolymers of acrylic and methacrylic acid esters, zein, waxes, shellac, and hydrogenated vegetable oils Commercially available alkylcelluloses are

Aquacoat, an aqueous dispersion of ethylcellulose available from FMC, and Surelease, an aqueous dispersion of ethylcellulose available from Colorcon); and acrylic polymers include Eudragit® RS and RL, which are copolymers of acrylic and methacrylic acid esters having a low content, *e.g.*, 1:20 or 1:40, of quaternary ammonium compounds.

It is important to include an effective amount of a wetting agent in the controlled release formulation described above in order to increase the bioavailability of compounds of Formula (1 0 0) with poor solubility. The wetting agent may be added, e.g., by spraying while mixing the granulate. Suitable wetting agents include polyethyleneglycols as esters or ethers, *e.g.*, polyethoxylated castor oil, polyethoxylated hydrogenated castor oil, polyethoxylated fatty acid from castor oil, or polyethoxylated fatty acid from hydrogenated castor oil. Commercially available wetting agents are Cremophor, Myrj, Polyoxyl 40 stearate, Emerest 2675, Lipal 395 and PEG 3350.

Thereafter, a formulator need only blend the desired compound of Formula (1.0.0) and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with plain, *i.e.*, crystalline, sucrose, lactose, dextrose, *etc.*, to form an excipient. The granulate form has certain advantages including the fact that it can be optimized for flow and compressibility; it can be tableted, formulated in a capsule, extruded and spheronized with an active medicament to form pellets, etc.

The pharmaceutical excipients prepared in accordance with the present invention may be prepared according to any agglomeration technique to yield an acceptable excipient product. In wet granulation techniques, the desired amounts of the heteropolysaccharide gum, the homopolysaccharide gum, and the inert diluent are mixed together and thereafter a moistening agent such as water, propylene glycol, glycerol, alcohol or the like is added to prepare a moistened mass. Next, the moistened mass is dried. The dried mass is then milled with conventional equipment into granules.

In still further embodiments of the controlled release formulations used in the present invention, a compound of Formula (1 0 0) having poor aqueous solubility forms a solid dispersion in a hydrophilic poloxamer polymer, said solid dispersion being blended with a water swellable hydroxypropylmethylcellulose, a 2% solution of which has a viscosity in the range 100-100,000 centipoise, to form a hydrogel matrix, and one or more tabletting ingredients to form a tablet core, said tablet core as such or following coating of the core with a polymeric coating being effective to achieve therapeutic levels of said compound of Formula (1 0.0) over extended periods of time following oral administration.

A surfactant component may be included, which is an anionic, cationic or non-ionic surfactant selected from sodium lauryl sulphate, a sodium carboxylate, an alkyl sulphate, a polyethylene glycol ester, a polyethylene ether, a sorbitan ester, an ethoxylated sorbitan ester, an alkyl trimethylammonium halide, and a mixture thereof The solid dispersion may also include an acid component selected from adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid Further, the solid dispersion may include a base component selected from calcium carbonate, calcium hydroxide, magnesium hydroxide, sodium bicarbonate, sodium carbonate, sodium citrate, and sodium hydroxide.

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide, and more especially, the poloxamer polyols are *a*-hydro-*w*-hydroxypoly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block copolymers, more generally known as polyethylene-propylene glycol copolymer or polyoxyethylene-polyoxypropylene copolymer Preferred poloxamers are those which contain between 60% and 90%, more especially between 70% and 80%, by weight of the polyoxyethylene portion. The polyoxyethylene segment is hydrophilic while the polyoxypropylene segment is hydrophobic. The poloxamers differ only in the relative amounts of propylene oxide and ethylene oxide added during manufacture. Poloxamer polyols (poloxamers) are known by the trade names Lutrol, Monolan and Pluronic. Poorly soluble compounds of Formula (1.0.0) are readily dispersible in the melt form of the poloxamers, and when cooled the mixture of compound of Formula (1 0.0), auxiliary agent(s), if present, and poloxamer forms a dry, hard solid which can be easily ground or milled

The solid oral dosage form of the above-mentioned embodiment may be in the form of a capsule or of a tablet. The tablet consists of a tablet core defined by a solid dispersion as already described, dispersed in a hydrogel matrix. The solid dispersion is compressed into a dosage form containing a polymer or mixture of polymers which when wet will swell to form a hydrogel The rate of release of a compound of Formula (1.0.0) from this dosage form is controlled both by diffusion from the swollen tablet mass and by erosion of the tablet surface over time. The rate of release of a compound of Formula (1.0.0) may be controlled both by the amount of polymer *per* tablet and by the inherent viscosities of the polymers used A preferred water swellable polymer is hydroxypropylmethylcellulose (HPMC).

The solid dispersion is in the form of an instant release tablet core which is adapted for direct compression followed by coating with the rate-controlling membrane. A primary consideration with such a formulation is the selection of suitable tablet ingredients to impart the desired effect while compressing easily; accordingly, the solid dispersion is suitably blended with standard tablet excipients such as a standard compressing base, a

compressible sugar, a solubilising agent and a lubricating agent. In this type of dosage form, release of a compound of Formula (1 0 0) is controlled *via* a diffusion mechanism

In order to obtain the desired release profile suitable for once-daily administration, the rate-controlling membrane will suitably contain a major proportion of a pharmaceutically acceptable film-forming, water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer Water soluble polymers include polymers which are freely permeable to water, while water insoluble polymers include polymers which are slightly permeable to water Preferably the water soluble polymer in the membrane, if present, is selected from polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carregeenan, xanthan, polyethylene glycol, and mixtures thereof The incorporation of various hydrophilic agents into the polymer coating so as to form channels in said coating can be used and in general leads to a more linear release rate. Such hydrophilic agents include fumaric acid, citric acid, tartaric acid, sodium citrate, sodium bicarbonate, sodium fumarate, sodium carbonate, monosaccharides and disaccharides. An especially suitable monosaccharide is glucose Alternatively, the water soluble polymer in the membrane can be replaced by a polymeric material which is freely permeable to the active ingredient and water and comprises a copolymer of acrylic and methacrylic acid esters. A suitable polymer which is freely permeable to various poorly soluble compounds of Formula (1.0.0) and water is that sold as Eudragit RL.

Other pharmaceutically acceptable film-forming, water soluble polymers which may be used include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, beta-glycan acetate, acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, polyamide, polyurethane, sulfonated polystyrene, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate, cellulose acetate chloracetate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicaprylate, cellulose dipentanlate, cellulose acetate valerate, cellulose acetate *p*-toluenesulfonate, cellulose acetate butyrate, and other semi-permeable polymers such as those described in U.S Pat. No 4, 285,987, and selectively permeable polymers formed by the coprecipitation of a polycation and a polyanion as disclosed in U.S Pat. Nos. 3,173,876, 3,276,586, 3,541,005, 3,541,006 and 3,546,142.

The water insoluble polymer is preferably selected from ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl

methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane, and mixtures thereof The water insoluble polymer of the membrane may also comprise naturally occurring polymers or resins, *e.g.*, shellac, chitosan, gum juniper, wax or a wax-like substance, zein, hydrogenated vegetable oils, or a mixture thereof

The water insoluble polymer in the membrane may also be replaced by a polymeric material which is slightly permeable to the active ingredient and water and comprises a copolymer of acrylic and methacrylic acid esters, *e.g.*, a polymer sold as Eudragit RS, or a polymer whose permeability is pH dependent and sold as Eudragit L, Eudragit S, or Eudragit E. Eudragit S is preferred Eudragit polymers are polymeric lacquer substances based on acrylates and/or methacrylates. Eudragit RL and Eudragit RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups which are present as salts and give rise to the permeability of the lacquer films Eudragit is freely permeable and Eudragit RS is slightly permeable, both independent of pH Eudragit S is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester, which is insoluble in acids and pure water, but becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis. The permeability of Eudragit S is pH dependent, since above pH 6 0 the polymer becomes increasingly permeable.

The coating solution/suspension of the polymeric material comprises one or more polymer(s) dissolved/suspended in a suitable solvent or mixture of solvents The concentration of the polymeric material in the coating solution/suspension is determined by the viscosity of the final solution/suspension The addition of a plasticizing agent to the polymeric solution/ suspension may be necessary, depending on the formulation, to improve the elasticity and stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage Such changes may affect the rate of release of a compound of Formula (1 0.0). Suitable plasticizing agents include polyethylene glycol, propylene glycol, glycerol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and varying percentages of acetylated monoglycerides

Because ethylcellulose, a preferred hydrophobic polymer material, has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is necessary to plasticize the ethylcellulose before using the same as a coating material. The plasticization of the ethylcellulose may be accomplished either by so-called "internal plasticization" and "external plasticization " The suitability of a plasticizer depends

on its affinity or solvating power for the polymer and its effectiveness at interfering with polymer-polymer attachments. Such activity imparts the desired flexibility by relieving molecular rigidity Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, *e.g*, most often from about 1 to about 50 percent by weight of the film-former Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application Most preferably, about 20% plasticizer is included in the aqueous dispersion of acrylic polymer ,

An important parameter in the determination of a suitable plasticizer for a polymer is related to the glass transition temperature (Tg) of the polymer The glass transition temperature is related to the temperature or temperature range where there is a fundamental change in the physical properties of the polymer This change does not reflect a change in state, but rather a change in the macromolecular mobility of the polymer Below the Tg, the polymer chain mobility is severely restricted Thus, for a given polymer, if its Tg is above room temperature, the polymer will behave as a glass, being hard, non-pliable and rather brittle, properties which are too restrictive in film coating since the coated dosage form may be subjected to a certain amount of external stress Incorporation of suitable plasticizers into the polymer matrix effectively reduces the Tg, so that under ambient conditions the films are softer, more pliable and often stronger, and thus better able to resist mechanical stress

Other aspects of suitable plasticizers include the ability of the plasticizer to act as a good "swelling agent" for the ethylcellulose, and the solubility profile of the polymer film in water Examples of suitable plasticizers for ethylcellulose include dibutyl sebacate, diethyl phthalate, triethyl citrate and tibutyl citrate, although other plasticizers, *e.g.*, acetylated monoglycerides, phthalate esters, and castor oil, may be used Examples of suitable plasticizers for the above-described acrylic polymers include citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and 1,2-propylene glycol Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic polymers such as Eudragit RL and RS lacquer solutions, include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin

A suitable aqueous dispersion of ethylcellulose is Aquacoat sold by FMC Corp , which is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase, consequently, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat with a suitable plasticizer Another suitable aqueous

dispersion of ethylcellulose is Surelease sold by Colorcon, Inc., which is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebecate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

Coating the active tablet core with a differentially permeable membrane allows active dissolution and diffusion from the micro-environment of the active core Especially suitable polymers for this purpose are cellulose and poly(methacrylate) based polymers, and the coating is suitably performed in a C F 360 granulator Preferred solvents for use in polymer application/coating include acetone, isopropyl alcohol and industrial methylated spirit. A plasticized aqueous dispersion of hydrophobic polymer may be applied onto a tablet core by spraying, using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on A sufficient amount of the aqueous dispersion of hydrophobic polymer to obtain a predetermined controlled release of a compound of Formula (1.0.0) when the coated substrate is exposed to aqueous solutions, *e g* , gastric fluid, is preferably applied, taking into account the physical characteristics of said compound of Formula (1.0.0), the manner of incorporation of the plasticizer, *etc.* After coating with the hydrophobic polymer, a further overcoat of a film-former, such as hydroxypropylmethylcellulose, *e.g* , Opadry, is optionally applied to the tablets. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the tablets.

The problem of stability of controlled release pharmaceutical formulations using aqueous dispersions of hydrophobic polymers, *i.e.*, that the dissolution release profile changes on ageing, may be overcome by curing the coated tablet at a temperature greater than the glass transition temperature of the aqueous dispersion of plasticized hydrophobic polymer and at a necessary relative humidity until an endpoint is reached at which said substrate attains a dissolution profile which is substantially unaffected by exposure to accelerated storage conditions, *e.g* , of about 37°-40° C and about 75- 80% relative humidity for three months or longer

Controlled release coatings for compounds of Formula (1 0.0) may also include release-modifying agents such as cellulose acetate phthalate disclosed in U.S Pat. No. 2,196,768, shellac, zein, hydroxypropylmethyl cellulose phthalate, sandarac, modified shellac, *etc* Suitable release-modifying agents may also encompass erosion-promoting agents such

as starch, including corn starch, rice starch, carboxymethyl starch, potato starch, and other vegetable starches, modified starch, and starch derivatives This category includes other erosion-promoting agents such as gums, *e.g.*, xanthan gum, alginic acid, other alginates, bentonite, veegum, agar, guar, locust bean gum, gum arabic, quince psyllium, flax seed, okra gum, arabinogiactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, *etc.*, cross-linked polyvinylpyrrolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, κ-carrageenan, λ-carrageenan, gum karaya, biosynthetic gum, *etc.*

Controlled release coatings for compounds of Formula (1.0.0) may also include materials useful for making microporous lamina in the environment of use. Materials useful for making the microporous lamina include polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain, microporous materials prepared by the phosgenation of a dihydroxyl aromatic such as bisphenol, a microporous poly(vinylchloride), microporous polyamides such as polyhexamethylene adipamide, microporous modacrylic copolymers including those formed from poly(vinychloride) and acrylonitrile, microporous styreneacrylate and its copolymers, porous polysulfones characterized by diphenylene sulfone in a linear chain thereof, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by esterification of a dicarboxylic acid or anhydride with an alkylene polyol, poly(alkylenesulfides), phenolics, polyesters, microporous polysaccharides having substituted anhydroglucose units exhibiting a decreased permeability to the passage of water and biological fluids, asymmetric porous polymers, cross-linked olefin polymers, hydrophobic or hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density, and materials described in U.S. Pat. Nos 3,595,752, 3,643,178, 3,654,066; 3,709,774, 3,718,532; 3,803,601, 3,852,224, 3,852,388, and 3,853,601, in British Pat. No 1,126,849, and in Chem Abst. Vol 71, 427F, 22573F, 1969

Additional microporous materials for forming microporous lamina include poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazole), collodion, regenerated proteins, semi- solid cross-linked poly(vinylpyrrolidone), microporous materials prepared by diffusion of multivalent cations into polyelectrolyte sols, microporous derivatives of poly(styrene) such as poly(sodium-styrenesulfonate), poly(vinyl benzyl trimethyl-ammonium chloride), microporous cellulosic acrylates and the like microporous polymers such as those described in U S Pat. Nos. 3,524,753, 3,565,259; 3,276,589, 3, 541,055, 3,541,006, 3,546,142, 3,615,024, 3,646,178, and 3,852,224 Pore-formers useful for forming the microporous lamina in the environment of use include solids and pore-forming liquids

The term pore-former also embraces micropath formers, and removal of the pore and/or pore-former leads to both embodiments The expression pore-forming liquids generically embraces semi-solids and viscus fluids The pore-formers can be inorganic or organic. The term pore-former for both solids and liquids includes substances that can be dissolved, extracted or leached from the precursor microporous wall by fluid present in the environment of use to form open-celled type microporous lamina. The pore-forming solids have a size, *e g*, of about 0 1 to 200 μ and they include alkali metal salts such as lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, and the like Organic compounds include polysaccharides such as sucrose, glucose, fructose, mannitol, mannose, galactose, sorbitol and the like. The pore-forming solids can be polymers soluble in the environment of use such as Carbowaxes, Carbopol, and the like The pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, poly(a-w)alkylenediols, and the like. The pore-formers are non-toxic and on their removal from lamina, channels and pores are formed through the lamina that fill with fluid present in the environment use.

The controlled release coatings used to deliver compounds of Formula (1 0.0) may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S Pat. Nos. 3,845,770; 3,916,889; 4,063,064, and 4,088, 864 The passageway can have any shape such as round, trianguler, square, elliptical, irregular, *etc.*

Other classes of controlled release delivery systems may be used to administer the compounds of Formula (1 0 0). For example, osmotic devices have demonstrated utility in delivering therapeutic agents to an environment of use in a controlled manner over prolonged periods of time. Known devices of this type include tablets, pills, and capsules. The art has endeavored to develop new membranes that deliver active agents by diffusion and/or osmotic pumping For example, U.S Patent No 4,235,236 discloses an osmotic device that delivers a therapeutic agent by the combined mechanisms of diffusion and osmotic pumping The device comprises a microporous wall surrounding a compartment containing an active agent and an expandable member The expandable member consists of a semipermeable, flexible or expandable film surrounding a member selected from the group consisting of an osmotically effective solute, a gas generating couple and a swellable polymer The external wall of the device is formed of a microporous material through which the active agent is delivered, which allows the release of the active agent at a steady rate, the so called zero-order release. Suitable devices of this and related types may be used to deliver a compound of Formula (1.0 0).

U.S Patent No. 4,327,725 discloses an osmotic device comprising a semipermeable wall surrounding two layers, one layer containing an active agent and the other an expandable hydrogel. A passageway in the wall communicates the active agent layer with the environment of use Cellulose acylate is used to make the semipermeable membrane. U.S Patents No. 5,612,059 and No. 5,698,220 disclose the use of asymmetric membranes in delivery devices These membranes may be permeable, semipermeable, perforated or unperforated and can deliver an active substance by the combined mechanisms of diffusion and osmotic pumping The asymmetric membranes may be made with 398-10 cellulose acetate from Eastman. EP 636386 and EP 553392 disclose an active agent composition coated with an aqueous dispersion of plasticized acrylic polymer, which is subjected to a particular curing process. The resulting controlled release formulation has a stable dissolution profile despite exposure to a variety of storage conditions. U.S. Patent No. 5,543,155 discloses a controlled delivery pharmaceutical composition core surrounded by a wall comprising an ammonium methacrylate copolymer that is permeable to low molecular weight molecules This controlled delivery pharmaceutical composition contains an active pharmaceutical compound and hydroxypropyl methylcellulose (HPMC) as the hydrophilic polymer Tablets having a bi-layered core are prepared with a hydrophilic polymer layer comprising high molecular weight HPMC having a viscosity higher than 1000 cP in a 2% aqueous solution Suitable devices and formulations of this and related types may be used to deliver a compound of Formula (*1.0.0*).

Osmotic devices of this type have a bi-layered core, one layer containing the active agent and the other being a swellable placebo layer, surrounded by a semipermeable membrane. The placebo layer consists mainly of a swellable polymer and/or a hydrogel that, while absorbing fluid from the environment of use, expands and exerts pressure over the layer that contains the active agent thereby releasing the active agent through a passageway in the wall The art teaches that perforation of the semipermeable membrane should be carried out selectively on the side of the membrane that is adjacent to the layer comprising the active agent In fact, if the membrane is perforated adjacent the placebo layer, the active agent will not be released. If two perforations are carried out, one adjacent the active-agent layer and the other adjacent the swellable polymer layer, referred to as the "push" layer, both the active agent and the swellable polymer are released, resulting in loss of the "push" effect. U.S Patent No 5,543,155 also discloses perforation of the membrane adjacent both layers of the core, however, a specific high molecular weight polymer is required to prevent the loss of the push layer leaving a significant number of available hydrophilic polymers unavailable for use in these devices. U S Patent No 5,516,527 discloses a device that can include a preformed passageway and plural pores The device requires the formation of a phase separated coating that ultimately forms a porous membrane

Another device that would be suitable for controlled release of a compound of Formula (1 0 0) comprises a) a core located approximately at the center of the device consisting of an expandable hydrophilic polymer and optionally an osmagent, the core being able to absorb and/or imbibe fluids from the environment of use, b) a composition immediately surrounding the core consisting of a compound of Formula (1 0.0) and, optionally, an osmagent and/or an osmopolymer; c) a membrane immediately surrounding the composition consisting of a mixture of a cellulose acylate (ester), a methacrylate salt copolymer and a plasticizer, where the membrane permits delivery of a compound of Formula (1.0.0) through a combination of diffusion and osmotic pumping, and d) at least one preformed passageway and plural micropores in the membrane that communicate the composition with the outside of the device. The micropores in the wall are formed during preparation of the wall or during exposure to fluids in an intended environment of use Methods of preparing walls wherein the micropores form in the environment of use are well known and described in, among others, U S Patents Nos. 3,845,770; 3,916,899; 4,063,064, 4,088,864, 4,816,263, 4,200,098, 4,285,987, and 5,912,268.

Osmagents or osmotically effective compounds are generally soluble in the fluid that enters into a device of the type described above through a wall thereof, creating an osmotic pressure gradient across the wall The fluid and components of the device layer will generally form a solution or suspension comprising a compound of Formula (1.0.0) to be delivered Exemplary osmagents include high or low molecular weight compounds, organic and inorganic compounds such as salts, acids, bases, chelating agents, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d- mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, combinations thereof and other similar or equivalent materials known in the art. Preferred osmagents include potassium chloride, sodium tartrate, glucose, mannitol, sodium acetate, sodium chloride, sodium sulfate, sodium citrate, potassium tartrate, sorbitol, sucrose and combinations thereof The device layer comprising a compound of Formula (1.0.0) can also comprise an osmopolymer such as those used for the core, preferably poly(alkylene oxide) and, more preferably, poly(ethylene oxide) with an average molecular weight between about 100,000 and 8,000,000

It is known in the art that it is desirable to have a method for reducing the severity of or eliminating or avoiding the occurrence of one or more side effects of a therapeutic agent which inhibits PDE4 , and that one of these methods comprises administering the therapeutic agent in a controlled release formulation which results in a delay in the appearance in the plasma of detectable amounts of said therapeutic agent and results in a reduction of rate of rise in plasma concentration of said therapeutic agent by at least about 10%, as compared

with that of an immediate release formulation containing the same amount of therapeutic agent administered by the same route. At least a 10 minute delay in onset of increasing plasma concentrations is a preferred practice, although a delay of somewhere between 10 and 45 minutes, say 30 minutes, or greater (1 hour or more) are also useful and practicable This timing of delay can be measured by reference to the onset of absorption as measured against an immediate release (IR) tablet, although an IR formulation is but one possible standard

A 10% reduction in rate of rise of plasma concentration of therapeutic agent is a threshold for eliminating or reducing their occurrence or severity side effects with a given dose of therapeutic agent or for increasing the amount of therapeutic agent that is administered, either at a single point in time or when a titration or infusion technique is used Such reduction is determined by comparison to an immediate release preparation administered by the same route For example, if the oral route of administration is chosen as the approach to be taken, then an immediate release tablet or capsule is the standard against which to measure the 10% reduction in rate of rise

A preferred methodology for reducing the rate of rise and/or delaying onset of absorption is the controlled release technologies This involves formulating the therapeutic agent with excipients, which modulate and extend the period over which the active ingredient is released from the carrier This type of formula is sometimes described as a sustained release formulation or a non-immediate release delivery system "Controlled release" is intended to cover any formulation which can be characterized as having a release profile wherein a portion of its drug load is released over time, either episodically or continuously over time. It also includes preparations where the initial release of therapeutic agent is delayed as a result of an external barrier or coating which is selectively soluble in the environment where the formulation is placed, or a preparation where the coating does not break down in the environment into which the formulation is initially introduced, but then migrates to another environment in which the external coating is soluble or is broken down, after which the drug is released over time. By way of further illustration and explanation, these delivery systems can be characterized as i) delayed release, ii) controlled or prolonged release, iii) site-specific release, or iv) receptor release.

A more detailed explanation of these different systems is available in the likes of Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co Easton, Pennsylvania, U.S.A. 18042, or later additions of Drugs and Pharmaceutical Sciences, v 29 "Controlled Drug Delivery- Fundamentals and Applications, Second Edition" edited by Joseph R. Robinson and Vincent H Lee, published by Marcel Dekker Inc. These systems may be dissolution-dependent as illustrated by encapsulated dissolution products or matrix dissolution

products Or, they may be formulated using osmotic systems or ion exchange resins. The most preferred approach is to provide an oral controlled release product based on matrix dissolution technology

A delay in onset of absorption and a reduced rate of absorption may be correlated with reduced side effects when a known PDE4 inhibitor is administered to patients in an oral controlled release preparation containing three times the amount of therapeutic agent as that of an immediate release tablet which was not well tolerated It will also be observed that the controlled tablet results in a reduced rate of absorption, which is reflected in a reduced rate of rise in plasma concentrations but gives a Cmax several hours later which exceeds the Cmax associated with adverse side effects in an immediate release tablet. That is, when an immediate release tablet is given to a patient, the Cmax and side effects correlate strongly This correlation was not observed with the controlled release formulation even though it resulted in a higher Cmax. It is not clear whether the results seen with a controlled release preparation are dependent on or related to one or both of these observations, or to another factor or combination of factors, such as Tmax, ka, Tlag (absorption lag-time), or some other factor or phenomenon Regardless of what the underlying mechanism is, the result is that it is now possible to significantly increase the amount of PDE4 inhibitor administered at a particular time point and avoid the tolerability challenges associated with PDE4 inhibitors in certain segments of the population.

Controlled release preparations can be prepared by selecting excipients from any number or type of materials which provide the requisite controlled release profile needed to avoid side effects while allowing for a significant increase in the amount of therapeutic agent contained in the formulation, as compared with an immediate release preparation. A preferred approach is to use a matrix dissolution technology based on acrylic acid polymers Carbomer is the non-proprietary name for these materials They are high molecular weight polymers prepared by cross linking acrylic acids with the likes of allylsucrose or allyl ethers of pentaerythritol Such polymers also go by the name acritamer or carbopol. The chemical name and CAS registry number for the class is carboxypolymethylene [54182-57-91 Exemplary carbomers are carbomer 910 [91315-32- 1], carbomer 934 [9007-16-3], carbomer 934P [9003- 01-4] and carbomer 940 [76050-42-5] These polymers contain between 56-68% of carboxylic acid groups, calculated on a dry basis A blend of two or more carbomers of differing molecular weight can be used to modify and manipulate the release rate.

The preferred excipients for effecting release rate are carbomers, particularly a combination of two or more different carbomers Especially preferred are those carbomers known as Carbopols and manufactured by BF Goodrich Preferred carbomers are: Carbomer 934P (Carbopol 974P), and Carbomer 94 1 P (Carbopol 97 1 P)

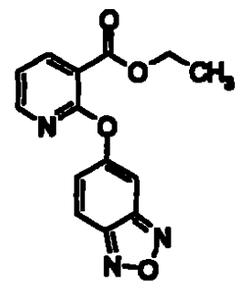
A preferred formulation will have between about 1-25% by weight of therapeutic agent, preferably an amount between 3-20% and optionally an amount between about 5 and 15%

DETAILED DESCRIPTION OF THE INVENTION

11.0 Preparations and Working Examples

Preparation 1a

2-[Benzo[2,1,3]oxadiazol-5-yloxy]-nicotinic acid ethyl ester of Formula (5.0.1):



(5.0.1)

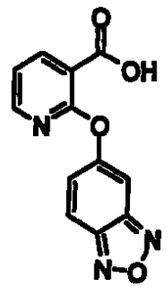
A mixture of 5 5 g (29.4 mmol) 2-chloro nicotinic acid ethyl ester, 4.0 g (29.4 mmol) 5-hydroxybenzofurazan and 20.1 g (61 7 mmol) cesium carbonate in 125 ml dry dimethylforamide was heated at 90°C for five days The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed successively with sodium bicarbonate solution, water, brine then dried (Na_2SO_4) and concentrated *in vacuo* to give a solid Recrystallization from diethyl ether/pentane gave 2.2 g (26%) solid

^{1}H-NMR ($CDCl_3$): δ 8.3 (m, 2H), 7.8 (d, 1H, J=10 Hz), 7.2 (m, 3H), 4.4 (q, 2H, J=7 Hz), 1.4 (t, 3H, J=7 Hz).

GC-MS (m/z). 285 (M^+, 20), 122 (100).

Preparation 1b

2-[Benzo[2,1,3]oxadiazol-5-yloxy]-nicotinic acid of Formula (5 0.2).



(5 0.2)

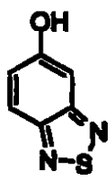
A mixture of 2.2 g (7 7 mmol) 2-[benzo[2,1,3]oxadiazol-5-yloxy]-nicotinic acid ethyl ester and 23 1 ml (23 1 mmol) 1M LiOH in 75 ml tetrahydrofuran was stirred overnight at room temperature. The tetrahydrofuran was evaporated *in vacuo* and the aqueous mixture acidified with 1N HCl The resulting precipitate was filtered and dried to give 1 9 g (96%) solid

^{1}H-NMR (CH_3OD) δ 8.4 (d, 1H, J=8 Hz), 8 3 (dd, 1H, J=2, 5 Hz), 8 0 (d, 1H, J=9 Hz), 7 6 (s, 1H), 7.5 (d, 1H, J=9 Hz), 7.2 (dd, 1H, 5, 8 Hz).

MS (m/z): 257 (M^+, 20), 256 (100).

Preparation 2

Benzo-[2,1,3]-thiadiazol-5-ol of Formula (5 0.3)



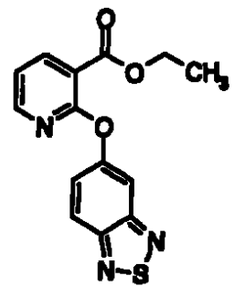
(5.0.3)

5-Methoxybenzo-2,1,3-thiadiazole (4 09 g, 24 6 mmol) was stirred with hydrobromic acid (60 mL, 165 mmol, 30% in acetic acid) at 80 °C 5 days The mixture was cooled to 10 °C and filtered The solids were purified by short column chromatography (50% ethyl acetate / hexane) Solvents were stripped *in vacuo* to afford 1 0 g of a yellow solid (27% yield).

^{1}H NMR (CD_3OD) δ 7.81 (d, 1H, J= 2 Hz), 7 79 (d, 1H, J= 2 Hz), 7.30 (s, 1H).

Preparation 3

2-(Benzo[2,1,3]thiadiazol-5-yloxy)-nicotinic acid ethyl ester of Formula (5.0.4).



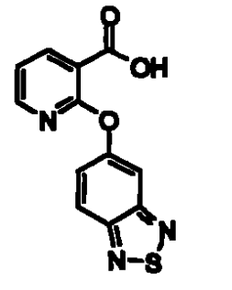
(5.0.4)

A mixture of 2-chloro-nicotinic acid ethyl ester (0.516 g, 3 mmol), benzo-[2,1,3]-thiadiazol-5-ol (0.46 g, 3 mmol) and cesium carbonate (2.07 g, 6 mmol) was stirred in 40 mL *N,N*-dimethylformamide at 80 °C for 48 hours The dark orange mixture was cooled and poured into water (600 mL) and extracted with ethyl acetate. The combined organic layers were washed with water and brine, and dried (Na_2SO_4). The mixture was concentrated *in vacuo* to give 0 74 g yellow solid (82 % yield).

MS (m/z) 302 (M^+, 20), 227 (100)

Preparation 4

2-(Benzo[2,1,3]thiadiazol-5-yloxy)-nicotinic acid of Formula (5.0 5):



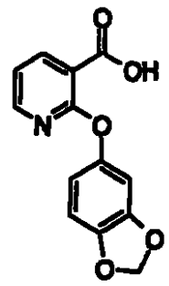
(5.0.5)

A solution of 2-(benzo[2,1,3]thiadiazol-5-yloxy)-nicotinic acid ethyl ester (0 74 g, 2 5 mmol) in tetrahydrofuran (2 78 ml) and 1 M LiOH (2 7 ml) was stirred over night. The mixture was diluted with water and acidified to pH 1 with 2 N hydrochloric acid and filtered to give a pale yellow solid (160 mg).

^{1}H NMR (CD_3OD) δ 8.37 (d, 1H, J= 6 Hz), 8.26 (dd, 1H, J= 2 Hz, 5 Hz), 8.00 (d, 1H, J= 9 Hz), 7 60 (t, 1H, J= 2 Hz), 7.50 (t, 1H, J= 2 Hz), 7.26 (d, 1H, J= 8 Hz).

Preparation 5

2-(Benzo-[1,3]dioxol-5-yloxy)-nicotinic acid of Formula (5.0 6):



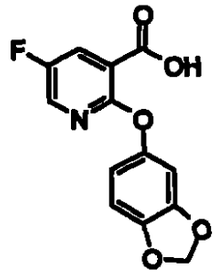
(5.0.6)

2-Chloro-nicotinic acid ethyl ester (10 g), benzo[1,3]dioxol-5-ol (sesamol, 8.2 g), and cesium carbonate (21 g) were mixed in anhydrous dioxane (40 mL) and the resulting slurry heated to reflux for 16 h In a separate flask, lithium hydroxide (12.9 g) was dissolved in water (80mL) with warming and then added to the refluxing mixture, which was heated for an additional 4 h The mixture was cooled to ambient temperature and concentrated in vacuo to remove the dioxane Concentrated hydrochloric acid was added dropwise until the pH = 3 The acidified solution was then extracted with ethyl acetate (7 x 100mL) to yield crude product, which was recrystallized from ethyl acetate to yield the purified title compound (10 8 g).

^{1}H NMR (CD_3OD) δ 8.28 (dd, J = 8 and 2 Hz, 2H), 7 13 (m, 1H), 6 79 (d, J = 8Hz, 1H), 6 62 (s, J = 2Hz, 1H), 6 53 (dd, J = 8 and 2Hz, 1H), 5 95 (s, 2H).

Preparation 6

2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-nicotinic acid of Formula (5.0 7).



(5 0 7)

2-Chloro-5-fluoro-nicotinic acid (synthesized in accordance with the procedures described in European patent. EP 0634413 A1) was converted to the corresponding ethyl ester with anhydrous ethanol and excess thionyl chloride, then worked up in the usual manner To 2-chloro-5-fluoro-nicotinic acid ethyl ester (5 0 g) in an oven-dried 250 mL flask was added cesium carbonate (9 60 g), sesamol (4 07 g), and 50 mL of anhydrous dioxane The reaction was stirred overnight at 100°C Lithium hydroxide (2 94 g) in 10 mL water was added, and the reaction was again allowed to stir overnight at 100°C The dioxane was then evaporated under a nitrogen stream The residue was then taken up in 50 mL water, acidified with conc.

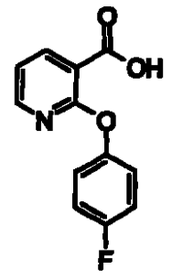
hydrochloric acid to pH = 3, and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo The dried residue was washed with ethyl acetate (20 mL) and dried under high vacuum, giving the title compound (2 96 g).

^{1}H NMR (CD_3OD) δ 8.09-8 04 (m, 2H), 6 76 (d, J = 9Hz, 1H), 6 61 (s, 1H), 6.51 (d, J = 7, 1H), 5 93 (s, 2H).

MS *m/z* 276 $(M + H)^+$

Preparation 7

2-(4-Fluoro-phenoxy)-nicotinic acid of Formula (5.0.8).



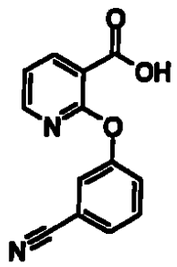
(5.0.8)

2-Chloro-nicotinic acid ethyl ester, 4-fluor enol, and cesium carbonate were mixed in anhydrous dioxane and the resulting slurry ɔeated to reflux for about 16 h. In a separate flask, lithium hydroxide was dissolved in water with warming and then added to the refluxing mixture, which was heated for an additional 4 h The mixture was cooled to ambient temperature and concentrated in vacuo to remove the dioxane. Concentrated hydrochloric acid was added dropwise until the pH = 3 The acidified solution was then extracted with ethyl acetate to yield crude product, which was recrystallized from ethyl acetate to yield the purified title compound (10.8 g).

MS *m/z* 232 $(M-H)^+$

Preparation 8

2-(3-Cyano-phenoxy)-nicotinic acid of Formula (5.0.9)

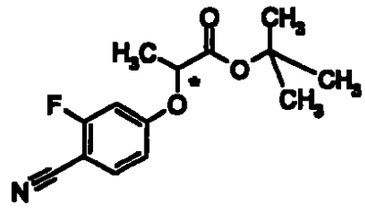


(5.0.9)

The compound of Formula (5.0.9) was prepared in a manner analogous to that described in *Preparation 7 above, replacing the 4-fluoro-phenol with 3-cyano-phenol*

Preparation 9

(±)-2-(4-Cyano-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester of Formula (5.0.10):



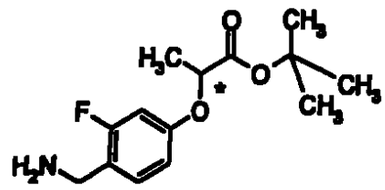
(5.0.10)

2-Fluoro-4-hydroxybenzonitrile (1 g, 7.29 mmol) was dissolved in *N, N*-dimethyl-formamide (20 mL) and stirred with potassium carbonate (1.1 g, 8.0 mmol) at rt for 2h. (±) 2-Bromopropionic acid *tert*-butyl ester (1.67 g, 8.0 mmol) was added and the reaction was stirred at rt for 72 hours. The reaction was quenched into dilute aqueous hydrochloric acid and extracted 2x with ethyl acetate. The pooled organics were dried (Na_2SO_4) and adsorbed onto silica gel, followed by purification by flash column chromatography (20% ethyl acetate/hexane) to afford 1.8 g colorless oil (93% yield).

^{1}H NMR ($CDCl_3$) δ 7.48 (t, 1H, J= 7.5 Hz), 6.68 (d, 1H, J= 9 Hz), 6.64 (d, 1H, J= 11 Hz), 4.55 (q, 1H, J= 7 Hz), 1.58 (d, 3H, J= 7 Hz), 1.41 (s, 9H)

Preparation 10

(±)-2-(4-Aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester of Formula (5 0 11)



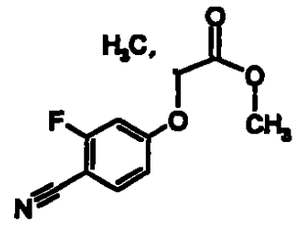
(5 0 11)

(±)-2-(4-Cyano-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester (1 77 g, 6 7 mmol) was shaken on a Parr shaker under 40 psi hydrogen for 30 min, using palladium hydroxide on carbon (1 g, 30% Pd by wt) in 200 mL anhydrous methanol The reaction mixture was filtered through sintered glass, and solvents removed *in vacuo* to afford 1 71 g colorless oil (95% yield)

MS (m/z)$^{+}$ 269 (M^{+}, 45), 168 (100)

Preparation 11

(R)-2-(4-Cyano-3-fluoro-phenoxy)-propionic acid methyl ester of Formula (5.0 12)



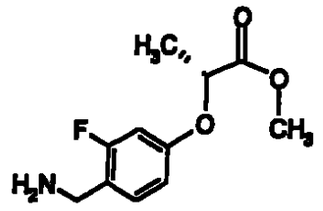
(5 0 12)

To a stirred solution of 2-fluoro-4-hydroxybenzonitrile (0 2 g, 1 5 mmol), methyl (*S*)-(-)-lactate (0 14 mL, 1.5 mmol) and triphenylphosphine (1 15 g, 4.4 mmol) at room temperature, diethyl azodicarboxylate (0 67 mL, 4.4 mmol) was added dropwise The mixture was stirred at room temperature overnight, diluted with ethyl acetate and washed successively with dilute aqueous sodium hydroxide, dilute aqueous hydrochloric acid, brine, and dried (Na_2SO_4) Solvents were stripped *in vacuo*. The resulting oil was washed with diethyl ether and the precipitate was filtered off The mother liquor was adsorbed onto silica gel and the product purified by flash column chromatography (20% dichloromethane/hexane), affording 0 12 g of a pink oil (36% yield)

^{1}H NMR ($CDCl_3$) δ 7 51 (t, 1H, J= 7 5 Hz), 6 71 (d, 1H, J= 9 Hz), 6 67 (d, 1H, J= 10 Hz), 4 78 (q, 1H, J= 7 Hz), 3 77 (s, 3H), 1 64 (d, 3H, J= 7 Hz)

Preparation 12

(R)-2-(4-Aminomethyl-3-fluoro-phenoxy)-propionic acid methyl ester of Formula (5.0 13)



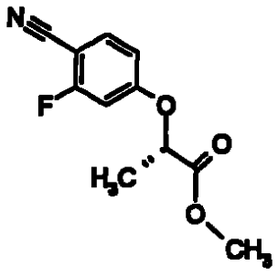
(5.0 13)

The compound of Formula (5 0 13) was prepared in a manner analogous to that described in Preparation 10, substituting (R)-2-(4-cyano-3-fluoro-phenoxy)-propionic acid methyl ester for the corresponding *tert*-butyl ester material

^{1}H NMR ($CDCl_3$). δ 7.41 (t, 1H, J= 8 Hz), 6 90 (br, 2H), 6 58 (m, 2H), 4.69 (q, 1H, J= 7 Hz), 4 00 (s, 2H), 3 71 (s, 3H), 1 56 (d, 3H, J= 7 Hz).

Preparation 13

(S)-2-(4-Cyano-3-fluoro-phenoxy)-propionic acid methyl ester of Formula (5.0 14)



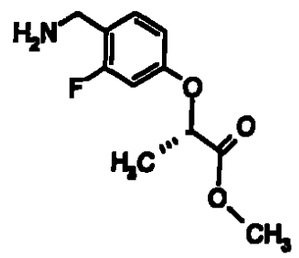
(5 0 14)

The compound of Formula (5 0 14) was prepared in a manner analogous to that described in Preparation 11, substituting methyl (*R*)-(+)-lactate for the methyl (*S*)-(—)-lactate

^{1}H NMR ($CDCl_3$) δ 7 51 (t, 1H, J= 7 5 Hz), 6 72 (d, 1H, J= 9 Hz), 6 67 (d, 1H, J= 10 Hz), 4 78 (q, 1H, J= 7 Hz), 3 77 (s, 3H), 1 64 (d, 3H, J= 7 Hz)

Preparation 14

(S)-2-(4-Aminomethyl-3-fluoro-phenoxy)-propionic acid methyl ester of Formula (5.0 15):



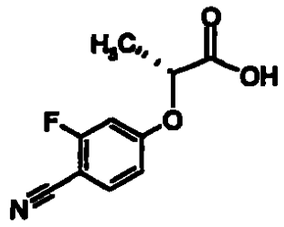
(5.0 15)

The compound of Formula (5.0 15) was prepared in a manner analogous to that described in Preparation 12, based on Preparation 10, substituting (–)-2-(4-cyano-3-fluoro-phenoxy)-propionic acid methyl ester for the corresponding (+) material.

^{1}H NMR ($CDCl_3$): δ 7.41 (t, 1H, J= 8 Hz), 6.90 (br, 2H), 6 58 (m, 2H), 4 69 (q, 1H, J= 7 Hz), 4 00 (s, 2H), 3 71 (s, 3H), 1 56 (d, 3H, J= 7 Hz).

Preparation 15

(R)-2-(4-Cyano-3-fluoro-phenoxy)-propionic acid of Formula (5 0 16)



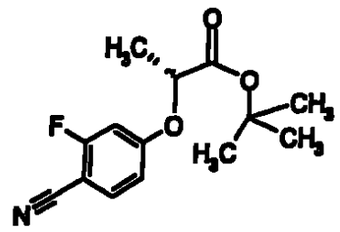
(5 0 16)

To a stirred solution of (R)-2-(4-cyano-3-fluoro-phenoxy)-propionic acid methyl ester (0.40 g, 1 8 mmol) in 50 mL 1 1 tetrahydrofuran/methanol at room temperature was added lithium hydroxide (5.5 mL 1 M aqueous solution, 5 5 mmol) and the solution was stirred over night. The reaction was quenched into dilute aqueous hydrochloric acid and extracted with ethyl acetate The organic layers were pooled and washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford a colorless oil (0.37 g, 98%)

^{1}H NMR ($CDCl_3$) δ 7 50 (t, 1H, J= 7 Hz), 6 69 (m, 2H), 4.81 (q, 1H, J= 7 Hz), 1 68 (d, 3H, J= 7 Hz).

Preparation 16

(R)-2-(4-Cyano-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester of Formula (5.0 17)



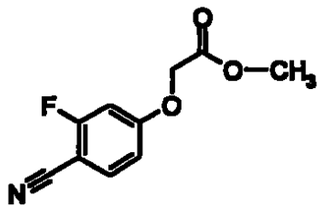
(5.0 17)

A solution of (R)-2-(4-cyano-3-fluoro-phenoxy)-propionic acid (55 mg, 026 mmol) in dry toluene (30 mL) and *N, N*- dimethylformamide di-*tert*-butyl acetal (0.25 mL, 1 05 mmol) was stirred at 90 °C 1 hour The reaction mix was adsorbed onto silica gel and purified by flash column chromatography (30% ethyl acetate/hexane) to afford 51 mg of a white solid (74% yield).

^{1}H NMR ($CDCl_3$): δ 7.48 (t, 1H, J= 7 Hz), 6 65 (m, 2H), 4 61 (q, 1H, J= 7 Hz), 1.58 (d, 3H, J= 7 Hz), 1.41 (s, 9H)

Preparation 17

(4-Cyano-3-fluoro-phenoxy)-acetic acid methyl ester of Formula (5.0 18)



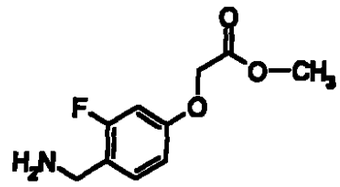
(5.0 18)

The compound of Formula (5 0 18) was prepared in a manner analogous to that described in Preparation 9, substituting bromoacetic acid methyl ester for the bromopropionic acid *tert*-butyl ester material

MS (m/z): 209 (M^+, 100)

Preparation 18

(4-Aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester of Formula (5 0 19)



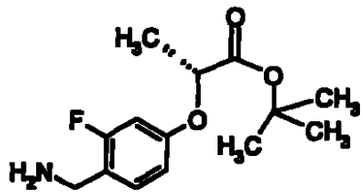
(5.0 19)

The compound of Formula (5.0 19) was prepared in a manner analogous to that described in Preparation 10, substituting (4-cyano-3-fluoro-phenoxy)-acetic acid methyl ester for the corresponding 2-(4-cyano-3-fluoro-phenoxy)-propionic acid tert-butyl ester material

MS (m/z). 212 (M^+, 100).

Preparation 19

(R)-2-(4-Aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester of Formula (5 0.20)



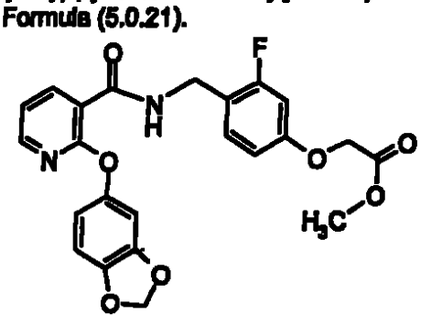
(5 0.20)

The compound of Formula (5 0.20) was prepared in a manner analogous to that described in Preparation 10, substituting (R)-2-(4-Cyano-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester for the corresponding (±)-2-(4-cyano-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester material

^{1}H NMR ($CDCl_3$): δ 7 17 (t, 1H, J= 9 Hz), 6 55 (t, 2H, J= 8 Hz), 4 53 (q, 1H, J= 7 Hz), 3 78 (s, 2H), 2.57 (br, 2H), 1 52 (d, 3H, J= 7 Hz), 1.39 (s, 9H)

Preparation 20

[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester of Formula (5.0.21).



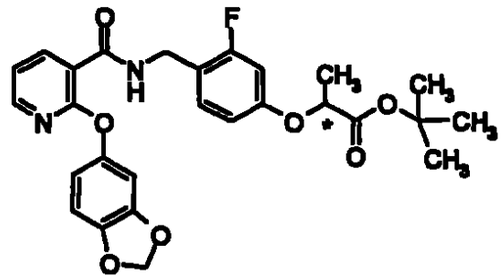
(5.0.21)

2-(Benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid (0 31 g, 1 1 mmol), (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester (0.46 g, 2 15 mmol), 1-hydroxybenzotriazole hydrate (0 16 g, 1.2 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.23 g, 1 2 mmol) were dissolved in 1 1 *N, N*-dimethylformamide / dichloromethane (40 mL) and stirred at room temperature over night. Solvents were removed *in vacuo*. The residue was taken up in ethyl acetate and washed successively with dilute aqueous hydrochloric acid, dilute aqueous sodium hydroxide, and brine, and dried (Na_2SO_4). The product was purified by flash column chromatography (20% ethyl acetate/hexane) to afford a yellow oil (0 19 g, 38%).

MS (m/z). 455 (M^++1, 100).

Preparation 21

(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester of Formula (5 0.22)



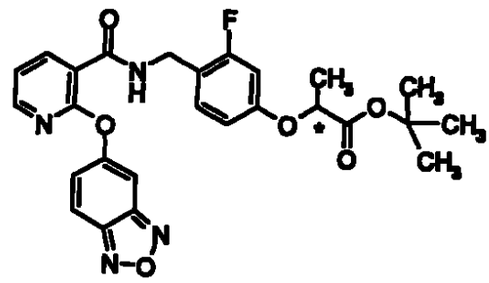
(5.0.22)

The compound of Formula (5 0.22) was prepared in a manner analogous to that described in Preparation 20, substituting (±)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester for the (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$) δ 8 58 (dd, 1H, J= 2 Hz, 8 Hz), 8 19 (dd, 2H, J= 2 Hz, 5 Hz), 7.26 (m, 1H), 7 10 (m, 1H), 6 78 (d, 1H, J= 8 Hz), 6 63 (d, 1H, J= 2 Hz), 6.55 (m, 2H), 5.99 (s, 2H), 4 62 (d, 2H, J= 5 Hz), 4 51 (q, 1H, J= 7 Hz), 1.53 (d, 3H, J= 7 Hz), 1.40 (s, 9H)

Preparation 22

(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester of Formula (5.0.23):



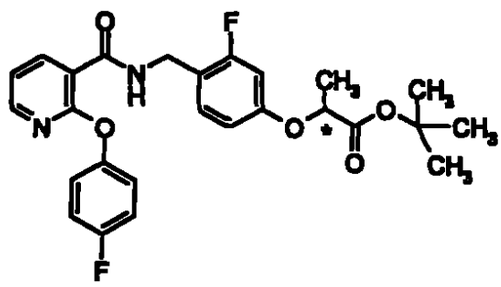
(5.0.23)

The compound of Formula (5 0.23) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(benzo[2,1,3]oxadiazol-5-yloxy)-nicotinic acid and (±)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester for the corresponding 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

^{1}H NMR ($CDCl_3$) δ 8 62 (dd, 1H, J= 2 Hz, 5 Hz), 8 18 (dd, 1H, J= 2 Hz, 5 Hz), 7.88 (t, 1H, J= 5 Hz), 7 85 (dd, 1H, J= 1 Hz, 9 Hz), 7 54 (s, 1H), 7.23 (m, 2H), 6 55 (m, 2H), 4 64 (d, 2H, J= 6 Hz), 4 52 (q, 1H, J= 7 Hz), 1 53 (d, 3H, J= 7 Hz), 1.39 (s, 9H)

Preparation 23

(±)-2-[3-Fluoro-4-({[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid *tert*-butyl ester of Formula (5 0.24)



(5 0.24)

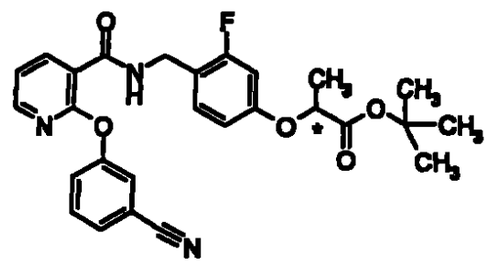
The compound of Formula (5 0.24) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(4-fluoro-phenoxy)-nicotinic acid and (±)-2-(4-aminomethyl-3-

fluoro-phenoxy)-propionic acid *tert*-butyl ester for the corresponding 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

MS (m/z) 484 (M^+, 100)

Preparation 24

(±)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid *tert*-butyl ester of Formula (5.0.25)



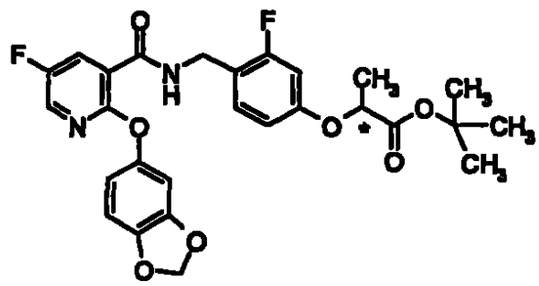
(5 0.25)

The compound of Formula (5 0.25) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(3-cyano-phenoxy)-nicotinic acid and (±)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester for the corresponding 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

MS (m/z) 491 (M^+, 100).

Preparation 25

(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester of the Formula (5 0.26).



(5.0.26)

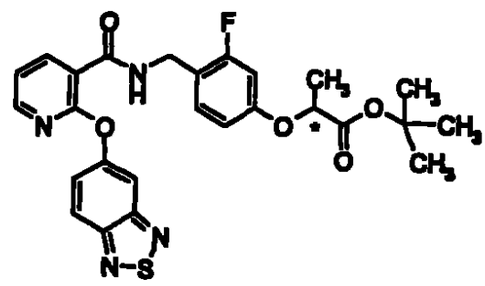
The compound of Formula (5 0 26) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-nicotinic acid and (±)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester for the corresponding 2-(benzo-

[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

MS (m/z) 529 (M^+, 100).

Preparation 26

(±)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester of the Formula (5 0.27):



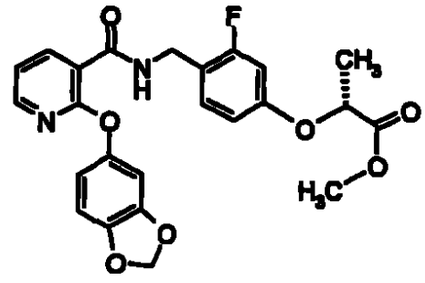
(5.0.27)

The compound of Formula (5 0.27) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(benzo[2,1,3]thiadiazol-5-yloxy)-nicotinic acid and (±)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester for the corresponding 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

MS (m/z). 524 (M^+, 100).

Preparation 27

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester of the Formula (5 0.28):



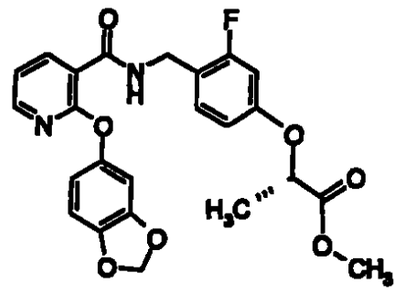
(5.0.28)

The compound of Formula (5 0.28) was prepared in a manner analogous to that described in Preparation 20, substituting (R)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid methyl ester for the corresponding (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester material.

MS (m/z) 469 (M^++1, 20), 455 (M^+-14, 100)

Preparation 28

(S)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester of the Formula (5 0.29):



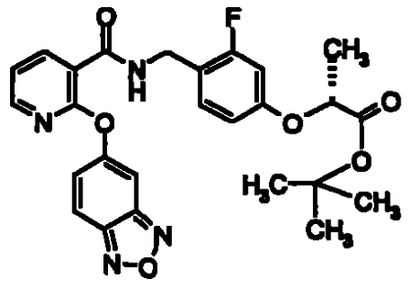
(5 0.29)

The compound of Formula (5.0.29) was prepared in a manner analogous to that described in Preparation 20, substituting (S)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid methyl ester for the corresponding (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$) δ 8 55 (dd, 1H, J= 2, 7 Hz), 8.26 (t, 1H, J= 5 Hz), 8 19 (dd, 1H, J= 2, 5 Hz), 7.27 (t, 1H, J= 9 Hz), 7 10 (m, 1H), 6 79 (d, 1H, J= 8 Hz), 6 55 (m, 3H), 5.98 (s, 2H), 4 68 (q, 1H, J= 6 Hz), 4 61 (d, 2H, J= 6 Hz), 3.71 (s, 3H), 1 57 (d, 3H, J= 7 Hz)

Preparation 29

(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester of Formula (5.0.30):



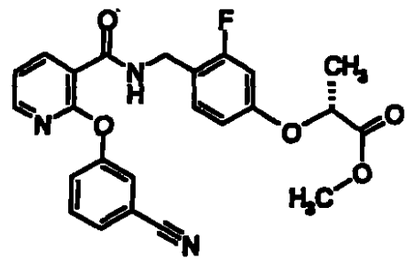
(5 0.30)

The compound of Formula (5 0 30) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(benzo[2,1,3]oxadiazol-5-yloxy)-nicotinic acid and (R)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid *tert*-butyl ester for the corresponding 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

^{1}H NMR ($CDCl_3$) 8.61 (dd, 1H, J= 2, 8 Hz), 8.18 (dd, 1H, J= 2, 5 Hz), 7.86 (t, 1H, J= 9 Hz), 7 84 (d, 1H, J= 10 Hz), 7 53 (s, 1H), 7.23 (m, 2H), 6.55 (m, 2H), 4.63 (d, 2H, J= 6 Hz), 4 52 (q, 1H, J= 7 Hz), 1.52 (d, 3H, J= 7 Hz), 1.38 (s, 9H).

Preparation 30

(R)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid methyl ester of the Formula (5 0.31).



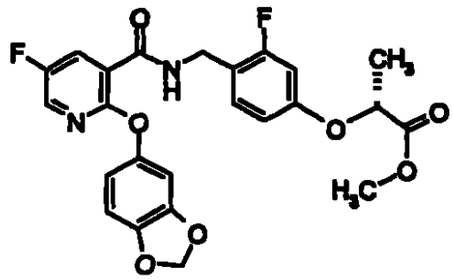
(5 0.31)

The compound of Formula (5 0 31) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(3-cyano-phenoxy)-nicotinic acid and (R)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid methyl ester for the corresponding 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

^{1}H NMR ($CDCl_3$). δ 8 59 (dd, 1H, J= 2, 8 Hz), 8 15 (dd, 1H, J= 2, 5 Hz), 8 00 (t, 1H, J= 5 Hz), 7 35 (m, 5H), 6.56 (m, 2H), 4 68 (q, 1H, J= 7 Hz), 4 62 (d, 2H, J= 6 Hz), 3 71 (s, 3H), 1.57 (d, 3H, J= 7 Hz).

Preparation 31

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester of Formula (5 0.32):



(5.0.32)

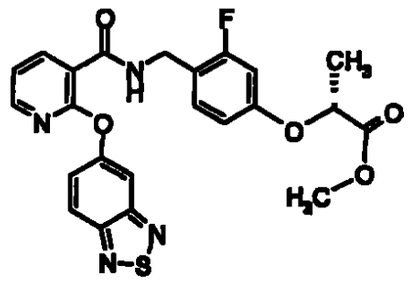
The compound of Formula (5.0 32) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-nicotinic acid and (R)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid methyl ester for the corresponding 2-(benzo-

[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

^{1}H NMR ($CDCl_3$) δ 8.32 (dd, 1H, J= 3, 8 Hz), 8.26 (s, 1H), 8 02 (d, 1H, J= 3 Hz), 7.28 (t, 1H, J= 8 Hz), 6 80 (d, 1H, J= 8 Hz), 6.56 (m, 3H), 6 00 (s, 2H), 4 68 (q, 1H, J= 7 Hz), 4 61 (d, 2H, J= 6 Hz), 3 72 (s, 3H), 1 57 (d, 3H, J= 7 Hz).

Preparation 32

(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester of Formula (5.0.33):



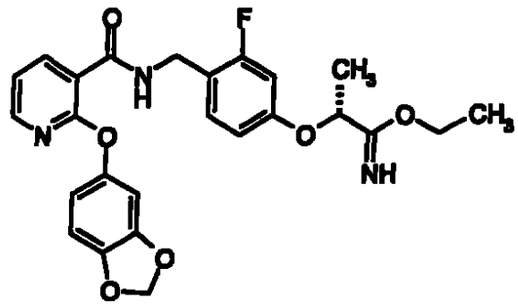
(5 0.33)

The compound of Formula (5.0 33) was prepared in a manner analogous to that described in Preparation 20, substituting 2-(benzo[2,1,3]thia-diazol-5-yloxy)-nicotinic acid and (R)-2-(4-aminomethyl-3-fluoro-phenoxy)-propionic acid methyl ester for the corresponding 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid and (4-aminomethyl-3-fluoro-phenoxy)-acetic acid methyl ester materials, respectively

^{1}H NMR ($CDCl_3$) δ 8 62 (dd, 1H J= 2, 8 Hz), 8 17 (dd, 1H, J= 2, 5 Hz), 8 10 (t, 1H, J= 5 Hz), 8 00 (dd, 1H, J= 1, 10 Hz), 7 74 (d, 1H, J= 3 Hz), 7.39 (dd, 1H, J= 2, 9 Hz), 7.30 (t, 1H, J= 9 Hz), 7 20 (m, 1H), 6 56 (m, 2H), 4 66 (m, 3H), 3 70 (s, 3H), 1 56 (d, 3H, J= 7 Hz)

Preparation 33

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionimidic acid ethyl ester of Formula (5 0.34):



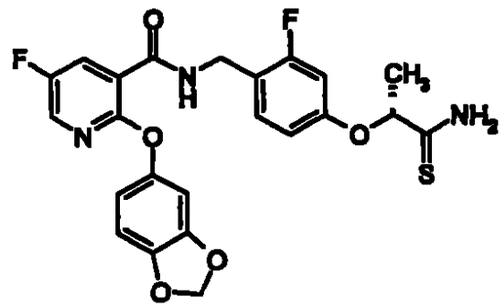
(5.0.34)

To a stirred solution of (R)-2-(benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide (0.4 g, 0 88 mmol) in dichloromethane (20 ml) triethyloxonium tetrafluoroborate (0 17 g, 0.88 mmol) was added. The reaction was stirred at room temperature 16h The reaction was adsorbed onto a small amount of silica gel and column chromatography (2% methanol/dichloromethane) afforded 160 mg of the desired product as a colorless oil (38% yield).

MS (m/z) 481 (M^+, 100).

Preparation 34

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(1-thiocarbamoyl-ethoxy)-benzyl]-nicotinamide of Formula (5 0.35):



(5 0.35)

A solution of (R)-2-(benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-5-fluoro-nicotinamide (1 0 g, 2 12 mmol) and Lawesson's reagent (0.52 g, 1.27 mmol) in dry tetrahydrofuran (10 ml) was stirred at room temperature 2 h The solvent was removed *in vacuo*. The residue was adsorbed onto silica gel and purified by column chromatography (20% ethyl acetate/hexane) to afford 1 01 g of a yellow solid (98% yield).

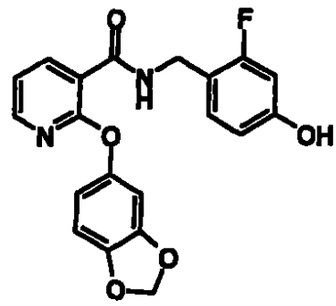
241

CO244

MS (m/z) 486 (M^+, 100)

Preparation 35

2-(Benzo[1,3]dioxol-5-yloxy)-N-(2-fluoro-4-hydroxy-benzyl)-nicotinamide of Formula (5 0.36)



(5 0.36)

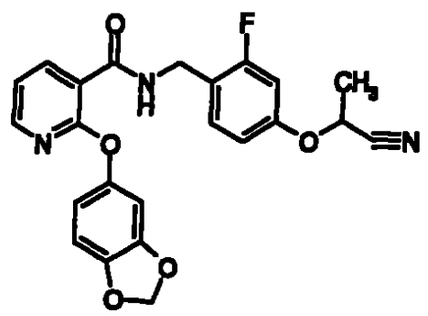
A solution of 4-aminomethyl-3-fluoro-phenol hydrochloride (4 75 g, 27 mmol) in *N, N*-dimethylformamide (20 ml) was added to a stirred solution of 2-(benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid (14 g, 54 mmol), 1-hydroxybenzotriazole hydrate (7.29 g, 54 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (10.37 g, 54 mmol), and triethylamine (3 76 ml, 27 mmol) in *N, N*-dimethylformamide (130 ml) at room temperature and stirred over night. The reaction was quenched into dilute aqueous hydrochloric acid and extracted with diethyl ether, then ethyl acetate The pooled organic layers were washed successively with dilute aqueous sodium hydroxide, water, and brine. The solvents were stripped *in vacuo* to afford 12.2 g crude The residue was dissolved in methanol (100 ml) and stirred with lithium hydroxide (10 ml, 1M) for 1 h to hydrolyze the ester of the *bis*-acylated product. Solvents were stripped *in vacuo*, the residue was diluted with water (200 ml) and saponified to pH 12 with sodium hydroxide The precipitate was filtered off, and the filtrate was acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (2x 200 ml). The pooled organics were washed with 2N sodium carbonate, then brine and dried ($MgSO_4$). The solvents were stripped *in vacuo* to afford pure product (5 7 g, 14 9 mmol) in 55% yield

^1H NMR ($CDCl_3$) 8 53 (dd, 1H, J= 2 Hz, 8 Hz), 8 16 (dd, 1H, J= 2 Hz, 5 Hz), 7 11 (m, 2H), 6 78 (d, 1H, J= 8 Hz), 6.61 (d, 1H, J= 2 Hz), 6 52 (m, 3H), 5 97 (s, 2H), 4.57 (s, 2H)

MS (m/z): 383 (M^++1, 10)

Preparation 36

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-cyano-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.0.37):



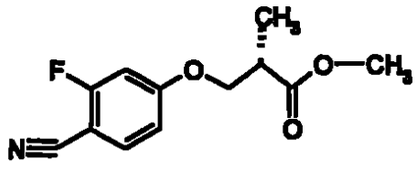
(5.0.37)

To a stirred solution of 2-(benzo[1,3]dioxol-5-yloxy)-N-(2-fluoro-4-hydroxy-benzyl)-nicotinamide (5 g, 13 1 mmol), (+/-)-lactonitrile (0.93 g, 13 1 mmol) and triphenylphosphine (3 78 g, 14.4 mmol) in tetrahydrofuran (200 mL) at room temperature, diethyl azodicarboxylate (2.3 mL, 14.4 mmol) was added dropwise with stirring The mixture was stirred at room temperature overnight. Solvents were stripped *in vacuo*, diluted with ethyl acetate and washed with dilute aqueous sodium hydroxide, brine, and dried ($MgSO_4$). Solvents were stripped *in vacuo* The resulting oil was washed with diethyl ether and the precipitate was filtered off The mother liquor was purified by flash column chromatography (35% ethyl acetate/hexane), affording 1 5 g white solid (26% yield).

^{1}H NMR ($CDCl_3$) 8 59 (d, 1H, J=8 Hz), 8.28 (t, 1H, J= 6 Hz), 8.21 (dd, 1H, J= 2 Hz, 4 Hz), 7.40 (t, 1H, J= 8 Hz), 7 12 (dd, 1H, J= 5 Hz, 8 Hz), 6 82 (d, 1H, J= 8 Hz), 6.66 (m, 3H), 6.00 (s, 2H), 4.83 (q, 1H, J= 7 Hz), 4 68 (d, 2H, J= 6 Hz), 1 76 (d, 3H, J= 7 Hz)

Preparation 37

(S)-3-(4-Cyano-3-fluoro-phenoxy)-2-methyl-propionic acid methyl ester of Formula (5.0.38):



(5 0.38)

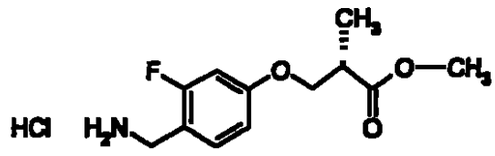
To a stirred solution of 2-fluoro-4-hydroxybenzonitrile (1 0 g, 7 3 mmol), (S)-3-hydroxy-2-methyl-propionic acid methyl ester (0 8 mL, 7 3 mmol) and triphenylphosphine (2.3 g, 8.8 mmol) at room temperature, diethyl azodicarboxylate (1.4 mL, 8.8 mmol) was added dropwise The mixture was stirred at room temperature overnight, diluted with ethyl acetate

and washed successively with dilute aqueous sodium hydroxide, dilute aqueous hydrochloric acid, brine, and dried ($MgSO_4$) Solvents were stripped *in vacuo*. The resulting oil was washed with diethyl ether and the precipitate was filtered off The mother liquor was adsorbed onto silica gel and the product purified by flash column chromatography (40% ethyl acetate/hexane), affording 0 14 g of a yellow oil (8% yield).

^{1}H NMR ($CDCl_3$). 7.49 (t, 1H, J= 8 Hz), 6 73 (d, 1H, J= 9 Hz), 6 70 (d, 1H, J= 9 Hz), 4.21 (dd, 1H, J= 7, 9 Hz), 4 01 (dd, 1H, J= 6, 9 Hz), 3 71 (s, 3H), 2.95 (m, 1H), 1.29 (d, 3H, J= 7 Hz)

Preparation 38

(S)-3-(4-Aminomethyl-3-fluoro-phenoxy)-2-methyl-propionic acid methyl ester hydrochloride of Formula (5 0.39):



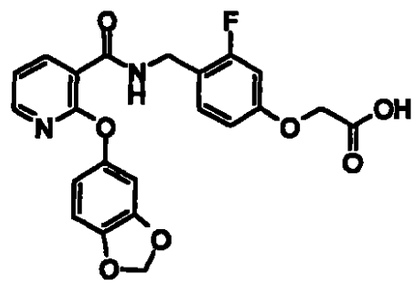
(5 0.39)

(S)-3-(4-Cyano-3-fluoro-phenoxy)-2-methyl-propionic acid methyl ester (0 14 g) was shaken on a Parr shaker under 50 psi hydrogen for 16 h, using palladium hydroxide on carbon (0 01 g, 30% Pd by wt) in anhydrous methanol (20 mL) and concentrated hydrochloric acid (0.5 mL). The reaction mixture was filtered through sintered glass, and solvents removed *in vacuo* to afford 0 18 g of a white solid (95% yield).

MS (m/z). 241 (M^+, 100)

Example 1

[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid of Formula (5.5 1):



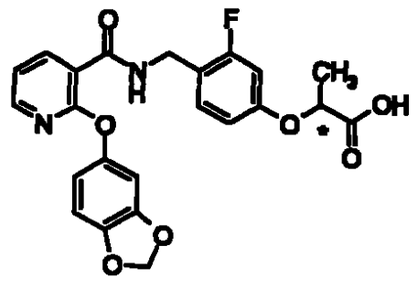
(5.5 1)

To a stirred solution of [4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester (0.40 g, 0.88 mmol) in tetrahydrofuran (10 mL) and methanol (2 mL) was added aqueous lithium hydroxide (2 mL, 1 M, 2 mmol) The reaction was stirred at room temperature 1 hour The solvents were stripped *in vacuo* and the residue partitioned between dilute aqueous hydrochloric acid and ethyl acetate. The aqueous was extracted with 2 aliquots ethyl acetate and the pooled organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford a yellow solid The crude product was recrystallized from ethyl acetate to afford 80 mg of a white crystalline solid (0 18 mmol, 21% yield) mp 180 °C

^{1}H NMR (CD_3OD). δ 8 52 (dd, 1H, J= 2, 8 Hz), 8.24 (br, 1H), 8 16 (dd, 1H, J= 2, 5 Hz), 7.29 (t, 1H, J= 4 Hz), 7 09 (dd, 1H, J= 5, 8 Hz), 6.77 (d, 1H, J= 8 Hz), 6 55 (m, 3H), 5.96 (s, 2H), 4.59 (d, 2H, J= 6 Hz), 4.52 (s, 2H)

Example 2

(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5.2):



(5.5.2)

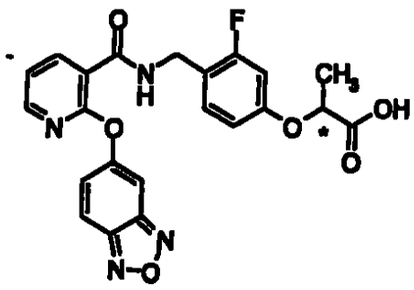
The compound of Formula (5 5.2) was prepared in a manner analogous to that described in Example 1, substituting (±)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester for the corresponding [4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester material

mp= 136.4-138.0 °C.

^{1}H NMR ($CDCl_3$) δ 8 59 (dd, 1H, J= 2, 8 Hz), 8.30 (t, 1H, J= 6 Hz), 8.21 (dd, 1H, J= 2, 5 Hz), 7.30 (t, 1, J= 8 Hz), 7 12 (dd, 1H, J= 5, 8 Hz), 6 81 (d, 1H, J= 8 Hz), 6.60 (s, 2H), 4 74 (q, 1H, J= 7 Hz), 4.63 (d, 2H, J= 6 Hz), 1 63 (d, 3H, J= 7 Hz).

Example 3

(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.3):



(5.5.3)

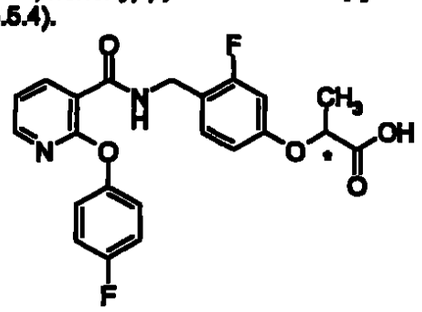
(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester (0 17 g, 0.33 mmol) was stirred in formic acid (5 mL) at room temperature 2 hours Formic acid was removed *in vacuo* and the product stored over night under high vacuum to afford a white solid (0 12 g, 80% yield).

^{1}H NMR ($CDCl_3$). δ 8.36 (dd, 1H, J= 2, 7 Hz), 8 09(dd, 1H, J= 2, 5 Hz), 8 03 (br, 1H), 7 75 (d, 1H, J= 9 Hz), 7.42 (s, 1H), 7 13 (m, 2H), 6.50 (m, 2H), 4 54 (q, 1H, J= 7 Hz), 4.49 (d, 1H, J= 6 Hz), 1.46 (d, 3H, J= 7 Hz).

MS (m/z). 452 (M^+, 100).

Example 4

(±)-2-[3-Fluoro-4-({[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.4).



(5 5.4)

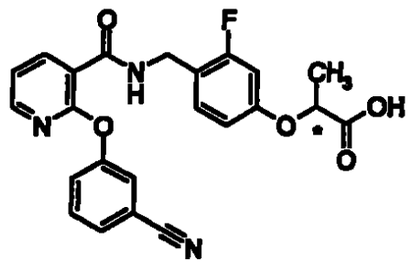
The compound of Formula (5 5 4) was prepared in a manner analogous to that described in Example 3 substituting (±)-2-[3-fluoro-4-({[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid *tert*-butyl ester for the corresponding (±)-2-[4-({[2-(benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester material

^{1}H NMR ($CDCl_3$). δ 8.58 (d, 1H, J= 7 Hz), 8.26 (s, 1H), 8 16 (d, 1H, J= 4 Hz), 7 10 (m, 4H), 6 60 (m, 2H), 4 72 (q, 1H, J= 7 Hz), 4 61 (d, 2H, J= 6 Hz), 1 62 (d, 3H, J= 7 Hz)

MS (*m/z*) 428 (M^+, 100).

Example 5

(±)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.5):



(5 5 5)

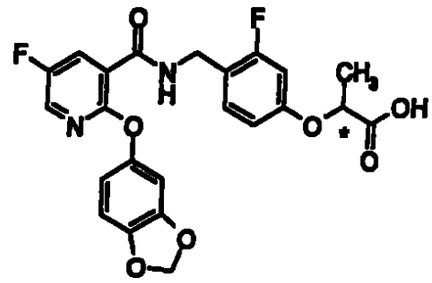
The compound of Formula (5.5 5) was prepared in a manner analogous to described in Example 3, substituting (±)-2-[3-fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid *tert*-butyl ester for the corresponding (±)-2-[4-({[2-(benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester material

^{1}H NMR ($CDCl_3$) δ 8 50(dd, 1H, J= 2, 6 Hz), 8 12 (dd, 1H, J= 2, 5 Hz), 8 03 (s, 1H), 7.35 (m, 4H), 7 15 (dd, 1H, J= 5, 8 Hz), 6 56 (m, 2H), 4 61 (q, 1H, J= 7 Hz), 4.57 (d, 2H, J= 6 Hz) 1.54 (d, 3H, J= 7 Hz).

MS (m/z): 435 (M^+, 100)

Example 6

(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.6):



(5.5.6)

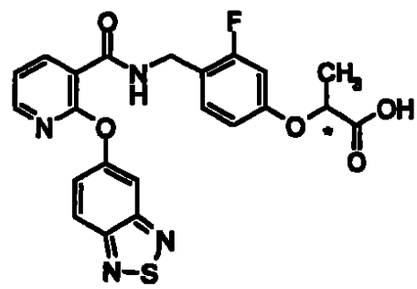
The compound of Formula (5.5.6) was prepared in a manner analogous to described in Example 3, substituting (±)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid for the corresponding (±)-2-[4-({[2-(benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid tert-butyl ester material.

^{1}H NMR ($CDCl_3$). δ 8.31 (dd, 1H, J= 3, 8 Hz), 8.02 (d, 1H, J= 3 Hz), 7.28 (t, 1H, J= 9 Hz), 7.23 (m, 1H), 6.79 (d, 1H, J= 8 Hz), 6.55 (m, 3H), 5.99 (s, 2H), 4.73 (q, 1H, J= 7 Hz), 4.60 (d, 2H, J= 6 Hz), 1.62 (d, 3H, J= 7 Hz).

MS (m/z). 472 (M^+, 100).

Example 7

(±)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.7):



(5.5.7)

The compound of Formula (5.5.7) was prepared in a manner analogous to that described in Example 3, substituting (±)-2-[4-({[2-(benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-

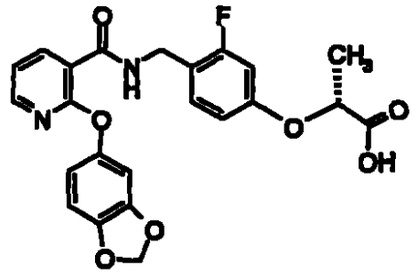
amino)-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester for the corresponding (±)-2-[4-({[2-(benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid *tert*-butyl ester material

^{1}H NMR ($CDCl_3$) δ 8 61 (d, 1H, J= 7 Hz), 8 18 (d, 1H, J= 5 Hz), 8 06 (s, 1H), 7.99 (d, 1H, J= 10 Hz), 7 64 (s, 1H), 7.43 (d, 1H, J= 9 Hz), 7.29 (t, 1H, J= 9 Hz), 6 60 (m, 2H), 4 72 (q, 1H, J= 7 Hz), 4 63 (d, 2H, J= 6 Hz), 1 61 (d, 3H, J= 7 Hz).

MS (m/z) 468 (M^+, 100).

Example 8

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.8):



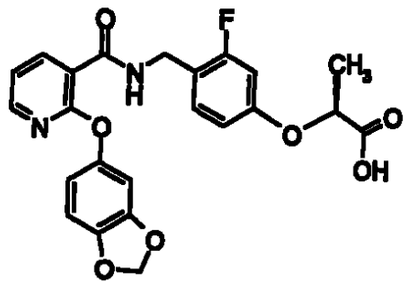
(5.5.8)

The compound of Formula (5 5 8) was prepared in a manner analogous to that described in Example 1, substituting (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester for the corresponding [4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$) δ 8.59 (dd, 1H, J= 2, 8 Hz), 8.31 (t, 1H, J= 6 Hz), 8.21 (dd, 1H, J= 2, 5 Hz), 7.30 (t, 1H, J= 8 Hz), 7 12 (dd, 1H, J= 5, 8 Hz), 6 81 (d, 1H, J= 8 Hz), 6.61 (m, 3H), 6 00 (s, 2H), 4 74 (q, 1H, J= 7 Hz), 4 63 (d, 2H, J= 6 Hz), 1 64 (d, 3H, J= 7 Hz)

Example 9

(S)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.9).



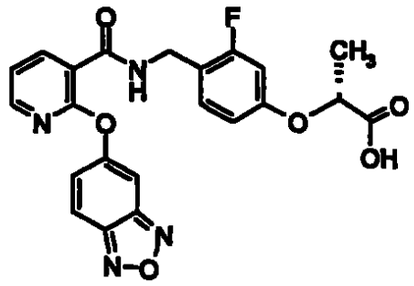
(5 5 9)

The compound of Formula (5.5.9) was prepared in a manner analogous to that described in Example 1, substituting (S)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester for the corresponding [4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$). δ 8 59 (dd, 1H, J= 2, 8 Hz), 8.31 (t, 1H, J= 8 Hz), 8.21 (dd, 1H, J= 2, 5 Hz), 7.30 (t, 1H, J= 8 Hz), 7 12 (dd, 1H, J= 5, 8 Hz), 6 81 (d, 1H, J= 8 Hz), 6 61 (m, 3H), 6 00 (s, 2H), 4.74 (q, 1H, J= 7 Hz), 4 63 (d, 2H, J= 6 Hz), 1 64 (d, 3H, J= 7 Hz)

Example 10

(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5 10)



(5 5 10)

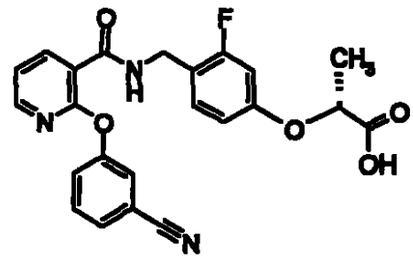
The compound of Formula (5 5 10) was prepared in a manner analogous to that described in Example 1, substituting (R)-2-[4-({[2-(benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester for the corresponding [4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$). δ 8 36 (dd, 1H, J= 2, 7 Hz), 8 09(dd, 1H, J= 2, 5 Hz), 8 03 (br, 1H), 7 75 (d, 1H, J= 9 Hz), 7 42 (s, 1H), 7 13 (m, 2H), 6.50 (m, 2H), 4 54 (q, 1H, J= 7 Hz), 4.49 (d, 2H, J= 6 Hz), 1.46 (d, 3H, J= 7 Hz).

MS (m/z). 452 (M^+, 100).

Example 11

(R)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.11):



(5.5 11)

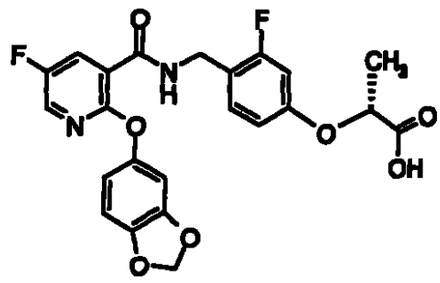
The compound of Formula (5 5 11) was prepared in a manner analogous to that described in Example 1, substituting (R)-2-[3-fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid methyl ester for the corresponding [4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$) δ 8 50(dd, 1H, J= 2, 6 Hz), 8 12 (dd, 1H, J= 2, 5 Hz), 8 03 (s, 1H), 7.35 (m, 4H), 7 15 (dd, 1H, J= 5, 8 Hz), 6.56 (m, 2H), 4 61 (q, 1H, J= 7 Hz), 4 57 (d, 2H, J= 6 Hz). 1 54 (d, 3H, J= 7 Hz).

MS (m/z) 435 (M^+, 100)

Example 12

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5 12)



(5.5.12)

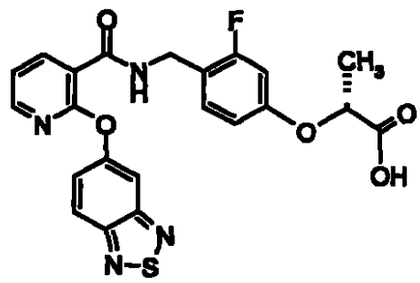
The compound of Formula (5 5 12) was prepared in a manner analogous to that described in Example 1, substituting (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester for the corresponding [4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$). δ 6 33 (dd, 2H, J= 3, 8 Hz), 6 04 (d, 1H, J= 3 Hz), 7 30 (t, 1H, J= 8 Hz), 6.80 (d, 1H, J= 8 Hz), 6 62 (m, 3H), 6 56 (dd, 1H, J= 2, 8 Hz), 6 01 (s, 2H), 4 74 (q, 1H, J= 7 Hz), 4 62 (d, 2H, J= 6 Hz), 1.65 (d, 3H, J= 7 Hz).

MS (m/z) 472 (M^+, 100)

Example 13

(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5 13)



(5.5.13)

The compound of Formula (5 5 13) was prepared in a manner analogous to that described in Example 1, substituting (R)-2-[4-({[2-(benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester for the corresponding [4-({[2-

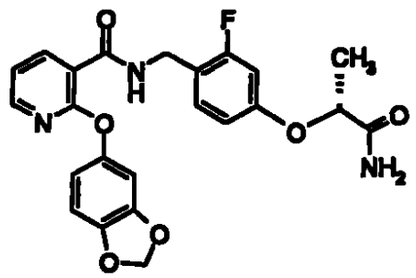
(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid methyl ester material

^{1}H NMR ($CDCl_3$) δ 8 60 (d, 1H, J= 7 Hz), 8 18 (d, 1H, J= 5 Hz), 8 06 (s, 1H), 7 99 (d, 1H, J= 10 Hz), 7 64 (s, 1H), 7.43 (d, 1H, J= 9 Hz), 7.29 (t, 1H, J= 9 Hz), 6 60 (m, 2H), 4 72 (q, 1H, J= 7 Hz), 4 63 (d, 2H, J= 6 Hz), 1 61 (d, 3H, J= 7 Hz)

MS (m/z) 468 (M^+, 100).

Example 14

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5 14):



(5.5 14)

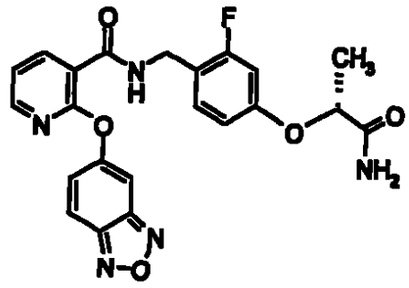
To a stirred solution of (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid (0.25 g, 0 55 mmol) in ethylene glycol dimethyl ether (20 mL) at –10 °C was added *N*-methyl morpholine (0 06 mL, 0 55 mmol) followed by dropwise addition of isobutyl chloroformate (0 071 mL, 0 55 mmol) The turbid solution was stirred at –10 °C 10 min Ammonia gas was bubbled through the reaction mixture 10 min, which was then warmed to room temperature and stirred a further 15 min The reaction mixture was partitioned between chloroform and water The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a white solid Flash column chromatography (1% methanol / dichloromethane) yielded 0 15 g of a white solid (60% yield)

^{1}H NMR ($CDCl_3$) δ 8 57 (d, 1H, J= 7 Hz), 8.24 (br, 1H), 8 19 (d, 1H, J= 5 Hz), 7.33 (t, 1H, J= 9 Hz), 7 10 (m, 1H), 6 80 (d, 1H, J= 8 Hz), 6 58 (m, 3H), 6.25 (br, 1H), 5 99 (s, 2H), 5.38 (br, 1H), 4 60 (m, 3H), 1 55 (d, 3H, J= 7 Hz)

MS (m/z). 454 (M^++1, 100)

Example 15

(R)-2-(Benzo[2,1,3]oxadiazol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5 5.15),



(5 5 15)

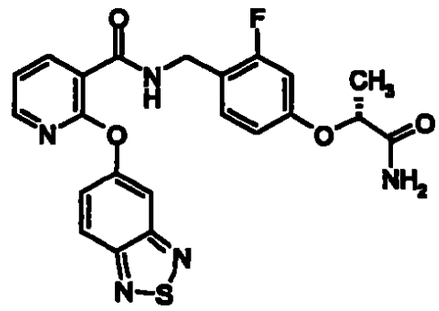
The compound of Formula (5.5.15) was prepared in a manner analogous to that described in Example 14, substituting (R)-2-[4-([]2-(benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-3-fluoro-phenoxy]-propionic acid for the corresponding (R)-2-[4-([]2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid material

^{1}H NMR ($CDCl_3$) δ 8 61 (dd, 1H, J= 2, 7 Hz), 8 19 (dd, 1H, J= 2, 5 Hz), 7.87 (t, 1H, J= 9 Hz), 7 52 (d, 1H, J= 2 Hz), 7.33 (s, 1H), 7.25 (t, 1H, J=5 Hz), 6 63 (m, 2H), 6.26 (br, 1H), 5.47 (br, 1H), 4.64 (d, 2H, J= 6 Hz), 4 58 (q, 1H, J= 7 Hz), 1 54 (d, 3H, J= 7 Hz)

MS (m/z): 452 (M^++1, 100).

Example 16

(R)-2-(Benzo[2,1,3]thiadiazol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5 5 16):



(5.5.16)

The compound of Formula (5 5 16) was prepared in a manner analogous to that described in Example 14, substituting (R)-2-[4-([]2-(benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-3-fluoro-phenoxy]-propionic acid for the corresponding (R)-2-[4-([]2-

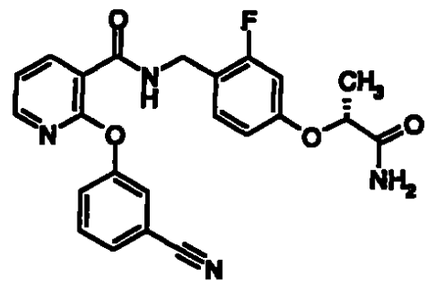
(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid material

^{1}H NMR ($CDCl_3$). δ 8 63 (dd, 1H, J= 2, 7 Hz), 8 19 (dd, 1H, J= 2, 5 Hz), 7.87 (t, 1H, J= 9 Hz), 7 52 (d, 1H, J= 2 Hz), 7.33 (s, 1H), 7.25 (t, 1H, J=5 Hz), 6 63 (m, 2H), 6.26 (br, 1H), 5.47 (br, 1H), 4.64 (d, 2H, J= 6 Hz), 4 57 (q, 1H, J= 7 Hz), 1.54 (d, 3H, J= 7 Hz)

MS (m/z) 468 (M^++1, 100).

Example 17

(R)-N-[4-(1-Carbamoyl-ethoxy)-2-fluoro-benzyl]-2-(3-cyano-phenoxy)-nicotinamide of Formula (5 5.17).



(5 5.17)

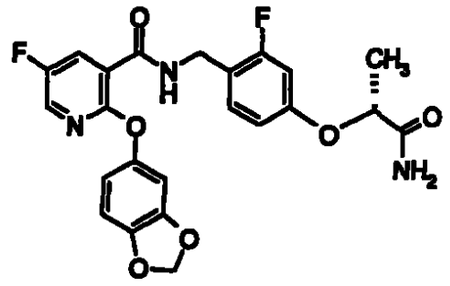
The compound of Formula (5 5 17) was prepared in a manner analogous to that described in Example 14, substituting (R)-2-[3-fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid for the corresponding (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid material

^{1}H NMR ($CDCl_3$)): δ 8 59 (dd, 1H, J= 2, 7 Hz), 8 16 (dd, 1H, J= 2, 5 Hz), 8.03 (t, 1H, J= 9 Hz), 7.38 (m, 4H), 6 63 (m, 2H), 6.27 (br, 1H), 5.48 (br, 1H), 4 59 (m, 3H), 1.55 (d, 3H, J= 7 Hz).

MS (m/z): 435 (M^++1, 100)

Example 18

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-5-fluoro-nicotinamide of Formula (5 5.18)



(5 5 18)

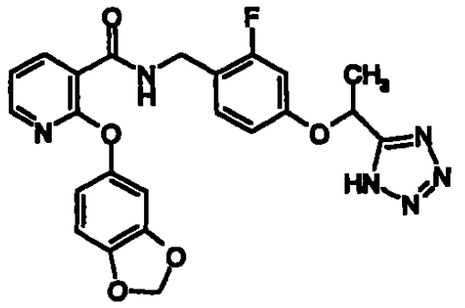
The compound of Formula (5 5 18) was prepared in a manner analogous to that described in Example 14, substituting (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid for the corresponding (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid material

^{1}H NMR ($CDCl_3$). δ 8.31 (m, 2H), 8 02 (d, 1H, J= 3 Hz), 7.32 (t, 1H, J= 8 Hz), 6.80 (d, 1H, J= 8 Hz), 6 60 (m, 3H), 6.26 (br, 1H), 6 00 (s, 2H), 5.35 (br, 1H), 4 07 (m, 3H), 1.55 (d, 3H, J= 7 Hz)

MS (m/z) 472 (M^++1, 100).

Example 19

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.19)



(5 5 19)

A solution of (±)-2-(benzo[1,3]dioxol-5-yloxy)-N-[4-(1-cyano-ethoxy)-2-fluoro-benzyl]-nicotinamide (1 5 g, 3 5 mmol) in anhydrous toluene (5 mL) was transferred to a small

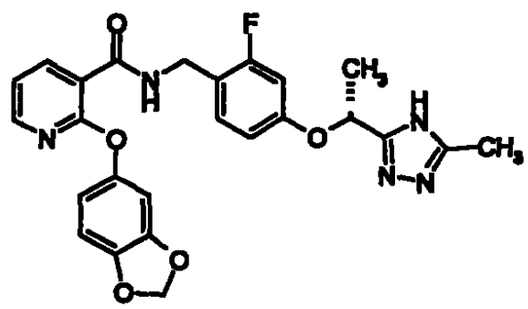
pressure flask. Dibutyltin oxide (0.53 g, 2 1 mmol) and trimethylsilyl azide (1 7 mL, 21 mmol) were added The tube was sealed and placed behind a blast shield The reaction was stirred 15 min at 55 °C, then warmed to 110 °C with stirring over night. The black reaction mix was cooled to 0-5 °C, the pressure flask opened, and the residue taken up in methanol Solvents were removed *in vacuo* and the residue taken up in ethyl acetate. The organic solution was washed twice with saturated aqueous sodium carbonate The aqueous phases were pooled and acidified with concentrated hydrochloric acid, and extracted twice with ethyl acetate. The pooled organic phases were dried ($MgSO_4$), concentrated, and loaded onto a silica gel column as a brown oil Purification by column chromatography (5% methanol/dichloromethane) afforded product as a white solid (0.46 g, 28%)

^{1}H NMR ($CDCl_3$) 8 58 (dd, 1H, J=2 Hz, 8 Hz), 8.43 (t, 1H, J= 6 Hz), 8.21 (dd, 1H, J= 2 Hz, 5 Hz), 7 13 (m, 2H), 6 79 (d, 1H, J= 8 Hz), 8.61 (d, 1H, J= 2 Hz), 6 53 (m, 3H), 5.99 (s, 2H), 5 72 (q, 1H, J= 7 Hz), 4 57 (d, 2H, J= 5 Hz), 1 78 (d, 3H, J= 8 Hz)

MS (m/z) 479 (M^++1, 40).

Example 20

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-{2-fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl}-nicotinamide of Formula (5 5.20):



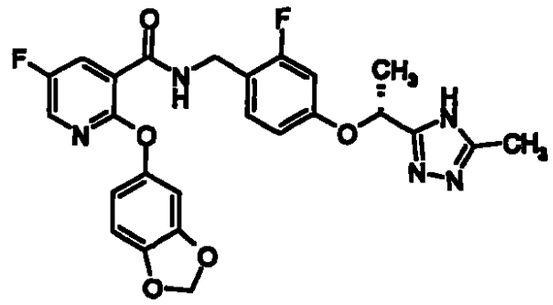
(5.5.20)

A solution of (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionimidic acid ethyl ester (0 16 g, 0 33 mmol) and acetic hydrazide (24 mg, 0.31 mmol) in *n*-butanol (20 ml) was stirred 20 h at 80 °C The reaction was cooled to room temperature and quenched into saturated aqueous oxalic acid and extracted with ethyl acetate The organic solution was dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by column chromatography (3% methanol/dichloromethane) to afford a sticky yellow solid (12 mg). The residue was further purified by preparatory thin layer chromatography (10% methanol/dichloromethane) to afford 7 mg of the desired compound (4%yield).

^{1}H NMR ($CDCl_3$) 8.52 (d, 1H, J= 7.8 Hz), 8.42 (s, 1H), 8.21 (dd, 1H, J= 5.0, 1.9 Hz), 7.19 (t, 1H, J= 8.3 Hz), 7.11 (m, 1H), 6.77 (m, 4H), 6.00 (s, 2H), 5.48 (d, 2H, J= 6.6 Hz), 4.60 (s, 2H), 2.45 (s, 3H), 1.75 (d, 3H, J= 6.7 Hz).

Example 21

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.21)



(5.21)

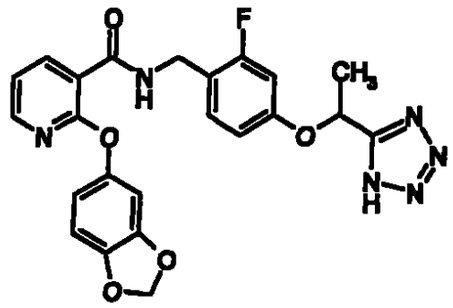
A solution of (R)-2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(1-thiocarbamoyl-ethoxy)-benzyl]-nicotinamide (0.1 g, 0.21 mmol) in pyridine (5 ml) was warmed with stirring to 70 °C. Anhyd. hydrazine (1.5 ml, 50 mmol) was added with stirring *via* a syringe. The reaction mixture was stirred at 70 °C 5 min, the cooled to room temperature. The solvent was removed *in vacuo*, and the residue to stored under house vacuum 1 h. The residue was subsequently taken up in fresh pyridine (5 ml). To this solution was added acetyl chloride (0.057 ml, 0.8 mmol) at room temperature, and the reaction mixture was stirred 2 h. The pyridine was removed *in vacuo*, and replaced with *N,N*-dimethylformamide (5 ml) and the resulting wolution was stirred at 130°C 4 h. The reaction was cooled to room temperature, quenched into water (50 ml) and extractedwith diethyl ether. The pooled extracts were dried ($MgSO_4$), filtered and concentrated to near-dryness, then loaded onto a silica gel column and purified by column chromatography (gradient 1% methanol/dicloromethane changing to 5% methanol/dichloromethane) to afford a white solid (7.6 mg, 7% yield).

MS (m/z). 509 (M^+, 20).

$[\alpha]_D$ = +24° ($CHCl_3$)

Example 22

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.22).



(5.5.22)

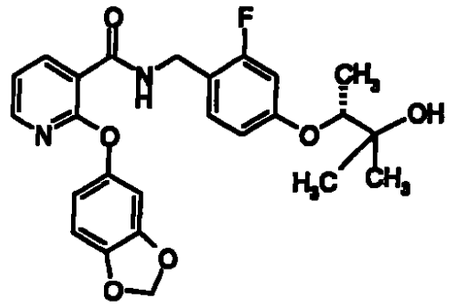
A solution of (±)-2-(benzo[1,3]dioxol-5-yloxy)-N-[4-(1-cyano-ethoxy)-2-fluoro-benzyl]-nicotinamide (1 5 g, 3 5 mmol) in anhydrous toluene (5 mL) was transferred to a small pressure flask. Dibutyltin oxide (0.53 g, 2 1 mmol) and trimethylsilyl azide (1 7 mL, 21 mmol) were added The tube was sealed and placed behind a blast shield The reaction was stirred 15 min at 55 °C, then warmed to 110 °C with stirring over night. The black reaction mix was cooled to 0-5 °C, the pressure flask opened, and the residue taken up in methanol Solvents were removed *in vacuo* and the residue taken up in ethyl acetate. The organic solution was washed twice with saturated aqueous sodium carbonate The aqueous phases were pooled and acidified with concentrated hydrochloric acid, and extracted twice with ethyl acetate The pooled organic phases were dried ($MgSO_4$), concentrated, and loaded onto a silica gel column as a brown oil Purification by column chromatography (6% methanol/dichloromethane) afforded product as a white solid (0.46 g, 28%).

^1H NMR ($CDCl_3$) 8 58 (dd, 1H, J=2 Hz, 8 Hz), 8.43 (t, 1H, J= 8 Hz), 8.21 (dd, 1H, J= 2 Hz, 5 Hz), 7 13 (m, 2H), 6 79 (d, 1H, J= 8 Hz), 6 61 (d, 1H, J= 2 Hz), 6 53 (m, 3H), 5.99 (s, 2H), 5 72 (q, 1H, J= 7 Hz), 4 57 (d, 2H, J= 5 Hz), 1 78 (d, 3H, J= 6 Hz)

MS (m/z)' 479 (M^++1, 40).

Example 23

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-(2-hydroxy-1,2-dimethyl-propoxy)-benzyl]-nicotinamide of Formula (5.5.23).



(5.5.23)

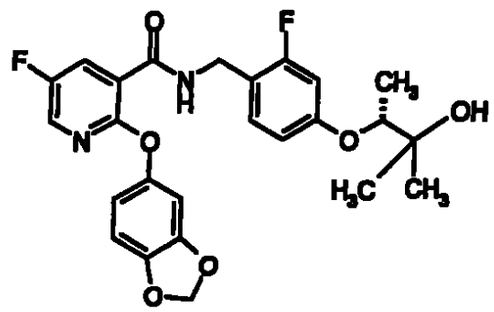
To a stirred solution of (R)-2-[4-([[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester (0 10 g, 0.213 mmol) in tetrahydrofuran (5 ml) at –10 °C, methyl magnesium chloride (3 0 ml, 1 07 mmol) was added, and stirred at –10 °C 15 min The solution was allowed to warm to room temperature and stirred a further 16 h The reaction was quenched into water and extraced with ethyl acetate. The pooled organics were dried ($MgSO_4$), filtered and concentrated to an opaque white oil The residue was purified by column chromatography (1 1 ethyl acetate/hexane), affording 40 mg white powder (40% yield)

^{1}H NMR ($CDCl_3$): 8.60 (d, 1H, J= 7.4 Hz), 8.25 (s, 1H), 8.21 (d, 1H, J= 4.6 Hz), 7.31 (t, 1H, J= 8.3 Hz), 7 12 (dd, 1H, J= 5.0, 7 9 Hz), 6.83 (d, 1H, J= 8.3 Hz), 6.67 (m, 4H), 6.00 (s, 2H), 4 64 (d, 2H, J= 4 6 Hz), 4 12 (q, 1H, J= 6 2 Hz), 1.25 (s, 6H), 1.22 (d, 3H, J= 6.2 Hz).

MS (m/z) 467 (M^+, 100)

Example 24

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(2-hydroxy-1,2-dimethyl-propoxy)-benzyl]-nicotinamide of Formula (5 5.24):



(5.5.24)

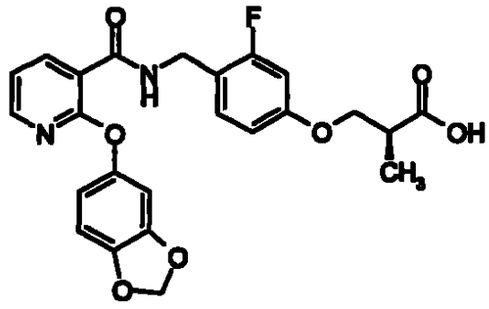
Prepared in a manner analogous to Example 23, substituting (R)-2-[4-({[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid methyl ester

^{1}H NMR ($CDCl_3$) 8.33 (dd, 1H, J= 8 3, 3.3 Hz), 8.30 (s, 1H), 8 03 (d, 1H, J= 2 9 Hz), 7.30 (t, 1H, J= 8 7 Hz), 6.81 (d, 1H, J= 8.3 Hz), 6.62 (m, 4H), 6.01 (s, 2H), 4 63 (d, 2H, J= 5.8 Hz), 4 12 (q, 1H, J= 6.2 Hz), 1.25 (s, 6H), 1.22 (d, 3H, J= 6.2 Hz)

MS (m/z): 487 (M^+ 100).

Example 25

(S)-3-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5 5.25):



(5 5.25)

2-(Benzo-[1,3]-dioxol-5-yloxy)-nicotinic acid (0 168 g, 0 65 mmol), (S)-3-(4-aminomethyl-3-fluoro-phenoxy)-2-methyl-propionic acid methyl ester hydrochloride (0 18 g, 0 65 mmol), 1-hydroxybenzotriazole hydrate (097 g, 0 72 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0 138 g, 0 72 mmol) and triethylamine were dissolved in *N*,

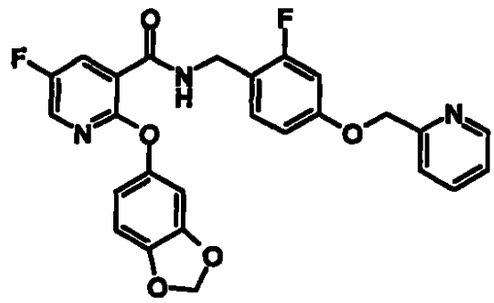
N-dimethylformamide (6 mL) and stirred at room temperature over night. The reaction was diluted in ethyl acetate and washed successively with dilute aqueous hydrochloric acid, dilute aqueous sodium hydroxide, and brine, and dried (Na_2SO_4). The product was purified by flash column chromatography (20% ethyl acetate/hexane). The residue was taken up in tetrahydrofuran (10 mL) and methanol (2 mL) and aqueous lithium hydroxide (2 mL, 1 M, 2 mmol). The reaction was stirred at room temperature 1 h The solvents were stripped *in vacuo* and the residue partitioned between dilute aqueous hydrochloric acid and ethyl acetate The aqueous was extracted with 2 aliquots ethyl acetate and the pooled organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford a white solid (0 12g, 39% yeild)

^{1}H NMR ($CDCl_3$) 8 60 (d, 1H, J= 8 Hz), 8.20 (m, 2H), 7.30 (t, 1H, J=8 Hz), 7 11 (m, 1H), 6 81 (d, 1H, J= 8 Hz), 6 62 (m, 3H), 6 00 (s, 2H), 4 63 (d, 2H, J= 6 Hz), 4 13 (dd, 1H, J= 7, 9 Hz), 3.93 (dd, 1H, J= 6, 9 Hz), 3 70 (s, 3H), 2 91 (m, 1H), 1.26 (d, 3H, J= 7 Hz)

MS (m/z). 469 (MH^+, 100).

EXAMPLE 26

2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-2-ylmethoxy)-benzyl]-nicotinamide of Formula (5 5.26).



(5 5.26)

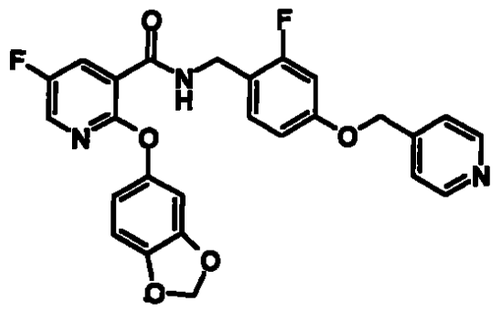
To a stirred solution of 100 mg (0.25 mmol) 2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-(2-fluoro-4-hydroxy-benzyl)-nicotinamide [Prepared analogous to preparation 35 by substituting 2-chloro-5-fluoro-nicotinic acid (EP 0634413 A1)], 10 mL DMF and 175 mg (1.25 mmol) potassium carbonate was added a solution of DMF(5 mL) containing 82 mg (0.5 mmol) 2-chloromethyl-pyridine hydrochloride (Aldrich) and 1 equivalent of triethyl amine. The resulting mixture was stirred for 3 days at room temperature Reaction mixture was poured into ice water (200 mL) and the resulting solid was filtered, washed with cold water and dried *in vacuo* to afford desired product.

MS (m/z) 492 (M^+, 100)

^{1}H-NMR ($CDCl_3$). 8.58 (d, 1H, J= 5Hz), 8.32 (dd, 1 H, J=4,9Hz), 8 02 (d, 1H, J= 3 Hz), 7 71 (dt, 1H, J= 2,10Hz), 7.47 (d, 1H, J= 2 Hz), 7.26 (m, 1H), 6.80 (d, 1H, J=8Hz), 6 71 (m, 3H), 6 62 (d, 1H, J=3Hz), 6 56 (dd, 1H, J= 2,8Hz), 6 00 (s, 2H), 5.2 (s, 2H), 4.63 (d, 2H, J=6Hz)

EXAMPLE 27

2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-4-ylmethoxy)-benzyl]-nicotinamide of Formula (5 5.27):



(5 5.27)

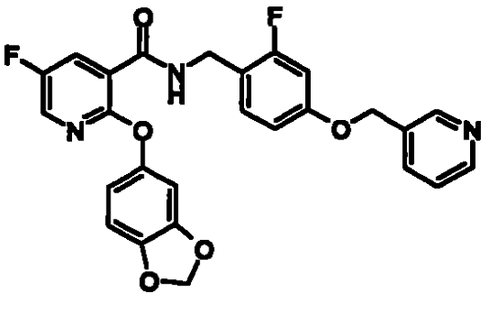
Prepared analogous to Example 26 by substituting 4-chloromethyl-pyridine hydrochloride (Aldrich).

MS (m/z): 492 (M^+, 100)

^{1}H-NMR ($CDCl_3$) 8.38 (m, 2 H), 8 02 (d, 1H, J= 3 Hz), 7 74 (m, 1H), 7.26 (m, 1H), 6.80 (d, 1H, J=8Hz), 6 71 (m, 3H), 6 62 (d, 1H, J=3Hz), 6 56 (dd, 1H, J= 2,8Hz), 6 00 (s, 2H), 5.2 (s, 2H), 4.63 (d, 2H, J=6Hz).

EXAMPLE 28

2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-3-ylmethoxy)-benzyl]-nicotinamide of Formula (5.5.28):



(5 5.28)

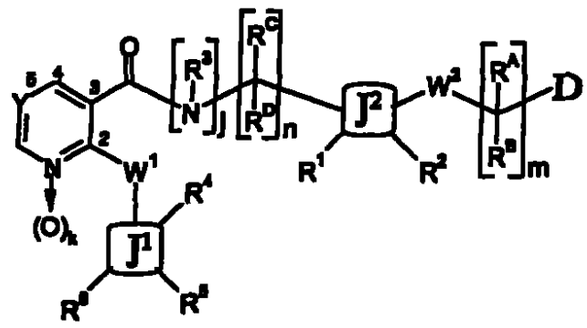
Prepared analogous to Example 26 by substituting 4-chloromethyl-pyridine hydrochloride (Aldrich).

MS (m/z) 482 (M^+, 100)

^{1}H-NMR ($CDCl_3$) 8.81 (s, 1H), 8 64 (d, 1H, J= 5Hz), 8.35 (m, 2 H), 8 02 (d, 1H, J= 3 Hz), 7 71 (dt, 1H, J= 2,10Hz), 7.47 (d, 1H, J= 2 Hz), 7 26 (m, 1H), 6.80 (d, 1H, J=8Hz), 6 71 (m, 3H), 6 62 (d, 1H, J=3Hz), 6 56 (dd, 1H, J= 2,8Hz), 6 00 (s, 2H), 5.2 (s, 2H), 4 63 (d, 2H, J=8Hz)

WHAT IS CLAIMED IS.

1 A compound of Formula (1.0.0):



(1.0.0)

— wherein —

-j is 0 or 1, provided that when j is 0, n must be 2;

-k is 0 or 1

-m is 1, 2, or 3,

-n is 1 or 2,

-W^1 and W^2 are independently —O—; —S(=O)$_t$— , where t is 0, 1, or 2; or -N(R^3)– where R^3 has the same meaning as defined below;

-Y is =C($R^1{}_a$)—, where $R^1{}_a$ has the same meaning as defined below; or -[N⇒(O)$_k$]— where k is 0 or 1,

— where —

—$R^1{}_a$ is a member selected from the group consisting of –H, –F, –Cl, –CN, –NO_2, –(C_1-C_4) alkyl, –(C_2-C_4) alkynyl, fluorinated–(C_1-C_2) alkyl; fluorinated-(C_1-C_3) alkoxy; -OR^{19}; and –C(=O)$NR^{22}{}_aR^{22}{}_b$,

— where —

—$R^{22}{}_a$ and $R^{22}{}_b$ are each independently –H, –CH_3, –CH_2CH_3, –$CH_2CH_2CH_3$, -$CH_2(CH_3)_2$, –$CH_2CH_2CH_2CH_3$, –$CH(CH_3)CH_2CH_3$, –$CH_2CH(CH_3)_2$, –$C(CH_3)_3$, cyclopropyl, cyclobutyl, or cyclopentyl,

-R^A and R^B are each a member independently selected from the group consisting of –H; –F; –CF_3, –(C_1-C_4) alkyl, –(C_3-C_7) cycloalkyl, phenyl, and benzyl, wherein said cycloalkyl, phenyl, and benzyl moieties are each independently substituted with 0 to 3 substituents R^{10};

— where —

—R^{10} is a member selected from the group consisting of phenyl, pyridyl, –F, -Cl, $-CF_3$, oxo (=O), $-OR^{16}$; $-NO_2$, –CN, $-C(=O)OR^{16}$; $-O-C(=O)R^{16}$; $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$, and $-S(=O)_2NR^{16}R^{17}$, where said phenyl or pyridyl is substituted by 0 to 3 R^{11},

— where —

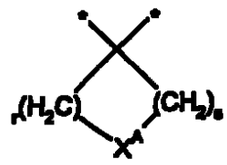
—R^{11} is –F, –Cl, $-CF_3$, –CN; $-NO_2$, –OH, $-(C_1-C_3)$ alkoxy; $-(C_1-C_3)$ alkyl, or $-NR^{16}R^{17}$,

— and —

—R^{16} and R^{17} are each a member independently selected from the group consisting of –H, $-(C_1-C_4)$ alkyl; $-(C_2-C_4)$ alkenyl; $-(C_3-C_6)$ cycloalkyl, phenyl; benzyl, and pyridyl, wherein said alkyl, alkenyl, cycloalkyl, phenyl, benzyl, or pyridyl is substituted by 0 to 3 substituents selected from the group consisting of –F, –Cl, $-CF_3$, –CN, and $-(C_1-C_3)$ alkyl,

— or —

$-R^A$ and R^B are taken together, but only in the case where m is 1, to form a spiro moiety of Formula (1.2.0):



(1.2.0)

— where —

—r and s are independently 0 to 4 provided that the sum of r + s is at least 1 but not greater than 5;

— and —

$-X^A$ is selected from $-CH_2-$, $-CH(R^{11})-$, or $C(R^{11})_2-$, where each R^{11} is selected independently of the other and each has the same meaning as defined above, $-NR^{16}-$, where R^{16} has the same meaning as defined below; –O–, and $-S(=O)_t-$, where t is 0, 1, or 2;

— and —

said spiro moiety of partial Formula (1.2 0) is substituted as to any one or more carbon atoms thereof, other than that defining X^A, by 0 to 3 substituents R^{14}, where R^{14} has the same meaning as defined below; as to a nitrogen atom thereof by 0 or 1 substituent R^{15}, where R^{15} has the same meaning as defined below; and as to a sulfur atom thereof by 0 or 2 oxygen atoms,

-R^C and R^D have the same meaning as defined above for R^A and R^B except that one of them must be –H, and they are selected independently of each other and of R^A and R^B;

-R^1 and R^2 may individually or together appear on any ring or rings comprising a meaning of the moiety J^2 as defined below; and R^1 and R^2 are each a member independently selected from the group consisting of –H, –F, –Cl, –CN, $–NO_2$, $–(C_1–C_4)$ alkyl, $–(C_2–C_4)$ alkynyl, fluorinated–$(C_1–C_3)$ alkyl, $–OR^{16}$; and $-C(=O)NR^{22}{}_aR^{22}{}_b$, where R^{16}, $R^{22}{}_a$, and $R^{22}{}_b$ have the same meanings as defined above;

-R^3 is –H, $–(C_1–C_3)$ alkyl, phenyl, benzyl, or $–OR^{16}$, where R^{16} has the same meaning as defined above;

-R^4, R^5 and R^6 may individually or together appear on any ring or rings comprising a meaning of the moiety J^1 as defined below; and R^4, R^5 and R^6 are each a member independently selected from the group consisting of

— the following —

-*(a)* –H, –F, –Cl, $-(C_2–C_4)$ alkynyl, $-R^{16}$; $–OR^{16}$; $–S(=O)_pR^{16}$; $–C(=O)R^{16}$; $-C(=O)OR^{16}$; $–OC(=O)R^{16}$; –CN, $-NO_2$, $-C(=O)NR^{16}R^{17}$, $–OC(=O)NR^{16}R^{17}$, $–NR^{22}{}_aC(=O)NR^{16}R^{17}$, $-NR^{22}{}_aC(=NR^{12})NR^{16}R^{17}$, $-NR^{22}{}_aC(=NCN)NR^{16}R^{17}$, $-NR^{22}{}_aC(=N-NO_2)NR^{16}R^{17}$, $-C(=NR^{22}{}_a)NR^{16}R^{17}$, $-CH_2C(=NR^{22}{}_a)NR^{16}R^{17}$, $–OC(=NR^{22}{}_a)NR^{16}R^{17}$, $–OC(=N–NO_2)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-CH_2NR^{16}R^{17}$, $-NR^{22}{}_aC(=O)R^{16}$; $-NR^{22}{}_aC(=O)OR^{16}$, $=NOR^{16}$; $–NR^{22}{}_aS(=O)_pR^{17}$ $-S(=O)_pNR^{16}R^{17}$, and $–CH_2C(=NR^{22}{}_a)NR^{16}R^{17}$,

— where —

–p is 0, 1, or 2; and $R^{22}{}_a$, R^{16}, and R^{17} have the same meanings as defined above,

-*(b)* $-(C_1–C_4)$ alkyl, and $–(C_1–C_4)$ alkoxy in the case where one or more of R^4, R^5, or R^6 has the meaning of $-OR^{16}$ under *(a)* above and R^{16} is defined as $-(C_1–C_4)$ alkyl, wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents –F or –Cl, or 0 or 1 substituent $(C_1–C_2)$ alkoxycarbonyl–, $(C_1–C_2)$ alkylcarbonyl–; or $(C_1–C_2)$ alkylcarbonyloxy–;

— and —

-(c) an aryl or heterocyclyl moiety selected from the group consisting of phenyl, benzyl, furanyl, tetrahydrofuranyl; oxetanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolidinyl, oxazolyl, oxazolidinyl; isoxazolyl, isoxazolidinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, pyrazolyl, pyrazolidinyl, oxadiazolyl, thiadiazolyl, imidazolyl, imidazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidinyl, piperazinyl, triazolyl, triazinyl, tetrazolyl, pyranyl, azetidinyl, morpholinyl, parathiazinyl, indolyl, indolinyl, benzo[*b*]furanyl; 2,3-dihydrobenzofuranyl, 2-*H*-chromenyl, chromanyl, benzothienyl; 1-*H*-indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl, quinolinyl, isoquinolinyl; phthalazinyl, quinazolinyl, quinoxalinyl, and purinyl, wherein said aryl and heterocyclyl moieties are each independently substituted with 0 to 2 substituents R^{14}

— where —

$-R^{14}$ is a member selected from the group consisting of $-(C_1-C_4)$ alkyl; $-(C_3-C_7)$ cycloalkyl, phenyl, benzyl, pyridyl, and quinolinyl, where said alkyl, cycloalkyl, phenyl, benzyl, pyridyl, or quinolinyl is substituted by 0, 1, or 2 substituents –F, –Cl, $-CH_3$, $-OR^{16}$, $-NO_2$, –CN, or $-NR^{16}R^{17}$, and said R^{14} group further consists of –F, -Cl, $-CF_3$, oxo (=O); $-OR^{16}$; $-NO_2$, –CN, $-C(=O)OR^{16}$; $-O-C(=O)R^{16}$; $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$, or $-S(=O)_2NR^{16}R^{17}$, where R^{16} and R^{17} have the same meanings as defined above;

— and further where —

$-R^{16}$ is a member independently selected from the group consisting of –H, $-NR^{16}R^{17}$, $-C(=O)R^{16}$; $-OR^{16}$; $-(C_1-C_4)$ alkyl–OR^{16}; $-C(=O)OR^{16}$; $-(C_1-C_2)$ alkyl-$C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$, $-(C_1-C_4)$ alkyl, $-(C_2-C_4)$ alkenyl, $-(CH_2)_u-(C_3-C_7)$ cycloalkyl where u is 0, 1 or 2; phenyl, benzyl, pyridyl, and quinolinyl, wherein said alkyl, alkenyl, alkoxy, cycloalkyl, phenyl, benzyl, pyridyl or quinolinyl is substituted with 0 to 3 substituents R^{12}; where R^{16} and R^{17} have the same meanings as defined above, and

— where —

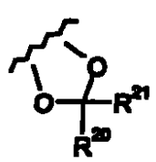
$-R^{12}$ is a member independently selected from the group consisting of –F; –Cl; $-CO_2R^{16}$; $-OR^{16}$; –CN, $-C(=O)NR^{16}R^{16}$, $-NR^{16}R^{16}$, $-NR^{16}C(=O)R^{16}$, $-NR^{16}C(=O)OR^{16}$; $-NR^{16}S(=O)_pR^{16}$, $-S(=O)_pNR^{16}R^{16}$, where p is 1 or 2, $-(C_1-C_4)$ alkyl, and $-(C_1-C_4)$ alkoxy in the case where R^{12} has the meaning of $-OR^{16}$ above and R^{16} is defined as $-(C_1-C_4)$ alkyl, wherein said alkyl and alkoxy are each independently substituted with 0 to 3 substituents independently selected from –F, –Cl, $-(C_1-C_2)$ alkoxycarbonyl, $-(C_1-C_2)$ alkylcarbonyl, and $-(C_1-C_2)$ alkylcarbonyloxy; where R^{16} has the same meaning as defined above; and

— where —

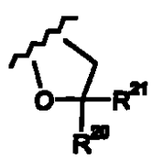
——R^{18} and R^{19} are independently selected from the group consisting of –H, -(C_1-C_4) alkyl, and phenyl, where said alkyl or phenyl is substituted by 0-3 of –F, or –Cl,

— or in the case where J^1 is phenyl —

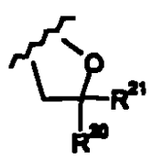
-(d) R^5 and R^6 are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3 1) through (1.3.15):



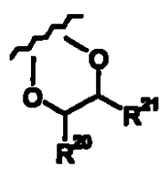
(1.3 1)



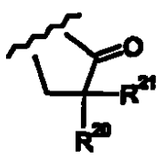
(1 3.2)



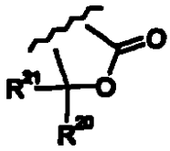
(1.3.3)



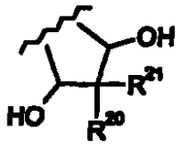
(1.3.4)



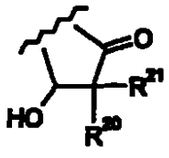
(1.3.5)



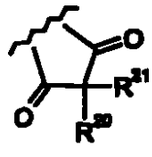
(1.3 6)



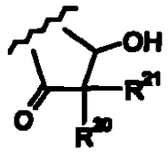
(1.3.7)



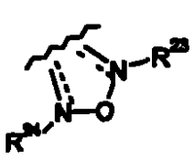
(1.3.8)



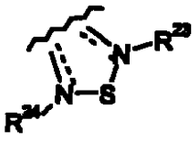
(1.3 9)



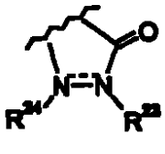
(1.3 10)



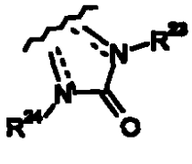
(1.3 11)



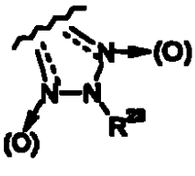
(1.3 12)



(1.3 13)



(1.3 14)



(1 3 15)

— wherein —

–R^{20} and R^{21} are each a member independently selected from the group consisting of –H, –F, –Cl, –CH_3, –CH_2F, –CHF_2, –CF_3, –OCH_3, and –OCF_3,

–R^{23} and R^{24} are each independently –H, –CH_3, –OCH_3, –CH_2CH_3, –OCH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2(CH_3)_2$, –$CH_2CH_2CH_2CH_3$, –$CH(CH_3)CH_2CH_3$, –$CH_2CH(CH_3)_2$, –$C(CH_3)_3$, or absent, in which case the dashed line – – – – represents a double bond;

-J^1 is a moiety comprising a saturated or unsaturated carbon ring system that is a 3- to 7-membered monocyclic, or that is a 7- to 12-membered, fused polycyclic; provided that J^1 is not a discontinuous or restricted biaryl moiety as defined under J^2 below; and wherein optionally one carbon atom of said carbon ring system may be replaced by a heteroatom selected from N, O, and S, where optionally a second carbon atom thereof, and further optionally a third carbon atom thereof may be replaced by N,

— wherein —

said moiety defining J^1 is substituted on any ring or rings thereof by R^4, R^8 and R^9, which have the same meaning as defined above;

-J^2 is a moiety comprising a saturated or unsaturated carbon ring system that is a 3- to 7-membered monocyclic, or that is a 7- to 12-membered, fused polycyclic; provided that J^2 is not a discontinuous or restricted biaryl moiety; and wherein optionally one carbon atom of said carbon ring system may be replaced by a heteroatom selected from N, O, and S, where optionally a second carbon atom thereof, and further optionally a third carbon atom thereof may be replaced by N,

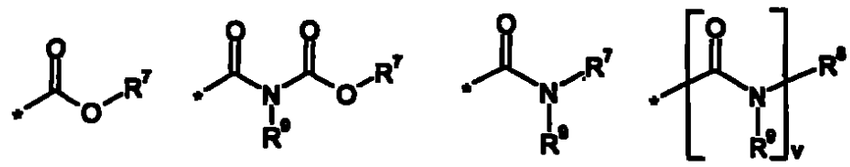
— wherein —

said moiety defining J^2 is substituted on any ring or rings thereof by R^1 and R^2, which have the same meaning as defined above;

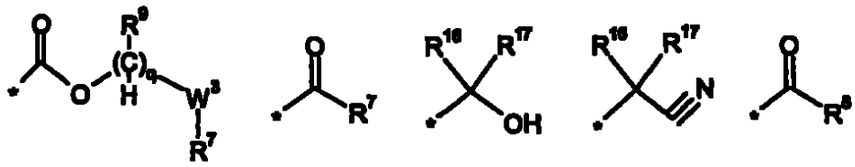
-D is a member independently selected from the group consisting of

— the following —

-(a) the group consisting of partial Formulas (1 1 1) through (1 1.9):



(1 1 1) (1 1.2) (1 1.3) (1 1.4)



(1 1 5) (1 1 6) (1 1 7) (1 1 8) (1 1 9)

— wherein —

—*** indicates the point of attachment of each partial Formula (1 1 1) through (1 1 9) to the remaining portion of Formula (1.0.0);

–q is 1, 2, or 3, provided that where q is 2 or 3, R^9 has the meaning of –H in at least one instance, or two instances, respectively;

–v 0 or 1,

–W^3 is —O—, —N(R^9)—, where R^9 has the same meaning as defined below; or —OC(=O)—;

–R^7 is a member independently selected from the group consisting of

— the following —

–*(1)* –H,

–*(2)* –(C_1-C_8) alkyl, –(C_2-C_8) alkenyl, or –(C_2-C_8) alkynyl, where said alkyl, alkenyl or alkynyl is substituted by 0 to 3 substituents R^{10}, where R^{10} has the same meaning as defined above;

–*(3)* –$(CH_2)_u$-(C_3-C_7) cycloalkyl where u is 0, 1 or 2, and further where said (C_3-C_7) cycloalkyl is substituted by 0 to 3 substituents R^{10} where R^{10} has the same meaning as defined above;

— and —

–*(4)* phenyl or benzyl, where said phenyl or benzyl is independently substituted by 0 to 3 substituents R^{10} where R^{10} has the same meaning as defined above,

–R^8 is a member independently selected from the group consisting of

— the following —

–*(1)* phenyl, tetrazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-3-on-5-yl, 1,2,3-triazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazolidin-2-on-4-yl, 1,3,4-oxadiazolyl; 1,3,4-oxadiazol-2-on-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-on-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-on-5-yl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, morpholinyl, perathiazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, succinimidyl, gluterimidyl, pyrrolidonyl, 2-piperidonyl, 2-pyridonyl, 4-pyridonyl, pyridazin-3-onyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl,

— and —

–*(2)* indolyl, indolinyl, isoindolinyl, benzo[*b*]furanyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, 2*H*-1-benzopyranyl, 2-*H*-chromenyl, chromanyl; benzothienyl, 1*H*-indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl, benzotriazinyl, phthalazinyl, 1,8-naphthyridinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyrazolo[3,4-*d*]pyrimidinyl, pyrimido[4,5-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridinyl, pyridopyridinyl, pteridinyl, and 1*H*-purinyl,

— where —

any moiety recited in *(1)* or *(2)* above is optionally substituted with respect to *(I)* any one or more carbon atoms thereof optionally by a substituent R^{14} where R^{14} has the same meaning as defined above; *(II)* any one or more nitrogen atoms thereof that is not a point of attachment of said moiety, optionally by a substituent R^{15} where R^{15} has the same meaning as defined above, and all tautomer forms thereof; and *(III)* any sulfur atom thereof that is not a point of attachment of said moiety, by 0, 1, or 2 oxygen atoms,

$-R^9$ is a member selected from the group consisting of –H, $-(C_1-C_4)$ alkyl, $-(C_3-C_7)$ cycloalkyl, phenyl, benzyl, pyridyl, $-C(=O)OR^{16}$; $-C(=O)R^{16}$; $-OR^{16}$; $-(C_1-C_2)$ alkyl–OR^{16}; and $-(C_1-C_2)$ alkyl–$C(=O)OR^{16}$; where R^{16} has the same meaning as defined above;

— and D is further selected from —

-(b) a moiety comprising a member selected from the group consisting of $-O-P(=O)(OH)_2$ (phosphoric), –PH(=O)OH (phosphinic), $-P(=O)(OH)_2$ (phosphonic); $-[P(=O)(OH)-O(C_1-C_4)$ alkyl] (alkylphosphono), $-P(=O)(OH)-O(C_1-C_4)$ alkyl) (alkylphosphinyl); $-P(=O)(OH)NH_2$ (phosphoramido), $-P(=O)(OH)NH(C_1-C_4)$ alkyl and $-P(=O)(OH)NHR^{25}$ (substituted phosphoramido); $-O-S(=O)_2OH$ (sulfuric); $-S(=O)_2OH$ (sulfonic), $-S(=O)_2NHR^{25}$ or $-NHS(=O)_2R^{25}$ (sulfonamido) where R^{25} is $-CH_3$, $-CF_3$, or o-toluyl, and acylsulfonamido selected from the group consisting of $-C(=O)NHS(=O)_2R^{25}$; $-C(=O)NHS(=O)_2NH_2$, $-C(=O)NHS(=O)_2(C_1-C_4)$ alkyl, $-C(=O)NHS(=O)_2NH(C_1-C_4)$ alkyl, $-C(=O)NHS(=O)_2N[(C_1-C_4)$ alkyl$]_2$, $-S(=O)_2NHC(=O)(C_1-C_4)$ alkyl, $-S(=O)_2NHC(=O)NH_2$, $-S(=O)_2NHC(=O)NH(C_1-C_4)$ alkyl, $-S(=O)_2NHC(=O)N[(C_1-C_4)$ alkyl$]_2$, $-S(=O)_2NHC(=O)R^{25}$; $-S(=O)_2NHCN$, $-S(=O)_2NHC(=S)NH_2$, $-S(=O)_2NHC(=S)NH(C_1-C_4)$ alkyl, $-S(=O)_2NHC(=S)N[(C_1-C_4)$ alkyl$]_2$, and $-S(=O)_2NHS(=O)_2R^{25}$;

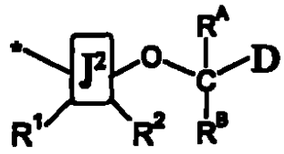
— where —

$-R^{25}$ is –H, $-(C_1-C_4)$ alkyl, phenyl, or $-OR^{16}$, where R^{16} has the same meaning as defined above;

— or —

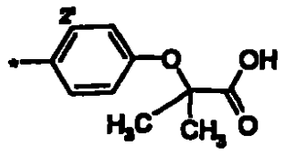
a pharmaceutically acceptable salt thereof

2. A compound according to Claim 1 wherein the right-hand terminus thereof, where *m* is 1, is represented by partial Formula (1.0 5)

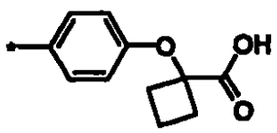


(1.0.5)

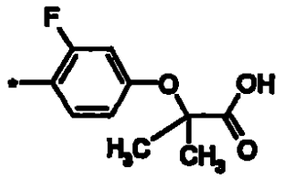
where " * " is a symbol representing the point of attachment of the moiety of partial Formula (1 0 5) to the remaining portion of a compound of Formula (1 0 0); where R^A and R^B are both -H, or one is –H and the other is $–CH_3$, or both are $–CH_3$, or both are taken together to form spiro-cyclopropyl or spiro-cyclobutyl, R^1 is –H, $-OCH_3$, or 2'–F, R^2 is -H, and the moieties J^2 and D are selected such that, said moiety of partial Formula (1 0 5) is a member selected from the group consisting of partial Formulas (1 5 1) through (1 5.54)



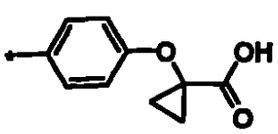
(1.5 1)



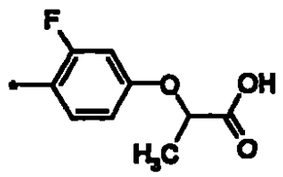
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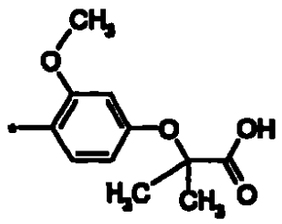
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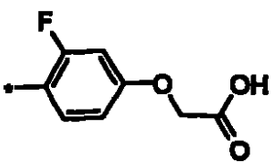
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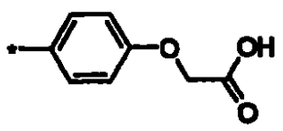
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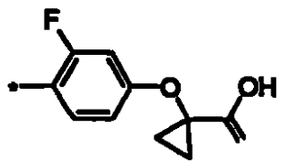
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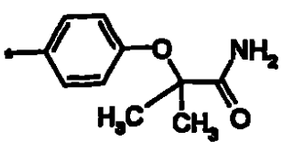
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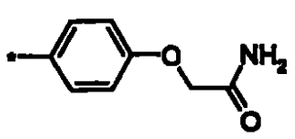
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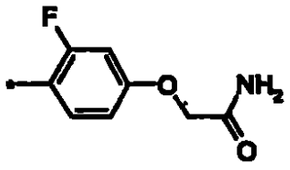
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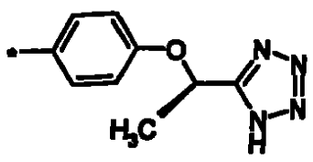
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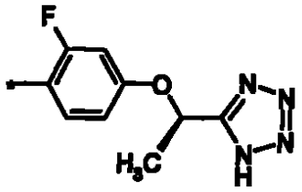
(1 5 11)



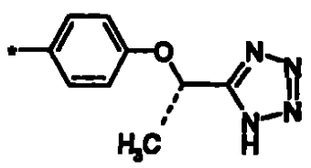
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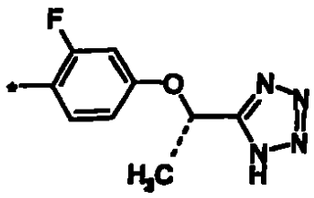
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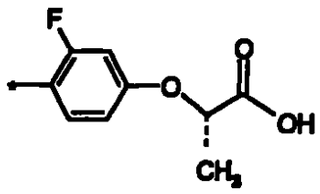
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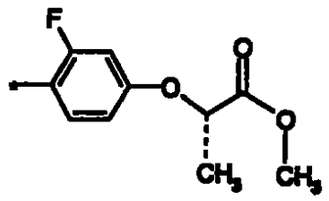
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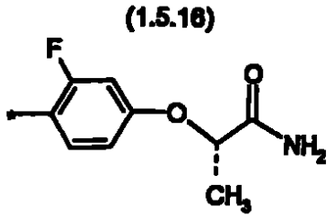
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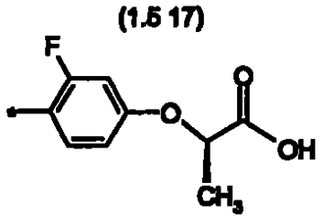
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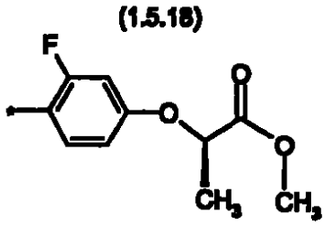
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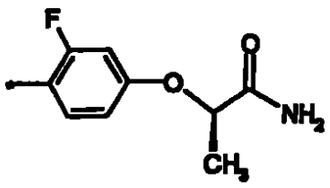
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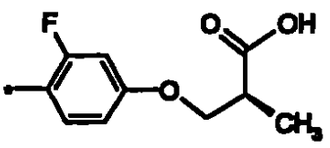
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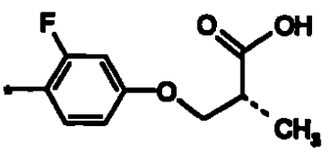
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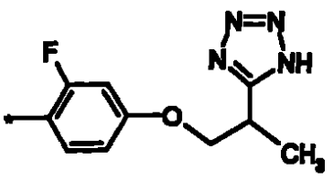
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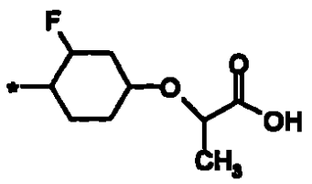
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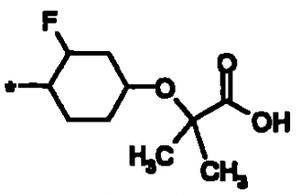
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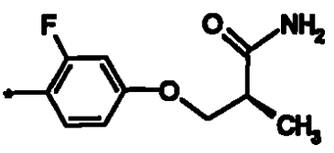
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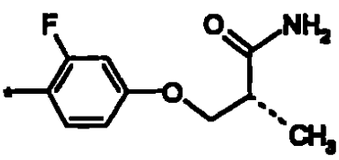
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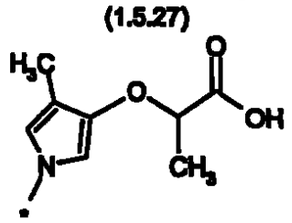
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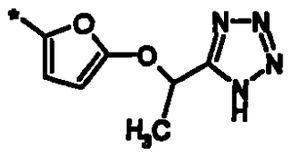
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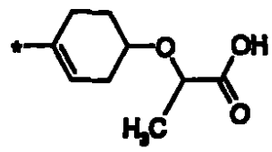
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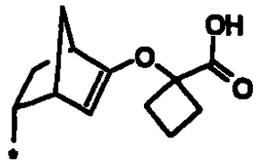
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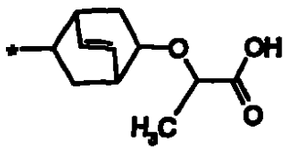
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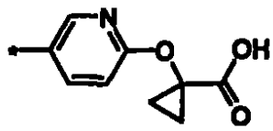
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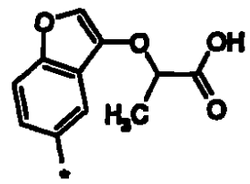
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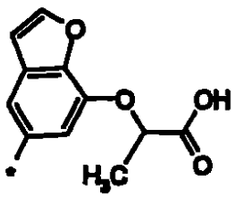
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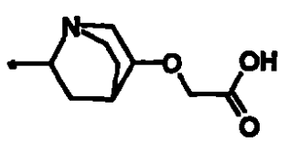
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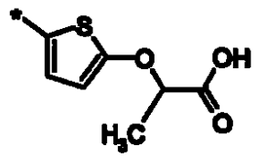
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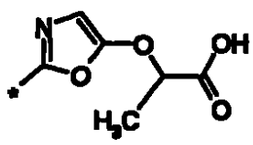
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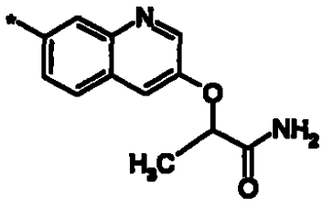
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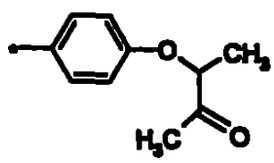
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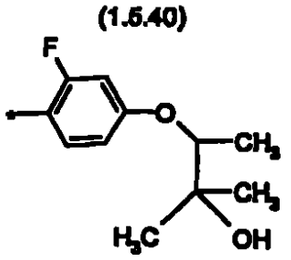
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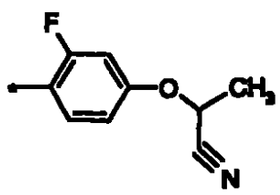
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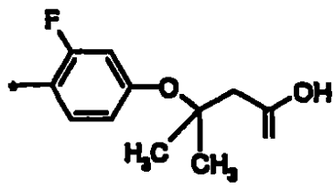
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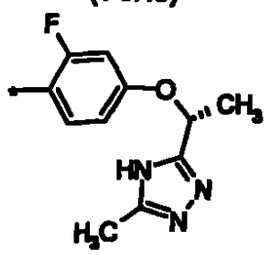
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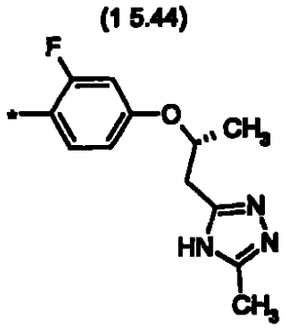
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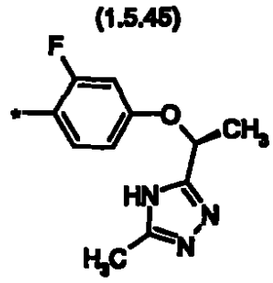
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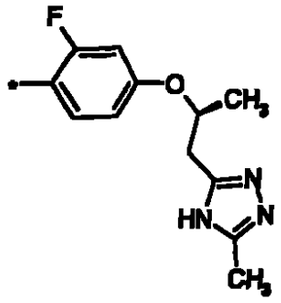
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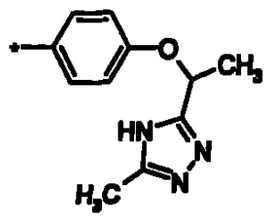
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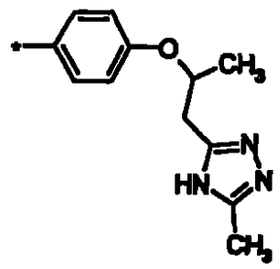
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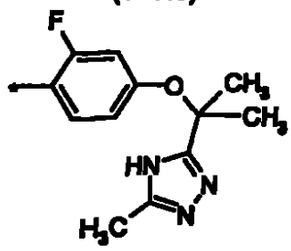
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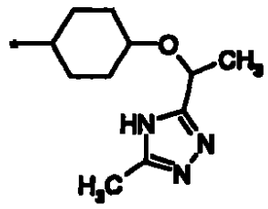
(1 5 50)



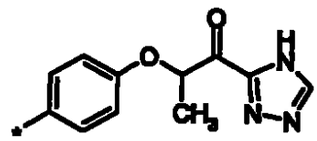
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(1 5.52)



(1.5.53)

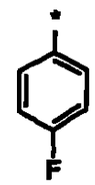


(1 5.54)

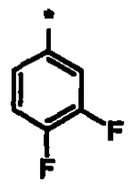
– wherein –

—*** indicates the point of attachment of each said group of partial Formula (1 0 5) represented by partial Formulas (1 5 1) through (1 5 54) to the remaining portion of Formula (1 0.0).

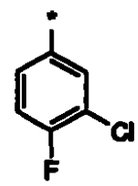
3 A compound according to Claim 1 wherein J^1 and the substituents R^4, R^5, and R^6 are selected in such a way that a portion of the left-hand terminus of a compound of Claim 1 is a member selected from the group consisting of partial Formulas (2.0 1) through (2 0 72).



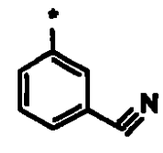
(2 0 1)



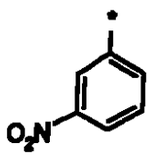
(2 0.2)



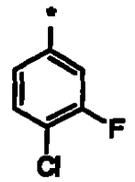
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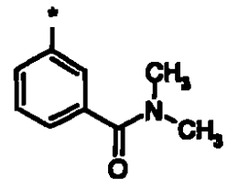
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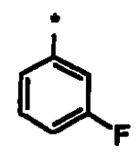
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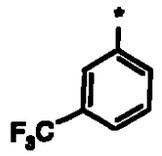
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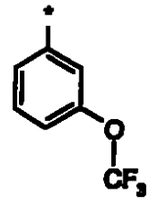
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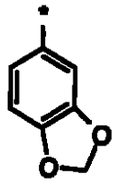
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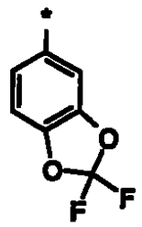
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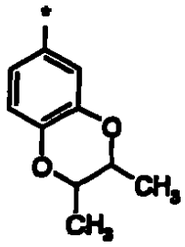
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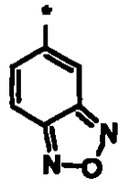
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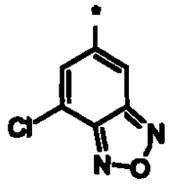
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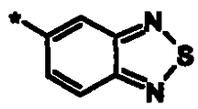
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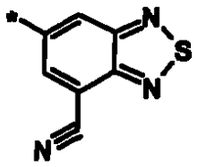
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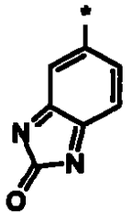
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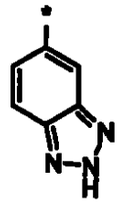
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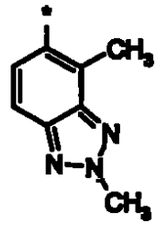
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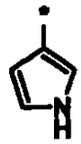
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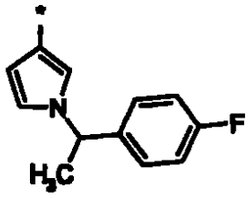
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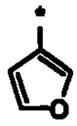
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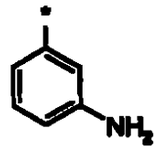
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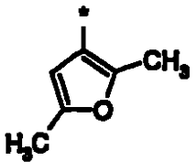
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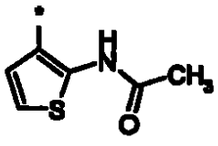
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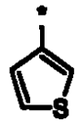
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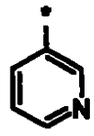
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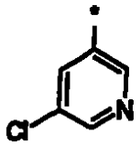
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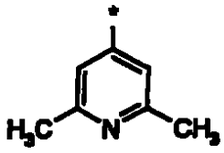
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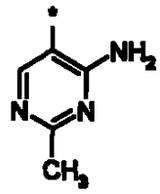
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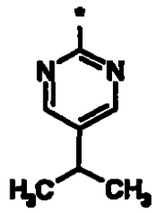
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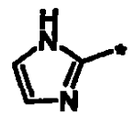
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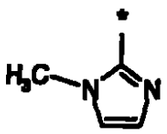
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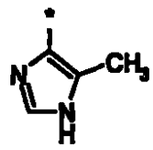
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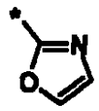
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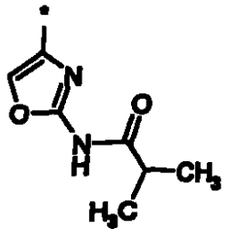
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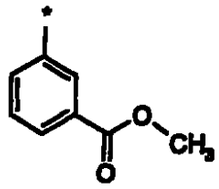
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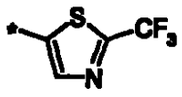
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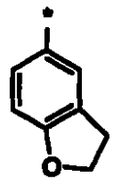
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(2.0.38)



(2.0.39)



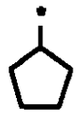
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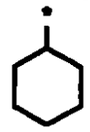
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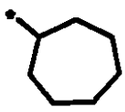
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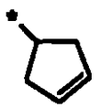
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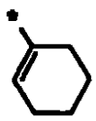
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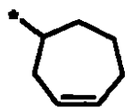
(2 0.45)



(2 0.46)



(2 0.47)



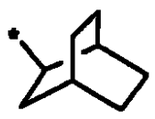
(2.0.48)



(2.0.49)



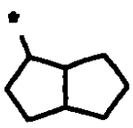
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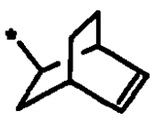
(2 0 51)



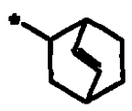
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(2 0.53)



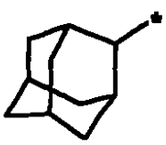
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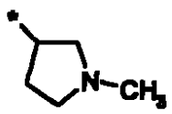
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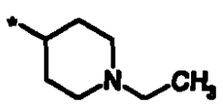
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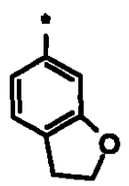
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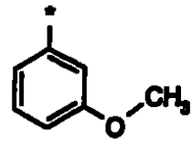
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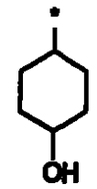
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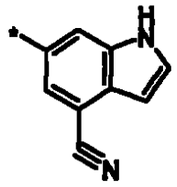
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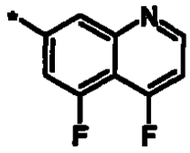
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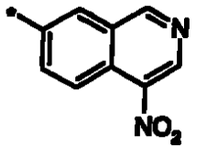
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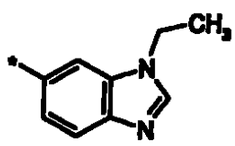
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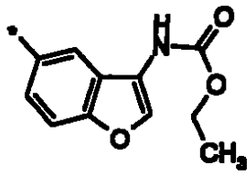
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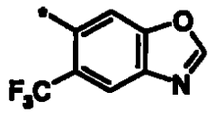
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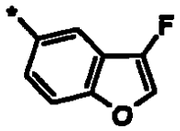
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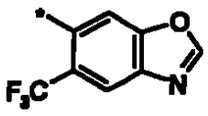
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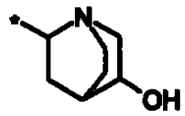
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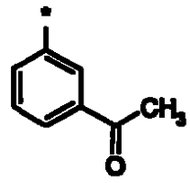
(2 0.69)



(2.0 70)

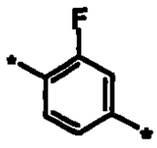


(2.0 71)

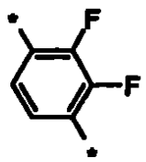


(2.0 72)

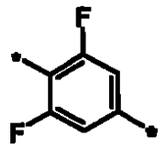
4 A compound according to Claim 1 wherein J^2 and the substituents R^1 and R^2 are selected in such a way that a portion of the right-hand terminus of a compound of Claim 1 is a member selected from the group consisting of partial Formulas (2 5 1) through (2.5.50).



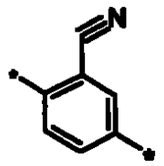
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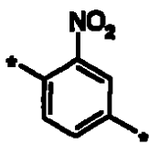
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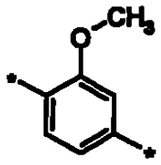
(2 5 3)



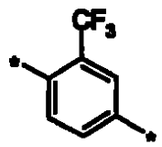
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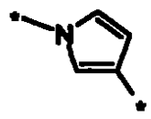
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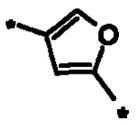
(2.5 6)



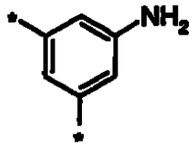
(2 5 7)



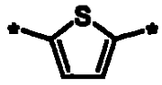
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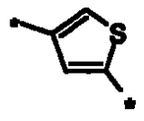
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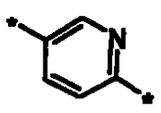
(2 5 10)



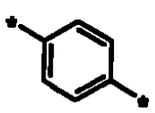
(2 5 11)



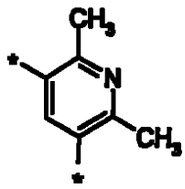
(2 5 12)



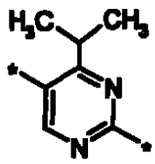
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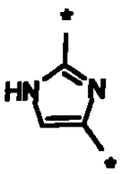
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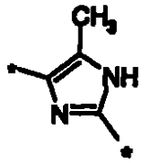
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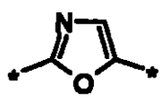
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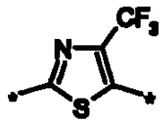
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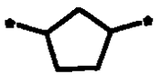
(2 5 18)



(2.5.19)



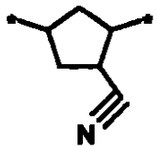
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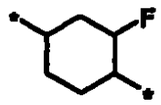
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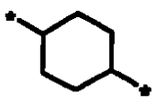
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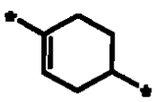
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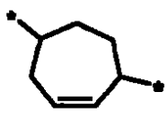
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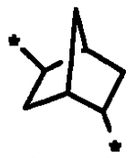
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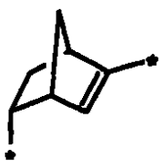
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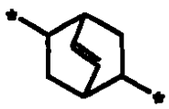
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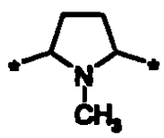
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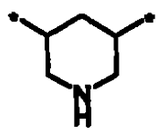
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(2 5.30)



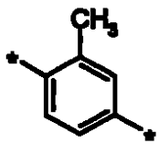
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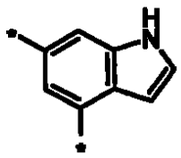
(2 5 32)



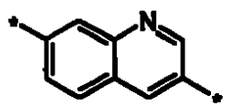
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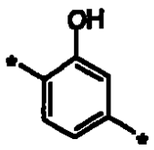
(2 5.34)



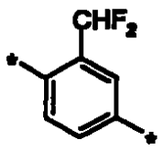
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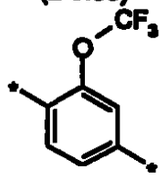
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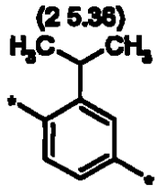
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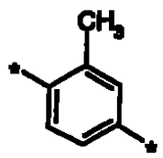
(2 5 38)



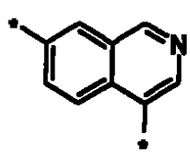
(2.5 39)



(2.5.40)



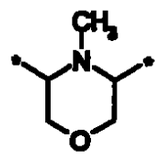
(2 5.41)



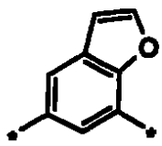
(2.5.42)



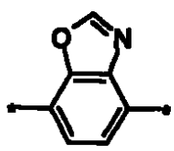
(2 5.43)



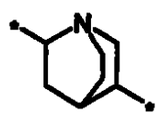
(2.5.44)



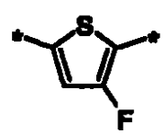
(2 5.45)



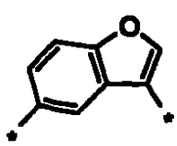
(2 5.46)



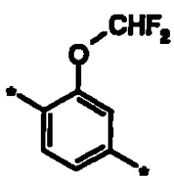
(2 5.47)



(2.5.48)

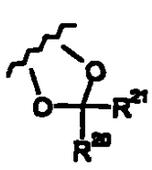


(2 5.49)

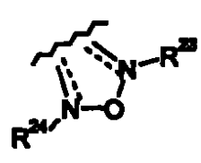


(2.5.50)

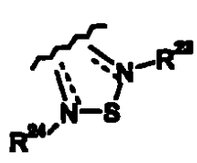
5 A compound according to Claim 1 wherein R^5 and R^6 as taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1 3 1), (1.3 11), (1.3.12), and (1.3.15)



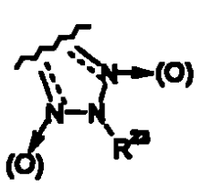
(1.3 1)



(1.3 11)



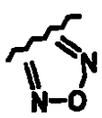
(1.3.12)



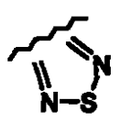
(1.3 15)

where R^{20}, R^{21}, R^{23}, and R^{24} have the same meaning as defined in Claim 1

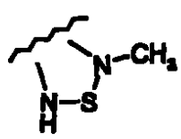
6 A compound according to Claim 8 wherein R^5 and R^6 are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (2.1 1), (2.1.4) through (2 1 6), (2 1 11), and (2 1 16) through (2 1.20):



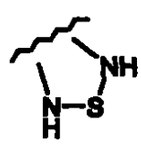
(2.1 1)



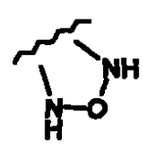
(2 1 4)



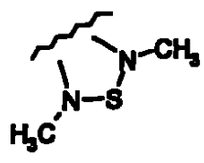
(2.1 5)



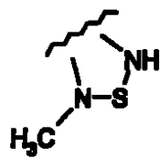
(2 1 6)



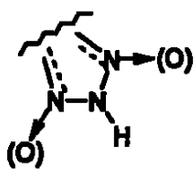
(2.1 11)



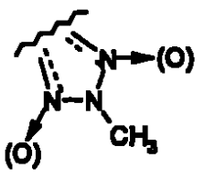
(2 1 16)



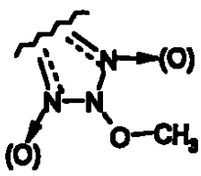
(2.1 17)



(2 1 18)



(2 1 19)



(2.1.20)

wherein the dashed line ---- in partial Formulas (2 1 16), (2 1 19), and (2 1.20) represents a double bond where no oxygen atom is attached to the corresponding nitrogen atom, and represents a single bond where an oxygen atom is attached to said corresponding nitrogen atom

7 A compound according to Claim 1 wherein said compound is a member selected from the group consisting of the following

[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-acetic acid of Formula (5 5.1),

(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5.2);

(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.3);

(±)-2-[3-Fluoro-4-({[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5 5.4),

(±)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5 5 5);

(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5 6);

(±)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5 7);

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5.8);

(S)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5 5 9);

(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5 10);

(R)-2-[3-Fluoro-4-({[2-(3-cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5 5 11);

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.12),

(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (5.5.13);

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5.14);

(R)-2-(Benzo[2,1,3]oxadiazol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5.15),

(R)-2-(Benzo[2,1,3]thiadiazol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5 16);

(R)-N-[4-(1-Carbamoyl-ethoxy)-2-fluoro-benzyl]-2-(3-cyano-phenoxy)-nicotinamide of Formula (5.5 17);

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(1-carbamoyl-ethoxy)-2-fluoro-benzyl]-5-fluoro-nicotinamide of Formula (5.5 18);

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5 5 19);

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5 5.20);

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5 5.21);

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.22);

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-(2-hydroxy-1,2-dimethyl-propoxy)-benzyl]-nicotinamide of Formula (5 5.23),

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(2-hydroxy-1,2-dimethyl-propoxy)-benzyl]-nicotinamide of Formula (5.5.24),

(S)-3-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5 5.25);

2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-2-ylmethoxy)-benzyl]-nicotinamide of Formula (5 5.26),

2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-4-ylmethoxy)-benzyl]-nicotinamide of Formula (5.5.27);

2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-(pyridin-3-ylmethoxy)-benzyl]-nicotinamide of Formula (5.5.28);

[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.29),

[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5 30);

(±)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.31);

(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5 5.32);

(±)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.33),

(±)-2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5 5.34);

(±)-2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.35),

(±)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5 5.36);

(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5 37);

(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5 5 38);

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5 5.39);

(R)-2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.40);

(R)-2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.41);

(R)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-propionic acid of Formula (5.5.42),

[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.43);

[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.44);

[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5 5.45);

[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.46);

[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.47);

[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-acetic acid of Formula (5.5.48);

(±)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.49);

(±)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5 5.50);

(±)-2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5 5), of Formula (5.5 51),

(±)-2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.52);

(±)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5 5 53),

(R)-2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5 54);

(R)-2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5 5 55),

(R)-2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.56);

(R)-2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5 5.57);

(R)-2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5 58),

(R)-2-[4-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5.59);

2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5 5 60);

2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5.61);

2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5 62);

2-[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5.5 63);

2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-2-methyl-propionic acid of Formula (5 5.64);

2-Methyl-2-[4-({[2-(2-methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (5.5 65);

[5-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-acetic acid of Formula (5 5 66);

(±)-2-[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2 2.2]oct-2-yloxy]-propionic acid of Formula (5.5.67);

(R)-2-[5-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-propionic acid of Formula (5 5 68),

2-[5-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-2-methyl-propionic acid of Formula (5 5 69),

2-[5-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-2-methyl-propionic acid of Formula (5.5 70);

(R)-2-[5-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-propionic acid of Formula (5.5 71);

[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-2-yloxy]-acetic acid of Formula (5.5.72);

2-[8-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2.2.2]oct-5-en-2-yloxy]-2-methyl-propionic acid of Formula (5 5.73);

(R)-2-[3-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[3.2 1]oct-8-yloxy]-propionic acid of Formula (5.5 74),

2-[3-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclopent-3-enyloxy]-propionic acid of Formula (5 5.75);

5-({[2-(2-Methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-bicyclo[2 2 1]hept-2-yloxy]-acetic acid of Formula (5.5 76);

2-[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-7-fluoro-bicyclo[2.2 1]hept-5-en-2-yloxy]-2-methyl-propionic acid of Formula (5.5.77);

(R)-2-[5-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-furan-2-yloxy]-propionic acid of Formula (5.5 7 .,

(±)-2-[6-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-pyridin-3-yloxy]-propionic acid of Formula (5.5 79),

[2-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-oxazol-5-yloxy]-acetic acid of Formula (5 5.80);

2-[2-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-thiazol-5-yloxy]-2-methyl-propionic acid of Formula (5.5.81);

(±)-2-[5-(1-{[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-ethyl)-pyridin-2-yloxy]-propionic acid of Formula (5 5.82);

2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-2-methyl-propionic acid of Formula (5 5.83);

2-[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5 5 84);

2-[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.85);

2-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.86),

2-[3-Fluoro-4-({[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-2-methyl-propionic acid of Formula (5.5.87);

2-[4-({[2-(3-Cyano-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5.88);

[4-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.89);

(±)-2-(3-Cyano-phenoxy)-N-[4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-cyclohexylmethyl]-nicotinamide of Formula (5 5.90);

(±)-2-(3-Cyano-phenoxy)-N-[4-[1-(1H-tetrazol-5-yl)-ethoxy]-cyclohexylmethyl]-nicotinamide of Formula (5.5 91);

(±)-N-[2-Fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-2-(3-methoxy-phenoxy)-nicotinamide of Formula (5 5.92);

N-[2-Fluoro-4-(pyridin-2-ylmethoxy)-benzyl]-2-(3-methoxy-phenoxy)-nicotinamide of Formula (5.5.93);

(±)-2-[3-Fluoro-4-({[2-(3-nitro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.94);

(±)-N-[2-Fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-2-(3-nitro-phenoxy)-nicotinamide of Formula (5.5 95);

(±)-N-[2-Fluoro-4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-2-(3-nitro-phenoxy)-nicotinamide of Formula (5.5 96);

[4-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5.97);

[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5 5 98);

[4-({[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-cyclohex-3-enyloxy]-acetic acid of Formula (5.5 99),

(R)-2-[4-({[2-(3-Methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 100),

(R)-2-[3-Fluoro-4-({[2-(3-methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 101);

(R)-2-[3-Fluoro-4-({[5-fluoro-2-(3-methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5 5 102);

(R)-2-[4-({[2-(3-Nitro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 103);

(R)-2-[4-({[2-(3-Chloro-4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 104);

(R)-2-[4-({[2-(3,4-Difluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 105);

(R)-2-[4-({[2-(2,3-Dihydro-benzofuran-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5.106);

(R)-2-[4-({[2-(2,3-Dihydro-benzofuran-6-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (5.5 107),

(S)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.108);

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5 109);

(R)-3-[4-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-2-methyl-propionic acid of Formula (5.5 110);

(S)-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(2-carbamoyl-propoxy)-2-fluoro-benzyl]-nicotinamide of Formula (5.5.111);

(R)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.112);

(±)-2-(3-Methoxy-phenoxy)-N-[4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5 113);

2-[5-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-thiophen-2-yloxy]-propionic acid of Formula (5.5.114); and

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-*N*-[2-fluoro-4-[1-methyl-2-oxo-2-(4*H*-[1,2,4]triazol-3-yl)-ethoxy]-benzyl]-nicotinamide of Formula (5.5.115).

8 A method of treating a subject suffering from a disease or condition mediated by the PDE4 isozyme in its role of regulating the activation and degranulation of human eosinophils, comprising administering to said subject in need of said treatment a therapeutically effective amount of a compound of Formula (1.0 0) as defined in Claim 1

9 A pharmaceutical composition for use in treating a subject suffering from a disease, disorder or condition mediated by the PDE4 isozyme, whereby it regulates the activation and degranulation of eosinophils, comprising a therapeutically effective amount of a compound of Formula (1 0 0) as defined in Claim 1 together with a pharmaceutically acceptable carrier therefor

10 A method of treatment according to Claim 11 wherein said disease, disorder, or condition is a member selected from the group consisting of (1) inflammatory diseases and conditions comprising joint inflammation, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, inflammatory bowel disease, ulcerative colitis, chronic glomerulonephritis, dermatitis, and Crohn's disease, (2) respiratory diseases and conditions comprising asthma, acute respiratory distress syndrome, chronic pulmonary inflammatory disease, bronchitis, chronic obstructive airway disease, and silicosis, (3) infectious diseases and conditions comprising sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, fever and myalgias due to bacterial, viral or fungal infection, and influenza, (4) immune diseases and conditions comprising autoimmune diabetes, systemic lupus erythematosis, graft vs. host reaction, allograft rejections, multiple sclerosis, psoriasis, and allergic rhinitis, and (5) other diseases and conditions comprising bone resorption diseases, reperfusion injury; cachexia secondary to infection or malignancy; cachexia secondary to human acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV) infection, or AIDS related complex (ARC); keloid formation, scar tissue formation; type 1 diabetes mellitus, and leukemia.

11 The combination of a compound of Formula (1 0 0) as defined in Claim 1 together with one or more members selected from the group consisting of the following.

(a) Leukotriene biosynthesis inhibitors, 5-lipoxygenase (5-LO) inhibitors, and 5-lipoxygenase activating protein (FLAP) antagonists selected from the group consisting of zileuton, ABT-761, fenleuton, tepoxalin, Abbott-79175, Abbott-85761, *N*-(5-substituted)-thiophene-2-alkylsulfonamides of Formula (5.2 8), 2,6-di-*tert*-butylphenol hydrazones of Formula (5.2.10); Zeneca ZD-2138 of Formula (5.2 11), SB-210661 of Formula (5.2.12), pyridinyl-

substituted 2-cyanonaphthalene compound L-739,010, 2-cyanoquinoline compound L-746,530, indole and quinoline compounds MK-591, MK-886, and BAY x 1005;

(b) Receptor antagonists for leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4 selected from the group consisting of phenothiazin-3-one compound L-651,392; amidino compound CGS-25019c; benzoxazolamine compound ontazolast; benzenecarboximidamide compound BIIL 284/260, compounds zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195,

(c) PDE4 inhibitors and inhibitors of the PDE4 isoform PDE4D,

(d) 5-Lipoxygenase (5-LO) inhibitors, and 5-lipoxygenase activating protein (FLAP) antagonists,

(e) Dual inhibitors of 5-lipoxygenase (5-LO) and antagonists of platelet activating factor (PAF);

(f) Leukotriene antagonists (LTRAs) of LTB_4, LTC_4, LTD_4, and LTE_4,

(g) Antihistaminic H_1 receptor antagonists cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine;

(h) Gastroprotective H_2 receptor antagonists;

(i) α_1– and α_2–adrenoceptor agonist vasoconstrictor sympathomimetic agents administered orally or topically for decongestant use, selected from the group consisting of propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride,

(j) one or more α_1– and α_2–adrenoceptor agonists as recited in (i) above in combination with one or more inhibitors of 5-lipoxygenase (5-LO) as recited in (e) above;

(k) Anticholinergic agents ipratropium bromide, tiotropium bromide; oxitropium bromide; pirenzepine, and telenzepine,

(l) β_1– to β_4–adrenoceptor agonists selected from the group consisting of metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol, and pirbuterol,

(m) Theophylline and aminophylline,

(n) Sodium cromoglycate;

(o) Muscarinic receptor (M1, M2, and M3) antagonists,

(p) COX-1 inhibitors (NSAIDs); and nitric oxide NSAIDs;

(q) COX-2 selective inhibitor rofecoxib;

(r) Insulin-like growth factor type I (IGF-1) mimetics,

(s) Ciclesonide;

(t) Inhaled glucocorticoids with reduced systemic side effects selected from the group consisting of prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate;

(u) Tryptase inhibitors;

(v) Platelet activating factor (PAF) antagonists;

(w) Monoclonal antibodies active against endogenous inflammatory entities,

(x) IPL 576,

(y) Anti-tumor necrosis factor (TNFα) agents selected from the group consisting of etanercept, infliximab, and D2E7;

(z) DMARDs selected from the group consisting of leflunomide;

(aa)TCR peptides,

(bb)Interleukin converting enzyme (ICE) inhibitors,

(cc) IMPDH inhibitors,

(dd)Adhesion molecule inhibitors including VLA-4 antagonists,

(ee)Cathepsins,

(ff) MAP kinase inhibitors,

(gg)Glucose-6 phosphate dehydrogenase inhibitors,

(hh)Kinin-B_1- and B_2-receptor antagonists;

(ii) Gold in the form of an aurothio group in combination with hydrophilic groups,

(jj) Immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate,

(kk)Anti-gout agents selected from the group consisting of colchicine,

(ll) Xanthine oxidase inhibitors selected from the group consisting of allopurinol,

(mm) Uricosuric agents selected from the group consisting of probenecid, sulfinpyrazone, and benzbromarone,

(nn) Antineoplastic agents that are antimitotic drugs selected from the group consisting of vinblastine and vincristine;

(oo) Growth hormone secretagogues;

(pp) Inhibitors of matrix metalloproteases (MMPs) that are selected from the group consisting of the stromelysins, the collagenases, the gelatinases, aggrecanase, collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11);

(qq) Transforming growth factor (TGFβ);

(rr) Platelet-derived growth factor (PDGF);

(ss) Fibroblast growth factor selected from the group consisting of basic fibroblast growth factor (bFGF);

(tt) Granulocyte macrophage colony stimulating factor (GM-CSF);

(uu) Capsaicin,

(vv) Tachykinin NK_1 and NK_3 receptor antagonists selected from the group consisting of NKP-608C, SB-233412 (talnetant); and D-4418,

(ww) Elastase inhibitors selected from the group consisting of UT-77 and ZD-0892, and

(xx) Adenosine A2a receptor agonists.

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DERIVADOS DE ETERES UTILES COMO AGENTES INHIBIDORES DE LAS ISOZIMAS PDE4

1 0 REFERENCIA A SOLICITUDES RELACIONADAS

Se hace referencia a la solicitud de patente internacional todavía en tramitación y a la Solicitud de Patente en los EE UU basada en ella, con el Nº de Serie PCT/IB98/00315, ambas presentadas el 10 de Marzo de 1998 (Expediente de Agente Nº PC9762A), y publicada como documento de Solicitud de Patente Internacional WO 98/45268 el 15 de Octubre de 1998, que reivindican la prioridad de la Solicitud con el Nº de Serie de serie 60/043403 presentada el 4 de Abril de 1997 (Expediente de Agente Nº PC9762), ahora abandonada, que describen derivados de nicotinamida que tienen actividad biológica como agentes inhibidores de las isozimas PDE4, y por lo tanto son utiles en el tratamiento de enfermedades y condiciones inflamatorias, respiratorias y alérgicas Nada de lo que se describe en las solicitudes antes mencionadas podría sugerir y enseñar a una persona con experiencia ordinaria en la tecnología pertinente los nuevos compuestos del presente invento, o su nivel inesperadamente alto de selectividad inhibidora para las isozimas PDE4

Se hace referencia también a la Solicitud de Patente en los EE UU también en tramitación con el Nº de Serie 09/345 185 presentada el 30 de Junio de 1999 (Expediente de Agente Nº PC10096A), que reivindica la prioridad de la Solicitud con el Nº de Serie 60/105 120 presentada el 21 de Octubre de 1998 (Expediente de Agente Nº PC10096), que describe compuestos y procedimientos para preparar derivados de nicotinamida sustituidos en N Sin embargo, los compuestos y procedimientos descritos no son iguales a los del presente invento

Se hace referencia además a las solicitudes también en tramitación presentadas en la misma fecha que la presente solicitud, Expedientes de Agente Nºs PC11712, PC11848, PC11893, PC11894, PC11895, y PC11897, que implican otras clases de derivados de nicotinamida útiles como agentes inhibidores de las isozimas PDE4 Las descripciones y divulgaciones de todas dichas solicitudes también en tramitación se incorporan a la presente por su referencia en su totalidad

2 0 ANTECEDENTES DEL INVENTO

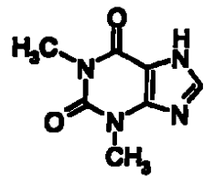
Las fosfodiesterasas de 3',5'-nucleótidos cíclicos (PDE's) constituyen una amplia clase de enzimas que se dividen en por lo menos once diferentes familias que son distintas unas de otras desde puntos de vista estructurales, bioquímicos y farmacológicos Las enzimas situadas dentro de cada familia se citan comúnmente como isoenzimas o isozimas Un total de más de quince productos de genes se incluye dentro

de esta clase, y adicionalmente una diversidad resulta a partir del empalme diferencial y del tratamiento posterior a la traduccion de esos productos de genes El presente invento se refiere a los cuatro productos de genes de la cuarta familia de las PDE's, es decir PDE4A, PDE4B PDE4C y PDE4D y su inhibición, inclusive una inhibición selectiva de las PDE4D Estas enzimas se citan colectivamente como constituyendo isoformas o subtipos de la familia de las isozimas PDE4 Más adelante en esta memoria se encontrará una descripción más detallada de la organización genómica, de la estructura molecular y de la actividad enzimática del empalme diferencial, de la regulación de la transcripción y de la fosfonlización, de la distribución y expresión, así como de la inhibición selectiva de los subtipos de las isozimas PDE4

Las PDE4 se caracterizan por una degradación hidrolítica selectiva con alta afinidad del segundo mensajero nucleótido cíclico, 3',5'-monofosfato-cíclico de adenosina (cAMP), y por una sensibilidad a la inhibición mediante el rolipram Cierto numero de agentes inhibidores selectivos de las PDE4 se han descubierto en los ultimos recientes años, y se han mostrado los efectos farmacológicos beneficiosos, que resultan de esa inhibición, en una diversidad de modelos de enfermedades Véanse, p ej , las citas de Torphy y colaboradores *Environ Health Perspect* **102** Suplemento 10, 79-84, 1994, Duplantier y colaboradores *J Med Chem* **39** 120-125, 1996, Schneider y colaboradores, *Pharmacol Biochem Behav* **50** 211-217, 1995, Banner y Page, *Br J Pharmacol* **114** 93-98, 1995, Barnette y colaboradores *J Pharmacol Exp Ther* **273** 674-679, 1995, Wright y colaboradores ' Differential *in vivo* and *in vitro* bronchorelaxant activities of CP-80633, a selective phosphodiesterse 4 inhibitor" (Actividades relajadoras de los bronquios diferenciales *in vivo* e *in vitro* del CP-80633, que es un agente inhibidor selectivo de fosfodiesterasas 4), *Can J Physiol Pharmacol* **75** 1001-1008, 1997, Manabe y colaboradores "Anti-inflammatory and bronchodilator properties of KF19514, a phosphodiesterase 4 and 1 inhibitor" (Propiedades anti-inflamatorias y dilatadoras de los bronquios del KF19514, que es un agente inhibidor de las fosfodiesterasas 4 y 1), *Eur J Pharmacol* **332** 97-107, 1997, y Ukita y colaboradores "Novel, potent, and selective phosphodiesterase-4 inhibitors as antiasthmatic agents synthesis and biological activities of a series of 1-pyridylnaphthalene derivatives" (Nuevos potentes y selectivos agentes inhibidores de fosfodiesterasas-4 como agentes antiasmáticos síntesis y actividades biológicas de una serie de derivados de 1-pirdil-naftaleno), *J Med Chem* **42** 1088-1099, 1999 Correspondientemente, continua habiendo un considerable interés en la tecnología con respecto al descubrimiento de agentes inhibidores selectivos adicionales de las PDE4

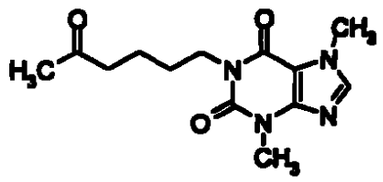
El presente invento se refiere también al uso de los agentes inhibidores selectivos de las PDE4 para el tratamiento terapéutico mejorado de un cierto numero de

enfermedades y condiciones inflamatorias, respiratorias y alérgicas, pero especialmente para el tratamiento del asma, de la enfermedad pulmonar obstructiva crónica (COPD, de *chronic obstructive pulmonary disease*), inclusive bronquitis crónica, enfisema y bronquiectasia, rinitis crónica, y sinusitis crónica Hasta ahora en el sector tecnológico, sin embargo, la terapia de primera línea para el tratamiento del asma y otras enfermedades obstructivas de las vías respiratorias, ha sido la que usa el agente inhibidor no selectivo de las PDE teofilina, así como pentoxifilina e IBMX, que se pueden representar por las Fórmulas (0 0 1), (0 0 2) y (0 0 3), respectivamente



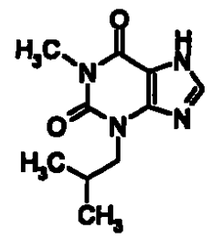
Teofilina

(0 0 1)



Pentoxifilina

(0 0 2)



IBMX

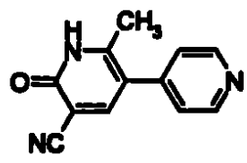
(0.0.3)

La teofilina, que tiene a las PDE como unas de sus dianas bioquímicas, además de su actividad dilatadora de los bronquios bien caracterizada, afecta a la vasculatura de pacientes que presentan una presión arterial pulmonar aumentada, suprime las respuestas celulares inflamatorias, e induce la apoptosis de eosinófilos Los sucesos adversos de la teofilina, del modo más corriente disritmias cardíacas y náuseas, son también mediados por inhibición de las PDE, conduciendo, sin embargo, a la investigación para descubrir agentes inhibidores más selectivos de las PDE, que sean capaces de suprimir tanto las funciones celulares inmunitarias *in vitro* como una inflamación pulmonar alérgica *in vivo* mientras que al mismo tiempo tengan perfiles mejorados de efectos colaterales Dentro de las vías respiratorias de pacientes que padecen de asma

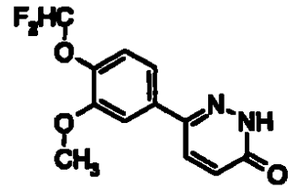
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y otras enfermedades obstructivas de las vías respiratorias, una de las PDE4 es la más importante de las isozimas PDE como una diana para el descubrimiento de fármacos a causa de su distribución en células de musculos lisos e inflamatorias de las vias respiratorias Varios agentes inhibidores de las PDE4 introducidos en el sector tecnológico hasta ahora han sido diseñados de manera tal que tengan un mejorado índice terapéutico concerniente a los efectos colaterales cardiovasculares, gastrointestinales y sobre el sistema nervioso central, que presentan las xantinas no selectivas antes mencionadas

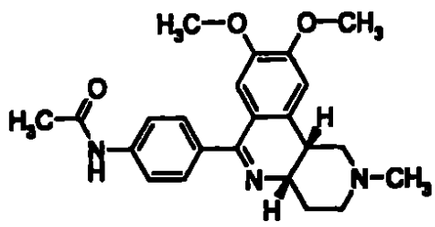
La obstrucción del flujo de aire y la inflamación de las vías respiratorias son características del asma así como de la COPD Mientras que el asma bronquial está caracterizado predominantemente por una inflamación eosinofílica, se manifiesta que los neutrófilos desempeñan un cometido principal en la patogénesis de la COPD Por lo tanto, las PDE que están implicadas en la relajación de los musculos lisos y son encontradas también en eosinófilos así como también en neutrófilos, constituyen probablemente un elemento esencial del progreso de ambas enfermedades Las PDE implicadas incluyen las PDE3 así como también las PDE4, y se han descubierto agentes inhibidores dilatadores de los bronquios que son dobles agentes inhibidores selectivos de las PDE3 y agentes inhibidores selectivos de las PDE3/4 Ejemplos de éstos son milrinona, que es un agente inhibidor selectivo de las PDE, así como zardaverina y benafentrina, ambos de los cuales son agentes inhibidores selectivos dobles de las PDE3/4, que se pueden representar por las Fórmulas (0 0 4), (0 0 5) y (0 0 6), respectivamente



Milrinona
(0 0 4)



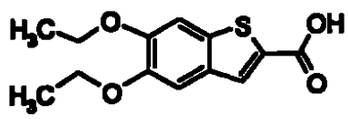
Zardaverina
(0 0 5)



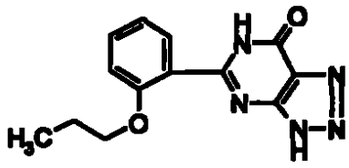
Benafentrina

(0 0 6)

Sin embargo, la benafentrina da como resultado una dilatación de los bronquios solamente cuando se administra por inhalacion, y la zardaverina produce solamente una dilatacion modesta y de corta duración de los bronquios La milrinona, un agente cardiotónico, induce una dilatación de los bronquios de corta duración y un pequeño grado de protección contra la constricción inducida de los bronquios, pero tiene señalados efectos desfavorables, p ej , taquicardia e hipotensión Se han obtenido también resultados insatisfactorios con un agente inhibidor débilmente selectivo de las PDE4, el tibenelast, y un agente inhibidor selectivo de las PDE5, el zaprinast, que se pueden representar por las Fórmulas (0 0 7) y (0 0 8)



Tibenelast
(0 0 7)



Zaprinast

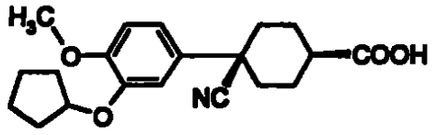
(0.0.8)

Se ha obtenido más éxito relativo en el sector tecnológico con el descubrimiento y el desarrollo de agentes inhibidores selectivos de las PDE4

In vivo, los agentes inhibidores de las PDE4 reducen el flujo entrante (influjo) de eosinófilos en los pulmones de animales estimulados por alergenos, al mismo tiempo que reducen también la constricción de los bronquios y la capacidad elevada de respuesta de los bronquios, que se produce después de un estímulo por alergenos Los agentes inhibidores de las PDE4 suprimen también la actividad de células inmunitarias, inclusive linfocitos T $CD4^+$, monocitos, células cebadas y basófilos, reducen el edema pulmonar;

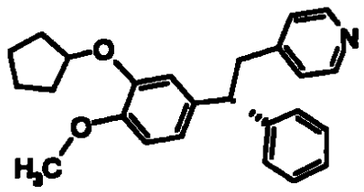
inhiben la neurotransmisión no colinérgica y no adrenérgica excitatoria (eNANC = de *excitatory nonadrenergic noncholinergic neurotransmission*), potencian la neurotransmisión no colinergica y no adrenergica inhibitoria (iNANC = de *inhibitory nonadrenergic noncholinergic neurotransmission*), reducen la mitogénesis de los musculos lisos de las vías respiratorias, e inducen una dilatación de los bronquios Los agentes inhibidores de las PDE4 suprimen también la actividad de un cierto numero de células inflamatorias asociadas con la patofisiología de la COPD, inclusive monocitos y macrófagos, linfocitos T $CD8^+$ y neutrófilos Los agentes inhibidores de las PDE4 reducen también la mitogénesis de los musculos lisos vasculares, e interfieren potencialmente con la capacidad de las células epiteliales de las vías respiratorias para generar mediadores pro-inflamatorios Mediante la puesta en libertad de proteasas neutras e hidrolasas ácidas a partir de sus gránulos, y la generación de especies con oxígeno reactivas, los neutrófilos contribuyen a la destrucción de los tejidos que está asociada con una inflamación crónica, y están implicados además en la patología de condiciones tales como enfisema

Agentes inhibidores selectivos de las PDE4 que se han descubierto hasta ahora que proporcionan ventajas terapéuticas e incluyen el SB-207,499, identificado como ARIFLO®, que se puede representar por la Fórmula (0 1 9)



SB-207,499 (0 1 9)

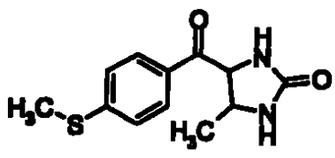
El SB-207,499, administrado por vía oral en dosificaciones de 5, 10 y 15 mg *b i d* (dos veces al día), ha producido aumentos significativos en el FEV_1 pasante (volumen de expiración forzada en 1 segundo) procedente de un placebo en la semana 2ª de un estudio que implica a un gran numero de pacientes Otro potente agente inhibidor selectivo de las PDE4, el CDP840, ha manifestado supresión de reacciones tardías a un alergeno inhalado después de 9,5 días de administración por vía oral en dosis de 15 y 30 mg en un grupo de pacientes con asma bronquial El CDP840 se puede representar por la Fórmula (0 0 9)

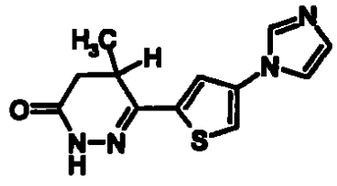


CDP840 (0 0 9)

Las PDE's se han investigado también como una terapia potencial de la enfermedad obstructiva de los pulmones, inclusive la COPD En un amplio estudio del SB-207,499 en pacientes con COPD, el grupo de pacientes que reciben 15 mg *b i d* han experimentado un mejoramiento progresivo en el FEV_1 pasante, alcanzando una diferencia media maxima comparada con un placebo de 160 ml en la semana 6ª, lo que representa un mejoramiento de 11% Véase la cita de Compton y colaboradores, "The efficacy of Anflo (SB207499), a second generation, oral PDE4 inhibitor, in patients with COPD" (La eficacia de Anflo, que es un agente inhibidor oral de las PDE4 de segunda generación, en pacientes con COPD), *Am J Respir Crit Care Med* **159**, 1999 Se ha observado que los pacientes con COPD grave tienen una hipertensión pulmonar, y se han conseguido disminuciones en la presión arterial pulmonar media en condiciones clínicas mediante administración por vía oral de los agentes inhibidores selectivos de las PDE3 milrinona y enoximona Se ha mostrado también que la enoximona reduce la resistencia de las vías respiratorias en pacientes hospitalizados con una COPD descompensada Véase la cita de Leeman y colaboradores, *Chest* **91** 662-6, 1987 Usando una inhibición selectiva de las PDE3 por motapizona y una inhibición selectiva de las PDE5 con zaprinast, se ha demostrado que la inhibición combinada de las PDE 3 y 5 ejerce una relajación de los anillos de arterias pulmonares, que corresponde ampliamente a la pauta de las isozimas PDE5, encontradas en el musculo liso de arterias pulmonares Véase Rabe y colaboradores, *Am J Physiol* **266** (LCMP 10) L536-L543, 1994 Las estructuras de la milrinona y del zaprinast se muestran anteriormente como las Fórmulas (0 0 4) y (0 0 8), respectivamente

Las estructuras de la enoximona y la motapizona se pueden representar por las Fórmulas (0 0 10) y (0 0 11), respectivamente



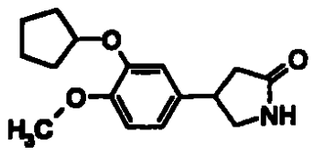


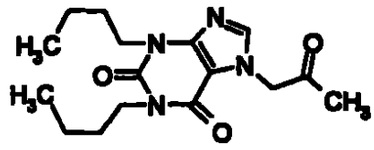
Enoximona (0 0 10)

Motapizona (0 0 11)

Los efectos de los agentes inhibidores de las PDE4 sobre diversas respuestas inflamatorias se pueden usar como bases para perfilar y seleccionar agentes inhibidores para estudios adicionales Estos efectos incluyen una elevación del nivel del cAMP y una

inhibición de la producción de superóxidos, una desgranulación, una quimiotaxis, y una liberación del factor de necrosis tumoral alfa (TNFα) en eosinófilos, neutrófilos y monocitos Los agentes inhibidores de las PDE4 pueden inducir emesis, es decir náuseas y vómitos, que, tal como se espera, es un efecto desfavorable El efecto desfavorable de una emesis resultó evidente cuando los agentes inhibidores de las PDE4 se investigaron en primer lugar para indicaciones del sistema nervioso central (SNC), tales como depresión, cuando se usaron rolipram y denbufilina en pruebas clínicas El rolipram y la denbufilina se pueden representar por las Fórmulas (0 0 12) y (0 0 13), respectivamente

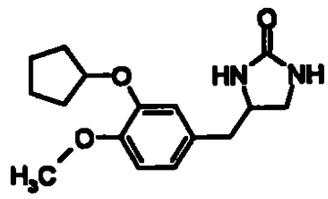




Rolipram (0 0 12)

Denbufilina (0 0 13)

El o los mecanismo(s) mediante el o los cuales los agentes inhibidores de las PDE4 pueden inducir potencialmente una emesis es o son incierto(s), pero un estudio del agente inhibidor de las PDE4 Ro-20-1724, sugiere que las náuseas y los vómitos se median por lo menos parcialmente por los centros de emesis en el cerebro Los sucesos desfavorables gastrointestinales pueden ser causados por efectos locales, p ej , el rolipram es un estimulador muy potente de la secreción de ácidos a partir de células parietales gástricas, y el resultante ácido en exceso, mediante producción de una irritación local, puede exacerbar las perturbaciones gastrointestinales El Ro-20-1724 se puede representar por la Fórmula (0 0 14)

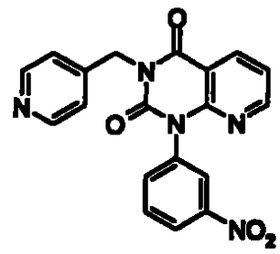


Ro-20-1724 (0.0 14)

Los esfuerzos realizados para minimizar o eliminar los efectos desfavorables antes mencionados, que algunas veces están asociados con los agentes inhibidores de las

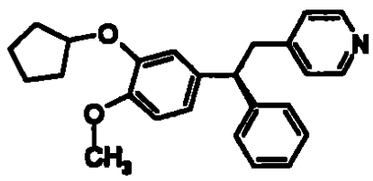
PDE4, han incluido crear agentes inhibidores que no penetran en el sistema nervioso central, y administrar los agentes inhibidores de las PDE4 por inhalación en lugar de por vía oral

Con respecto a los subtipos de las PDE4, A, B, C y D, se ha encontrado que la PDE4C es usualmente menos sensible a todos los agentes inhibidores, mientras que, con respecto a los subtipos A, B y D todavía no hay ninguna evidencia manifiesta de especificidad de un agente inhibidor, que es definida como una diferencia por un factor de 10 en los valores de IC_{50} (concentración inhibidora del 50%) Mientras que la mayor parte de los agentes inhibidores, especialmente el RS-25,344, son más potentes contra las PDE4D, esto no equivale a una selectividad La RS-25,344 se puede representar por la Fórmula (0 0 15)



RS-25,344 (0.0 15)

Por otra parte, hay un efecto estereoselectivo sobre la elevación del nivel del cAMP en una gama de tipos celulares, lo que ha sido demostrado por los resultados de una investigación del CDP840, mostrado anteriormente como la Fórmula (0 0 9), y de su enantiómero menos activo CT-1731, que está representado por la Fórmula (0 0 16)



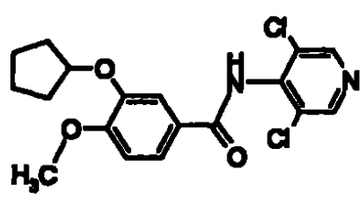
CT-1731 (0 0 16)

Se ha conocido desde hace algun tiempo que el rolipram tenía la capacidad de interactuar con un sitio de fijación de alta afinidad sobre membranas cerebrales, y posteriormente se demostró en el sector tecnológico que este sitio de fijación del rolipram con alta afinidad (S_r) que es distinto del sitio catalítico (S_c), existe en una PDE4A recombinante truncada y en una PDE4B recombinante de plena longitud Más recientemente, el S_r ha sido identificado en la totalidad de los cuatro subtipos de las PDE4 Véase Hughes y colaboradores *Drug Discovery Today* 2(3) 89-101, 1997 La

presencia del S_r manifiesta tener un profundo efecto sobre la capacidad de ciertos agentes inhibidores, tales como rolipram y RS-25,344, para inhibir la actividad catalítica de las isozimas PDE4

El impacto de los residuos sobre la fijación de un agente inhibidor es también importante Se ha mostrado que un unico reemplazo de aminoácidos (de alanina por aspartato) en la región catalítica de la PDE4B es crítica para la inhibición por rolipram, y esto manifiesta también ser un efecto de una clase, puesto que los agentes inhibidores afines RP-73,401 y Ro-20-1724 pierden también potencia en la enzima mutante No obstante, el cometido de la fijación de agentes inhibidores al S_c o al S_r, en términos de elevación del nivel de cAMP y de inhibición de las respuestas celulares, no se comprende totalmente en el momento actual

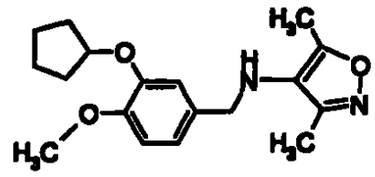
Se ha encontrado, en estudios con cobayas, que el RP-73,401 es activo en (1) la inhibicion de la eosinofilia pulmonar inducida por antígenos y de la peroxidasa de eosinófilos (EPO) Banner, K H , "The effect of selective phosphodiesterase inhibitors in comparison with other anti-asthma drugs on allergen-induced eosinophilia in guinea-pig airways" (El efecto de agentes inhibidores selectivos de fosfodiesterasas en comparación con otros fármacos anti-asmáticos sobre la eosinofilia inducida por alergenos en vías respiratorias de cobayas), *Pulm Pharmacol* 8 37-42, 1995, (2) la eosinofilia por lavado bronquio-alveolar (BAL, de bronchoalveolar lavage), inducida por antígenos Raeburn y colaboradores, "Anti-inflammatory and bronchodilator properties of RP73401, a novel and selective phosphodiesterase Type IV inhibitor" (Propiedades anti-inflamatorias y dilatadoras de los bronquios del RP73401, que es un nuevo y selectivo agente inhibidor de las fosfodiesterasas del Tipo IV), *Br J Pharmacol* 113 1423-1431, 1994, (3) la eosinofilia de las vías respiratorias, inducida por antígenos e hiper-capacidad de respuesta de las vías respiratorias (AHR, de *airway hyper-responsiveness*) inducida por el factor de activación de plaquetas (PAF, de *platelet activating factor*) y por ozono, Karlsson y colaboradores "Anti-inflammatory effects of the novel phosphodiesterase IV inhibitor RP73401" (Efectos anti-inflamatorios del nuevo agente inhibidor de las fosfodiesterasas IV RP73401), *Int Arch, Allergy Immunol* 107 425-426, 1995, y (4) la eosinofilia pleural inducida por IL-5 El desarrollo del RP-73,401, piclamilast, ha sido interrumpido El piclamilast se puede representar por la Fórmula (0 0 17)



Piclamilast (RP-73,401) **(0.0 17)**

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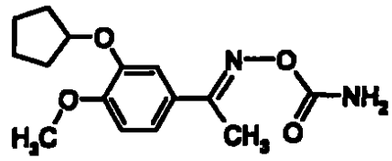
Una serie de compuestos afines, que está representada por los RPR-132294 y RPR-132703, de los que en estudios con ratas se ha demostrado que tienen actividad en la inhibición de un espasmo bronquial inducido por antígenos, Escott y colaboradores, "Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic ratio in rats and dogs" (Delineación del perfil farmacológico de los agentes inhibidores de las fosfodiesterasas 4 (PDE4) y análisis de la relación terapéutica en ratas y perros), *Br J Pharmacol* **123** (Proc Suppl) 40P, 1998, y Thurairatnam y colaboradores, "Biological activity and side effect profile of RPR-132294 y RPR-132703 - novel PDE4 inhibitors" (Actividad biológica y perfil de efectos colaterales de los RPR-132294 y RPR-132703 - nuevos agentes inhibidores de las PDE4), *XVth EFMC Int Symp Med Chem*, 1998 La estructura del RPR-132294 se puede representar por la Fórmula (0 0 18)



RPR-132294

(0 0 18)

Otro compuesto cuyo desarrollo ha sido interrumpido es el WAY-PDA-641, filaminast, del que en estudios con perros se ha encontrado que es activo en la inhibición de la constricción de los bronquios, inducida por serotonina El filaminast se puede representar por la Fórmula (0 0 19)



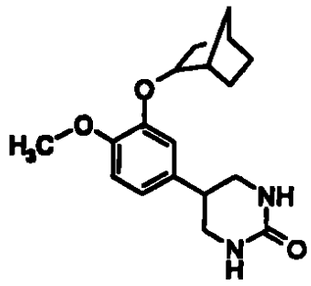
Filaminast (WAY-PDA-641)

(0 0 19)

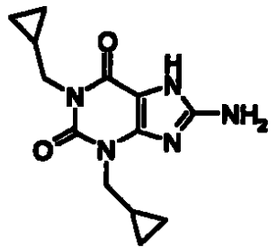
Se ha sugerido en el sector tecnológico que los agentes inhibidores de las PDE4 que tienen una alta afinidad junto al S_r se pueden correlacionar con una emesis y una secreción incrementada de ácidos gástricos Los RS-23,544, RP-73,401 y CP-80,633 provocan una emesis y tienen una alta afinidad junto al S_r. Los CDP840 y SB-207,499 tienen una afinidad comparativamente baja junto al S_r, pero el CDP840 tiene una potencia significativamente mayor junto al S_c que la que posee el SB-207,499 Se ha demostrado que el CDP840 proporciona una importante inhibición de la respuesta en

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fase tardía en el tratamiento del asma sin ninguno de los efectos desfavorables de náuseas y dolor de cabeza Otro agente inhibidor de las PDE4, del que se ha mostrado que tiene sucesos desfavorables de nauseas y vómitos es el BRL-61,063, también citado como cipamfilina, que se describe seguidamente con más detalle El desarrollo del CDP840 ha sido interrumpido mientras que el CP-80,633, atizoram, ha sido adelantado a los estudios clínicos Los CP-80 633 y BRL-61,063 pueden ser representados por las Fórmulas (0 0 20) y (0 1 12), respectivamente

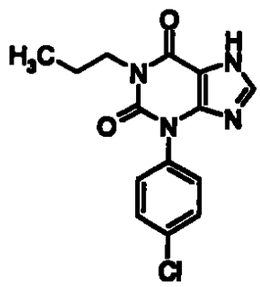


Atizoram (CP-80,633)
(0 0 20)



Cipamfilina (BRL-61,063)
(0 1 12)

Otro compuesto que se encuentra en fase de desarrollo es el LAS-31025, la arofilina, de la que en estudios con cobayas se ha encontrado que es activa en la inhibición de la constriccion de los bronquios, inducida por antígenos, Beleta, B J , "Characterization of LAS31025 a new selective PDE IV inhibitor for bronchial asthma" (Caracterización del LAS31025 un nuevo agente inhibidor selectivo de las PDE IV para el asma bronquial), *Third Int Conf On Cyclic Nucleotide Phosphodiesterase From Genes to Therapies*, Glasgow Reino Unido, 1996, Resumen 73 El LAS-31025, arofilina, se puede representar por la Fórmula (0 0 21)



Arofilina (LAS-31025)
(0 0 21)

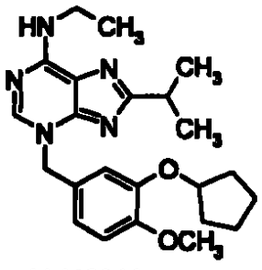
Un cierto numero de agentes inhibidores de las PDE4 han sido avanzados en su desarrollo Por ejemplo, los efectos del V-11294A sobre la liberación *ex vivo* de TNF

00309 305

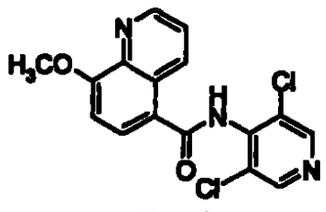
estimulada por LPS y la proliferación de linfocitos inducida por PHA, se han determinado en un estudio aleatorizado, doble ciego, controlado por placebo, en el que se ha encontrado que una dosis oral de 300 mg es eficaz para reducir los niveles de TNF y la proliferación de linfocitos, Landells y colaboradores, "Oral administration of the phosphodiesterase (PDE) 4 inhibitor, V11294A, inhibits ex-vivo agonist-induced cell activation" (La administración por vía oral del agente inhibidor de las fosfodiesterasas (PDE) 4, V11294A, inhibe la activación celular *ex vivo* inducida por agentes agonistas), *Eur Resp J* **12** (Supl 28) 362s, 1998, y Gale y colaboradores, "Pharmacodynamic-pharmacokinetic (PD/PK) profile of the phosphodiesterase (PDE) 4 inhibitor, V11294A, in human volunteers" (perfil farmacodinámico-farmacocinético (PD/PK) del agente inhibidor de las fosfodiesterasas (PDE) 4 V11294A, en voluntarios humanos), *Am J Respir Crit Care Med*, **159** A611, 1999

El compuesto D4418 ha sido administrado a voluntarios sanos en un estudio en Fase I controlado por placebo, aleatorizado en una dosis unica en escalamiento, Montana y colaboradores, "Activity of D4418, a novel phosphodiesterase 4 (PDE4) inhibitor, effects in cellular and animal models of asthma and early clinical studies" (Actividad de D4418, un nuevo agente inhibidor de las fosfodiesterasas 4 (PDE4), efectos en modelos celulares de animales con asma y estudios clínicos tempranos), *Am J Respir Crit Care Med* **159** A108, 1999 El D4418 es un agente inhibidor de las PDE4 moderadamente potente con un valor de IC_{50} de 200 nM Este compuesto presenta una buena absorción oral, una dosis de 200 mg proporciona una C_{max} en plasma de 1,4 µg/ml El D4418 ha sido interrumpido en su desarrollo debido a su potencia moderada, y ha sido reemplazado por el candidato al desarrollo preclínico D4396

Los V-11294A y D4418 se pueden representar por las Fórmulas (0 0 22) y (0 0 23), respectivamente



V-11294A
(0.0.22)

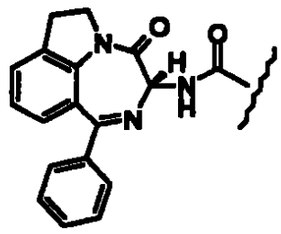


D4418

(0 0.23)

Otro compuesto el CI-1018, ha sido evaluado en 54 individuos, y no se informó de ningun suceso desfavorable en dosis hasta de 400 mg, Pruniaux y colaboradores,

"The novel phosphodiesterase inhibitor CI-1018 inhibits antigen-induced lung eosinophilia in sensitized brown-norway rats - comparison with rolipram" (El nuevo agente inhibidor de las fosfodiesterasas, CI-1018, inhibe una eosinofilia pulmonar inducida por antígenos en ratas noruegas pardas, comparación con rolipram), *Inflammation* S-04-6, 1999 Se ha demostrado que el CI-1018 tiene una buena biodisponibilidad por vía oral (57% en una rata) y una buena potencia oral con una ED_{50} (dosis eficaz del 50%) de 5 mg/kg en la misma especie El CI-1018 es un agente inhibidor relativamente débil de las PDE4 con una IC_{50} de 1,1 µm en células U937 El CI-1018 ha sido también identificado como, o asociado con una estructura tan estrechamente relacionada con el PD-168787, que se ha demostrado en estudios con ratas que presenta actividad en la inhibición de eosinofilia inducida por antígenos, Pascal y colaboradores, "Synthesis and structure-activity relationships of 4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]-diazepino[6,7,1-hi]indolines novel PDE4 inhibitors" (Síntesis y relaciones de actividad y estructura de las 4-oxo-1-fenil-3,4,6,7-tetrahidro-[1,4]-diazepino[6,7,1-hi] nuevos agentes inhibidores de las PDE4), *215th ACS* Dallas, EE UU , MEDI 50, 1998 Las estructuras infendas para los CI-1018 y PD-168787 pertenecen a una clase de diazepinonas cuyo núcleo puede ser representado por la Fórmula (0 0 24)

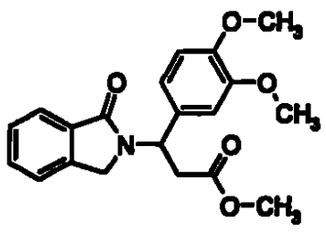


(0.0.24)

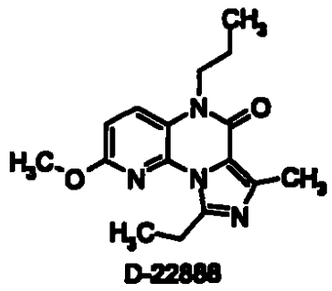
Los compuestos antes mencionados han sido también evaluados en modelos con animales que demuestran su actividad en la inhibición de las PDE4 Por ejemplo, se ha encontrado en estudios con cobayas, que el V-11294A es activo en la inhibición de la constricción de los bronquios, inducida por antígenos, Cavalla y colaboradores, "Activity of V-11294A, a novel phosphodiesterase 4 (PDE4) inhibitor, in cellular and animal models of atshma" (La actividad del V-11294A, que es un nuevo agente inhibidor de las fosfodiesterasas 4 (PDE4), en modelos celulares y de animales con asma), *Amer J Respir Crit Care Med* 155 A660, 1997 Se ha encontrado, en estudios con cobayas que el D4418 es activo en la inhibición de la constricción de los bronquios en fases temprana y tardía inducida por antígenos y la eosinofilia por BAL, Montana y colaboradores, *ibid* Se ha encontrado, en estudios con ratas, que el CI-1018 es activo en la inhibición de la eosinofilia inducida por antígenos, Burnouf y colaboradores, "Pharmaco-

logy of the novel phosphodiesterase Type 4 inhibitor, CI-1018" (Farmacología del nuevo agente inhibidor de las fosfodiesterasas del Tipo 4, CI-1018), *215th ACS Nat Meeting*, MEDI 008, 1998

Otros compuestos que han sido adelantados en su desarrollo incluyen los CDC-3052, D-22888, YM-58997, y roflumilast, que se pueden representar por las Fórmulas (0 0 27), (0 0 28), (0 0 29) y (0 0 30), respectivamente

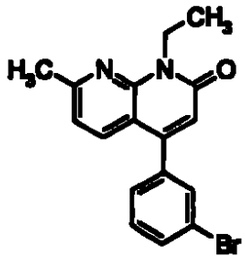


CDC-3052
(0 0.27)

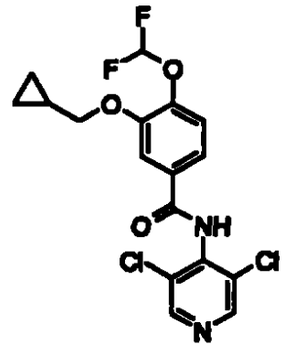


D-22888

(0.0.28)



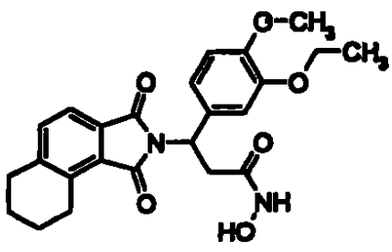
YM-58977
(0 0.29)



Roflumilast

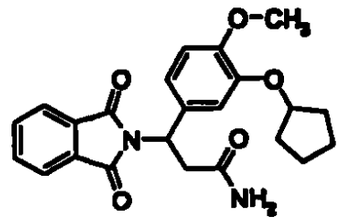
(0.0.30)

El CDC-3052 ha sido retirado del desarrollo pero ha sido sucedido por agentes inhibidores muy potentes de las PDE4, tales como el compuesto representado por la Fórmula (0 0 31) y por el compuesto anti-inflamatorio CDC-801 representado por la Fórmula (0 0 32), respectivamente



(0 0.31)

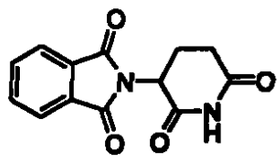
CDC-801



(0.0.32)

Se ha informado de que el compuesto de Fórmula (0 0 32) tiene unos valores de la IC_{50} de 42 pM y 130 nM como un agente inhibidor de las PDE4 y de la producción de TNF, respectivamente, Muller y colaboradores, "N-Phthaloyl beta-aryl-beta-amino derivatives Potent TNF-alpha and PDE4 inhibitors" (Derivados de N-ftaloil-beta-aril-beta-amino potentes agentes inhibidores de TNF-alfa y PDE4), *217th American Chemical Society*, Annheim, Alemania, MEDI 200 1999, y Muller y colaboradores, "Thalidomide analogs and PDE4 inhibition" (Compuestos análogos a talidomida e inhibición de las PDE4), Bioorg Med Chem Letts 8 2669-2674, 1998

El CDC-801 se encuentra entre una serie de compuestos basados en la talidomida y ha sido desarrollado principalmente para mejorar la actividad inhibidora del TNF-α que presenta la talidomida para el tratamiento de enfermedades autoinmunitarias La talidomida se puede representar por la Fórmula (0 0 33)



Talidomida (0 0 33)

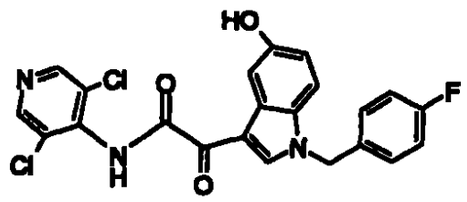
El CDC-801 ha sido estudiado tambien para el tratamiento de la enfermedad de Crohn, que es una enfermedad inflamatoria granulomatosa crónica de etiología desconocida que implica comúnmente al íleon terminal, con cicatrización y espesamiento de la pared intestinal, lo cual conduce frecuentemente a una obstrucción intestinal y a la formación de fístulas y abscesos La enfermedad de Crohn tiene una alta tasa de reaparición después del tratamiento

El YM-58997 tiene un valor de IC_{50} de 1,2 nM contra las PDE4 Takayama y colaboradores, "Synthetic studies on selective Type IV phosphodiesterase (PDE IV) inhibitors" (Estudios de síntesis sobre agentes inhibidores selectivos de las fosfodiesterasas del Tipo IV (PDE IV), *214th American Chemical Society*, Las Vegas, EE UU , MEDI 245, 1997 El YM-58997 tiene una estructura de 1,8-naftindin-2-ona, al igual que el YM-976

El roflumilast ha sido estudiado para el tratamiento tanto de la COPD como del asma, y tiene un valor de IC_{50} de 3,5 nM en modelos normalizados de cobayas *in vitro* con asma El uso del roflumilast y de un agente tensioactivo para el tratamiento del síndrome de ahogo respiratorio de adultos (ARDS = de *adult respiratory distress syndrome*) también ha sido descrito

Se ha mostrado que el AWD-12,281, que ahora es designado como loteprednol,

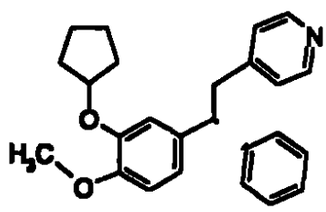
es activo en un modelo con ratas de rinitis alérgica, tal como se describe más adelante en una sección que se relaciona con la rinitis alérgica y del uso de los agentes inhibidores de las PDE4 para tratarla El AWD-12,281 se puede representar por la Fórmula (0 0 34)



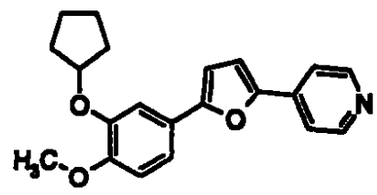
Lotaprednol (AWD-12,281)

(0.0.34)

Los compuestos relacionados en su estructura con el CDP840, que se muestra más arriba como de la Fórmula (0 0 9), incluyen al L-826,141, del que se ha informado que tiene actividad en un modelo con ratas de bronquitis, Gordon y colaboradores, "Anti-inflammatory effects of a PDE4 inhibitor in a rat model of chronic bronchitis" (Efectos anti-inflamatorios de un agente inhibidor de las PDE4 en un modelo con ratas de bronquitis crónica), *Am J Respir Crit Care Med* 159 A33, 1999 Otro de dichos compuestos está relacionado en su estructura con los informados en la cita de Perrier y colaboradores, "Substituted furans as inhibitors of the PDE4 enzyme" (Furanos sustituidos como agentes inhibidores de la enzima PDE4), *Bioorg Med Chem Letts* 9 323-326, 1999, y es representado por la Fórmula (0 0 35)



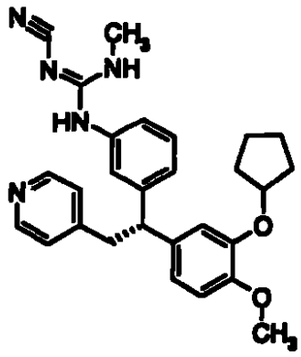
CDP840
(0.0 9)



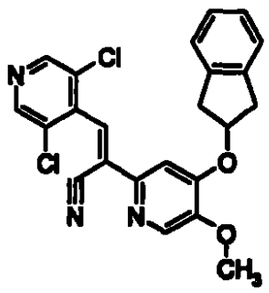
(0.0.35)

Otros compuestos, de los que se ha encontrado que son agentes inhibidores muy potentes de las PDE4, son los representados por las Fórmulas (0 0 36), (0 0 37) y (0 0 38)

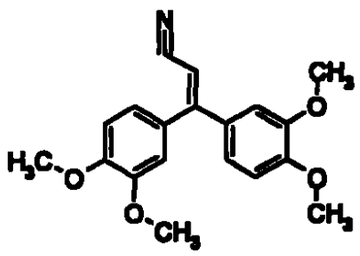
0031 310



(0.0.36)

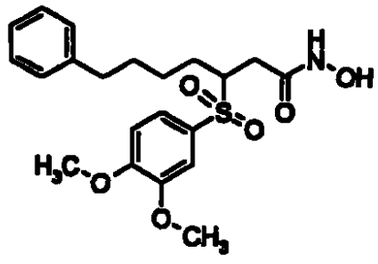


(0.0 37)

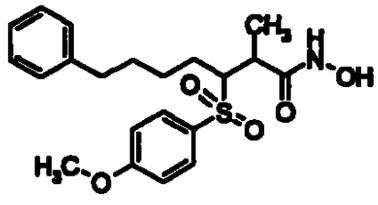


(0.0.38)

Se han creado compuestos que combinan en una unica molécula las actividades inhibidoras de las PDE4 y de la metaloproteinasa de matriz (MMP, de *matrix metalloproteinase*), Groneberg y colaboradores, "Dual inhibition of phosphodiesterase 4 and matrix metalloproteinases by an (arylsulfonyl)hydroxamic acid template" (Inhibición doble de las fosfodiesterasas 4 y de las metaloproteinasas de matriz por un molde de ácido (aril-sulfonil)hidroxámico), *J Med Chem* 42(4) 541-544, 1999 Dos ejemplos de dichos compuestos se representan por las Fórmulas (0 0 39) y (0 0 40)



(0 0.39)

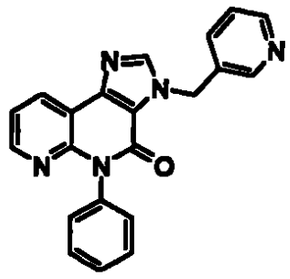


(0 0.40)

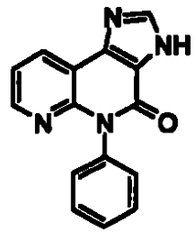
Los respectivos valores de IC_{50} para los compuestos de Fórmulas (0 1 36) y (0 1 37) obtenidos usando un análisis de las PDE4 de macrófagos de cobayas fueron de 1 nM y 30 nM

Se ha mostrado en estudios con cobayas que los compuestos identificados como KF19514 y KF17625 tienen actividad en la inhibición de las siguientes enfermedades constricción de los bronquios inducida por histamina e inducida por antígenos, eosinofilia pulmonar inducida por el PAF y eosinofilia por BAL inducida por antígenos, AHR inducida por acetil-colina (ACh), eosinofilia y neutrofilia por BAL inducidas por el PAF, y AHR, un espasmo bronquial inducido por antigenos, y constricción anafiláctica de los bronquios, Fujimura y colaboradores, "Bronchoprotective effects of KF-19514 and cilostazol in

guinea-pigs *in vivo*" (Efectos protectores de los bronquios de los KF-19514 y cilostazol en cobayas *in vivo*), *Eur J Pharmacol* 327 57-63, 1997, Manabe y colaboradores, *ibid*, Manabe y colaboradores, "KF19514, a phosphodiesterase 4 and 1 inhibitor, inhibits PAF-induces lung inflammatory responses by inhaled administration in guinea-pigs" (El KF19514, un agente inhibidor de las fosfodiesterasas 4 y 1, inhibe las respuestas inflamatorias pulmonares inducidas por el PAF mediante administración por inhalación a cobayas), *Int Arch Allergy Immunol* 144 389-399, 1997, Suzuki y colaboradores, "New bronchodilators, 3 Imidazo[4,5-c][1,8]naphthyridin-4(5H)-ones" (Nuevos dilatadores de los bronquios, 3 Imidazo[4,5-c][1,8]naftindin-4(5H)-onas) *J Med Chem* 35 4866-4874, 1992, Matsuura y colaboradores, "Substituted 1,8-naphthyridin-2(1*H*)-ones as selective phosphodiesterase IV inhibitors" (1,8-Naftindin-2(1*H*)-onas sustituidas como agentes inhibidores selectivos de las fosfodiesterasas IV), *Biol Pharm Bull* 17(4) 498-503, 1994, y Manabe y colaboradores, "Pharmacological properties of a new bronchodilator, KF17625" (Propiedades farmacológicas de un nuevo agente dilatador de los bronquios, KF17625), *Jpn J Pharmacol* 58 (Suppl 1) 238P, 1992 Los KF19514 y KF17625 se pueden representar por las Fórmulas (0 0 41) y (0 0 42)



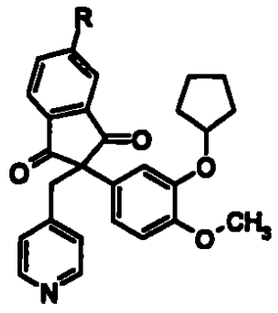
KF19514
(0 0 41)



KF17625
(0 0.42)

La potencia informada y la ausencia de emesis en una serie de indanodionas sugiere que es errónea la hipótesis de que éstas tienen efectos colaterales relacionados, tales como emesis, con la relación de afinidad para las enzimas PDE4 con respecto a la existente para el sitio de fijación de rolipram con alta afinidad (HARBS = de *high affinity rolipram binding site*) Dichas indanodionas pueden ser representadas por las Fórmulas (0 0 43) y (0 0 44)

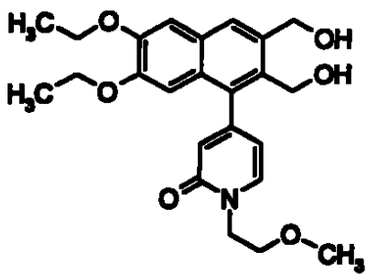
312



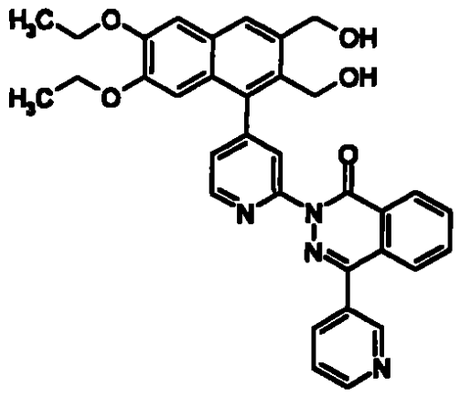
R = benciloxi (0 0 43)

R = [1 4']-piperidinil-1'-carboniloxi (0 0 44)

Los agentes inhibidores de las PDE4 que se han creado hasta el momento actual entran dentro de un importante numero de diferentes clases en términos de sus estructuras químicas Tales clases han sido tan diversas como las fenantridinas y las naftridinas Una clase de agentes inhibidores de las PDE4 son lignanos tales como el T-440, del que se ha demostrado que tiene actividad en la inhibición de lo siguiente - constricción de los bronquios en fase temprana, inducida por antigenos, histamina, LTD4, U-46619, Ach, neurocinina A y endotelina-1, constricción de los bronquios en fase temprana y en fase tardia inducida por alergenos, y eosinofilia por BAL, y AHR inducida por ozono y lesión epitelial de las vias respiratorias La optimización de la potencia inhibidora de las PDE4 que poseen dichos compuestos ha conducido al descubrimiento del T-2585, que es uno de los agentes inhibidores de las PDE4 más potentes que se hayan descrito hasta la fecha con un valor de IC_{50} de 0,13 nM contra las PDE4 de pulmones de cobayas Los T-440 y T-2585 se pueden representar por las Fórmulas (0 0 45) y (0 0 46)



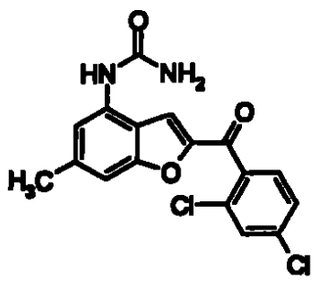
T-440
(0 0.45)



T-2585 (0.0.46)

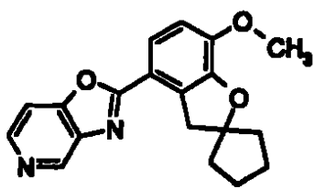
Otra clase de agentes inhibidores de las PDE4 consiste en benzofuranos y benzotiofenos En particular, se han utilizado anillos de furano y cromano como sustitutos

subrogados del ciclopentil-éter del farmacóforo rolipram Un ejemplo de dicho compuesto es uno que aparentemente está relacionado en su estructura con el BAY 19-8004, y que se puede representar por la Fórmula (0 0 47)



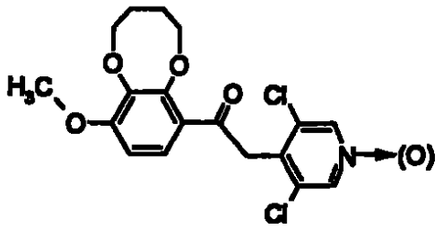
(0.0.47)

Se ha informado de que otro compuesto del tipo de benzofurano tiene un valor de IC_{50} de 2,5 nM y se puede representar por la Fórmula (0 0 48)



(0.0.48)

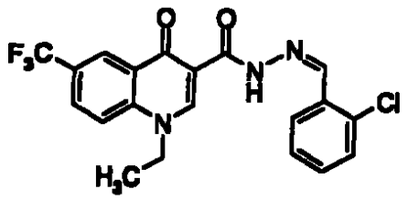
Un compuesto con una estructura relacionada que, sin embargo, no es un benzofurano, está caracterizado por un anillo de dioxicina condensado y se informa de que produce una inhibición casi completa de las PDE4 traqueal canina a 100 nM Este compuesto se puede representar por la Fórmula (0 0 49)



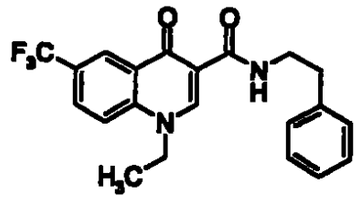
(0 0.49)

Las quinolinas y quinolonas constituyen una clase adicional de estructuras de agentes inhibidores de las PDE4 y sirven como sustitutos subrogados para el resto de catecol del rolipram Este compuesto y dos compuestos de estructura similar se pueden

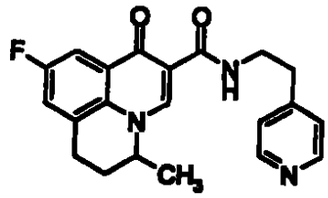
representar por las Fórmulas (0 0 50), (0 0 51) y (0 0 52)



(0 0 50)

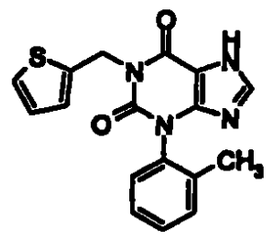


(0 0 51)



(0 0 52)

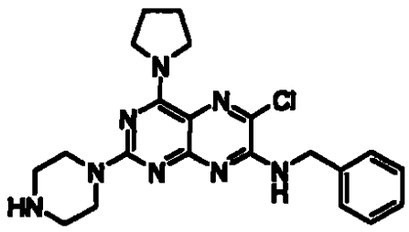
Las purinas, xantinas y ptendinas representan todavía otras clases adicionales de compuestos químicos a los que pertenecen los agentes inhibidores de las PDE4 hasta ahora descritos en el sector tecnológico El compuesto V-11294A descrito más arriba y representado por la Fórmula (0 0 22), es una purina Se ha descrito en el sector tecnológico un agente inhibidor de las PDE4, que es un compuesto de xantina, que es la clase de compuestos a la que pertenece la teofilina, Montana y colaboradores, "PDE4 inhibitors, new xanthine analogues" (Agentes inhibidores de las PDE4, nuevos compuestos análogos a xantina), *Bioorg Med Chem Letts* 8 2925-2930, 1998 El compuesto de xantina se puede representar por la Fórmula (0 0 54)



(0.0 54)

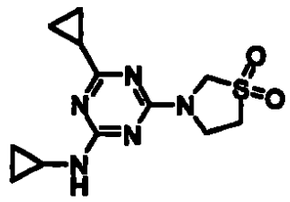
De un potente agente inhibidor de las PDE4, que pertenece a la clase de compuestos de ptendina, se ha demostrado que tiene un valor de IC_{50} de 16 nM contra una PDE4 derivada de células tumorales y que inhibe el crecimiento de células tumorales en concentraciones del orden de micromoles, Merz y colaboradores, "Synthesis of 7-Benzylamino-6-chloro-2-piperazino-4-pyrrolidinopteridine and novel derivatives free of positional Isomers Potent inhibitors of cAMP-specific phosphodiesterase and of

malignant tumor cell growth" (Síntesis de la 7-bencilamino-6-cloro-2-piperazino-4-pirrolidino-pteridina y de nuevos derivados exentos de isómeros de posición Potentes agentes inhibidores de una fosfodiesterasa específica para el cAMP y del crecimiento de células tumorales malignas), *J Med Chem* 41(24) 4733-4743, 1998 El agente inhibidor de las PDE4 del tipo de pteridina se puede representar por la Fórmula (0 0 55)

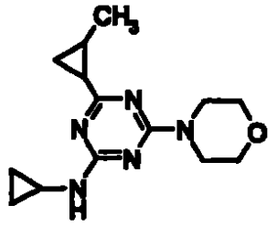


(0.0.55)

Las triazinas representan todavía una clase adicional de compuestos químicos, a la que pertenecen agentes inhibidores de las PDE4 que han sido descritos con anterioridad en el sector tecnológico Se han descrito dos de tales triazinas, que presentan actividad dilatadora de los bronquios y son potentes agentes relajantes en un modelo de tráquea de cobaya Estos compuestos, que se pueden representar por las Fórmulas (0 0 56) y (0 0 57) siguientes, son también agentes inhibidores moderadamente potentes de las PDE4, con unos valores de IC_{50} de 150 y 140 nM, respectivamente



(0.0 56)

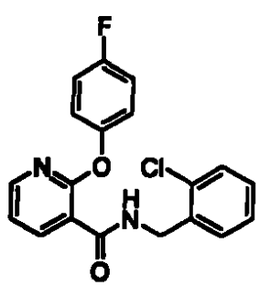


(0.0 57)

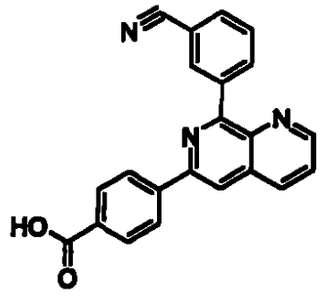
Una triazina que tiene una estructura de la que se supone está estrechamente relacionada con la de los compuestos de Fórmulas (0 0 56) y (0 0 57), es el UCB-29936, del que se ha demostrado que tiene actividad en un modelo con murinos de choque séptico, Danhaive y colaboradores, "UCB29936, a selective phosphodiesterase Type IV inhibitor, therapeutic potential in endotoxic shock" (UCB29936, un agente inhibidor selectivo de las fosfodiesterasas del Tipo IV, potencial terapéutico en el choque endotóxico), *Am J Respir Crit Care Med* 159 A611, 1999

Se han hecho también esfuerzos en el sector tecnológico para mejorar la

selectividad de los agentes inhibidores de las PDE4 con respecto a los subtipos A hasta D descritos más arriba Hay actualmente cuatro isoformas (subtipos) conocidas de la isoenzima PDE4, que abarcan siete variantes de empalme, que también se describen más arriba El ácido ribonucleico mensajero (ARNm) de la isoforma PDE4D es expresado en células inflamatorias tales como neutrófilos y eosinófilos, y se ha sugerido en el sector tecnológico que los agentes inhibidores selectivos D de la PDE4 proporcionarán una buena eficacia clínica con reducidos efectos colaterales Ha sido descrito un derivado de nicotinamida que presenta selectividad para la inhibición de la isoforma PDE4D, en el documento WO 98/45268, al igual que un derivado de naftiridina del que se informa que es un agente inhibidor selectivo de las PDE4D en el documento WO 98/18796 Estos compuestos se pueden representar por las Fórmulas (0 0 58) y (0 0 59), respectivamente

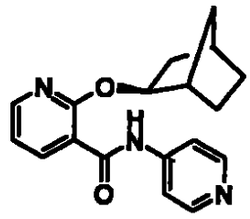


(0 0 58)

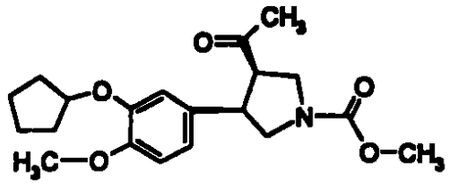


(0 0 59)

Se ha descrito en el sector tecnológico otro compuesto de nicotinamida, que puede ser util en el tratamiento de enfermedades del SNC tales como esclerosis multiple, documento de patente de Gran Bretaña GB-2327675, y se ha descrito en el sector tecnológico un derivado de rolipram que es un agente inhibidor de las PDE4 que se fija con igual afinidad tanto a los sitios catalíticos como a los sitios de HARB en una PDE4B2B humana, Tian y colaboradores "Dual inhibition of human Type 4 phosphodiesterase isostales by (R,R)-(+/-)-methyl-3-acetyl-4-[3-(cicIopentyloxy)-4-methoxyphenyl]-3-methyl-1-pyrrolidine carboxylate" (Inhibición doble de isostatos de las fosfodiesterasas del Tipo 4 humanas por el (R,R)-(+/-)-metil-3-acetil-4-[3-(ciclopentiloxi)-4-metoxi-fenil]-3-metil-1-pirrolidina-carboxilato de metilo), *Biochemistry* 37(19) 6894-6904, 1998 El derivado de nicotinamida y el derivado de rolipram se pueden representar por las Fórmulas (0 0 60) y (0 0 61), respectivamente



(0 0 60)

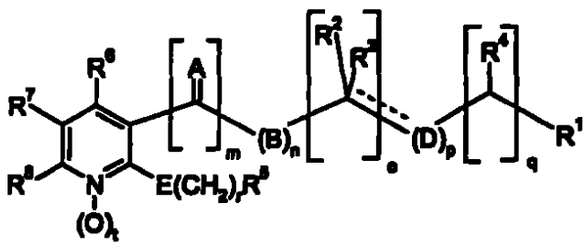


(0.0 61)

Una información adicional de antecedentes, que concierne a isozimas PDE4 selectivas se puede encontrar en publicaciones disponibles en el sector tecnológico, p ej , Norman, "PDE4 inhibitors 1999" (Agentes inhibidores de las PDE4 1999), *Exp Opin Ther Patents* 9(8) 1101-1118, 1999 (Ashley Publications Ltd), y Dyke y Montana, "The therapeutic potential of PDE4 inhibitors" (El potencial terapéutico de los agentes inhibidores de las PDE4), *Exp Opin Invest Drugs* 8(9) 1301-1325, 1999 (Ashley Publications Ltd)

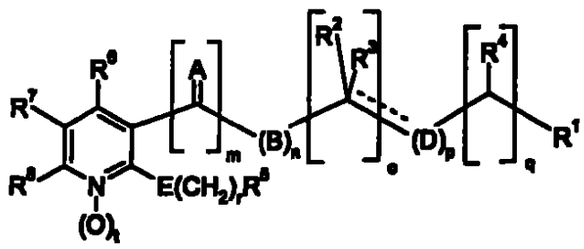
3.0 DESCRIPCIÓN DEL ESTADO DE LA TECNICA

El WO 98/45268 (Marfat y colaboradores), publicado el 15 de Octubre de 1998, describe derivados de nicotinamida que tienen actividad como agentes inhibidores selectivos de la isozima PDE4D Estos agentes inhibidores selectivos son representados por la Fórmula (0 1 1)



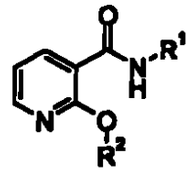
(0 1 1)

El documento de patente de los EE UU US 4 861 891 (de Saccomano y colaboradores), expedido el 29 de Agosto de 1989, describe compuestos de nicotinamida que actuan como agentes inhibidores de las fosfodiesterasas de cAMP independientes del calcio, y que son utiles como agentes antidepresivos, de Fórmula (0 1 2)



(0 1 1)

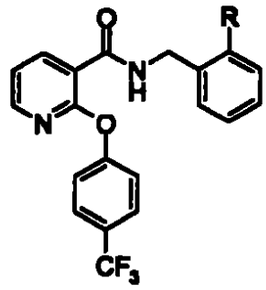
El nucleo de nicotinamida de un compuesto típico descrito en esta patente está enlazado directamente al grupo R^1, que se define como 1-piperidilo, 1-(3-indolil)etilo, alquilo C_1-C_4, fenilo, 1-(1-fenil-etilo), o bencilo opcionalmente mono-sustituido con metilo, metoxi, cloro o fluoro El sustituyente R^2 es biciclo[2 2 1]hept-2-ilo o



(0.1.2)

en que Y es H, F ó Cl, y X es H, F, Cl, OCH_3, CF_3, CN, COOH -C(=O)-alcoxi (C_1-C_4), $NH(CH_3)C(=O)$-(metil-carbamoílo) ó $N(CH_3)_2C(=O)$-(dimetil-carbamoílo)

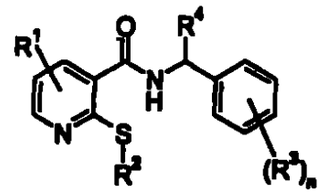
El documento US-4 692 185 (de Michaely y colaboradores) describe herbicidas tales como los de la Fórmula (0 1 3)



(0 1 3)

en que R es alquilo (C_1-C_4), halo-alquilo (C_1-C_4) o halo

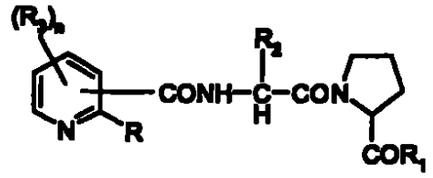
El documento de patente europea EP 550 900 (de Jeschke y colaboradores) describe herbicidas y nematocidas en plantas de Fórmula (0 1 4)



(0 1.4)

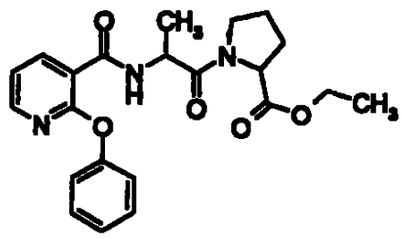
en que n es 0-3, R^1 se selecciona entre numerosos grupos, pero usualmente es H, 6-CH_3 ó 5-Cl, R^2 es alquilo, alquenilo, alquinilo, cicloalquilo, arilo o aril-alquilo, R1 y R2 son halo, CN, NO_2 alquilo, halo-alquilo, alcoxi, halo-alcoxi, alquil-tio, halo-alquil-tio, alquil-sulfonilo, halo-alquil-sulfonilo, arilo, arioxi o aril-tio, y R^4 es alquilo

El documento EP 500 989 (de Mollner y colaboradores) describe agentes inhibidores de la ACE de Fórmula (0 1 5)



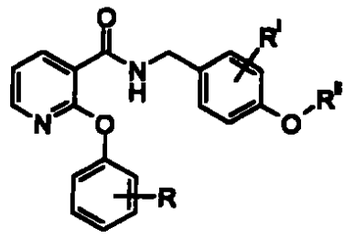
(0 1.5)

en que n es 0-3, R es OH, SH COOH, NH_2, halo, OR_4, SR_4, $COOR_4$, NHR_4 ó $N(R_4)_2$, en que R_4 es alquilo inferior, arilo opcionalmente sustituido, o acilo, R_1 es OH, alcoxi inferior, aril-alcoxi inferior opcionalmente sustituido, aril-oxi o amino disustituido, R_2 es alquilo inferior o amino-alquilo inferior, y R1 y R2 son halo, NO_2 alquilo inferior, halo-alquilo inferior, aril-alquilo inferior, o arilo Realizaciones especificas que se describen incluyen compuestos tales como el de la Fórmula (0 1 6)



(0 1 6)

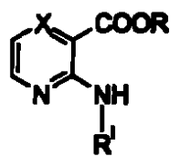
El documento de patente francesa FR 2 140 772 (de Anes) describe compuestos de los que se afirma que tienen utilidad como analgésicos, tranquilizantes, antipiréticos, antiinflamatorios y antirreumáticos, de Fórmula (0 1 7)



(0 1 7)

en que R es 1 ó 2 sustituyentes seleccionados entre alquilo inferior, trihalo-metilo, alcoxi y halo, R' es H o alquilo y R" es hidrógeno o alquilo

El documento de patente japonesa JP 07 304775 (de Otsuka y colaboradores) describe derivados de naftiridina y piridopirazina que tienen unas acciones anti-inflamatorias, moduladoras de inmunidad, analgésicas, antipiréticas, antialérgicas y antidepresivas También se describen compuestos intermedios de Fórmula (0 1 8)

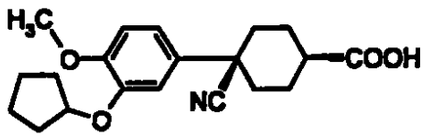


(0 1 8)

en que X puede ser CH y R y R son en cada caso alquilo inferior

Con respecto a las memorias descriptivas de las patentes antes identificadas y de las solicitudes de patente publicadas antes identificadas, se apreciará que solamente la descripción del documento WO 98/45268 (de Marfat y colaboradores) se refiere a la inhibición de las isozimas PDE4 El estado de la técnica contiene también información con respecto a compuestos enteramente distintos en su estructura química de los de la Fórmula (1 0 0) del presente invento pero que, por otro lado, poseen una actividad biológica similar a la de los compuestos de Fórmula (1 0 0) Patentes y solicitudes de patente publicadas representativas, que divulgan dicha información, se ilustran más adelante

Los documentos US 5 552 438, US 5 602 157, y US 5 614 540 (todas ellas otorgadas a Christensen) las cuales comparten la misma fecha de prioridad de 2 de Abril de 1992, se refieren a un agente terapéutico identificado como ARIFLO®, que es un compuesto de Fórmula (0 1 9) y se denomina como se indica seguidamente

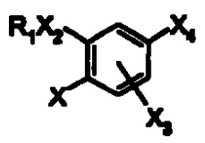


ARIFLO®

Ácido cis-[4-ciano-4-(3-ciclopentil-oxi-4-metoxi-fenil)-ciclohexano-1-carboxílico

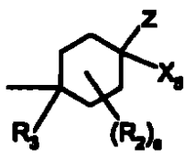
(0 1 9)

El compuesto de Fórmula (0 1 9) entra dentro del alcance del documento US 5 552 438 que describe un género de compuestos de Fórmula (0 1 10)



(0 1 10)

en la que R_1 = -$(CR_4R_5)_rR_6$ en que r = 0 y R_6 = cicloalquilo C_{3-8}, X = YR_2 en que Y = O y R_2 = -CH_3, X_2 = 0, X_3 = H, y X_4 = un resto de la Fórmula parcial (0 1 10 1)



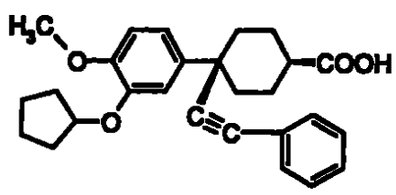
(0 1 10 1)

en la que X_5 = H, s = 0, R_1 y R_2 = CN y Z = $C(O)OR_{14}$ en que R_{14} = H Las descripciones de los documentos US 5 602 157 y US 5 614 540 difieren de la del documento US 5 552 438 y entre ellas en cuanto a la definición del grupo R_3, que es CN en el caso del compuesto ARIFLO® Se describe que una preferida forma de sal del compuesto ARIFLO® es la sal de tris(hidroximetil)-amonio-metano

El documento US 5 863 926 (de Christensen y colaboradores) describe compuestos análogos al compuesto ARIFLO®, p ej , el de Fórmula (0 1 11)

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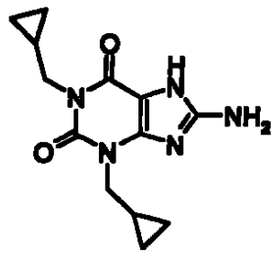
00326



(0 1 11)

El documento WO 98/18793 (de Webb y colaboradores) describe un procedimiento para preparar el compuesto ARIFLO® y compuestos afines El documento WO 95/00139 (de Barnette y colaboradores) reivindica un compuesto que tiene una relación de IC_{50} de aproximadamente 0,1 o mayor en lo que se refiere a la IC_{50} de la forma catalítica de las PDE IV, que fija al rolipram con una alta afinidad, dividida por la IC_{50} para la forma que fija el rolipram con una baja afinidad, pero en una reivindicación subordinada restringe el alcance de la misma a un compuesto del que antes del 21 de Junio de 1993 no se sabía que era un agente inhibidor de las PDE4

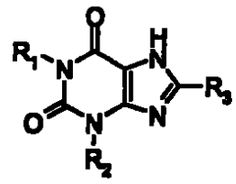
El documento WO 99/20625 (de Eggleston) describe formas polimorfas cristalinas de la cipamfilina para el tratamiento de enfermedades mediadas por las PDE_4 y el TNF, de Fórmula (0 1 12)



Cipamfilina

(0 1 12)

El documento WO/99/20280 (de Griswold y colaboradores) describe un método de tratar el prurito por administración de una cantidad eficaz de un agente inhibidor de las PDE4 p ej , un compuesto de Fórmula (0 1 13)



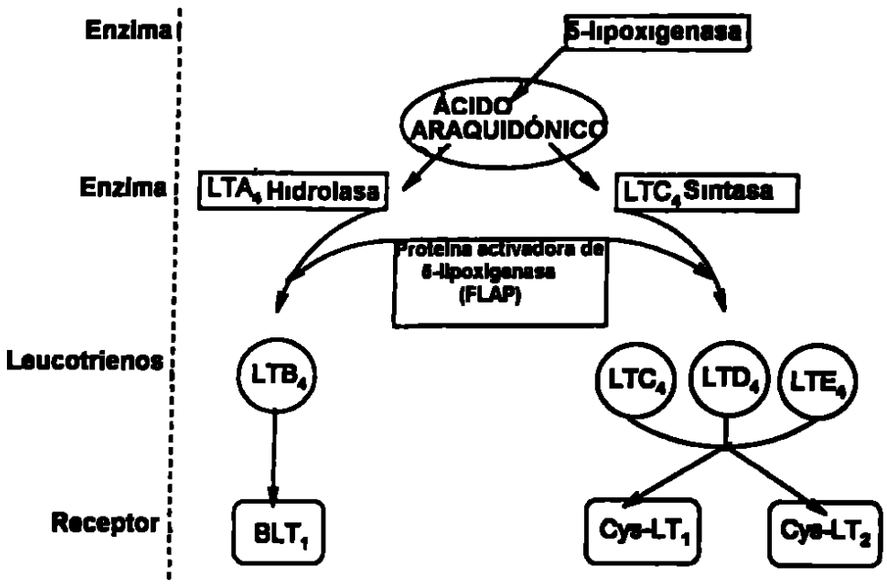
(0 1 13)

El documento US 5 922 557 (de Pon) describe una línea celular CHO-K1 que expresa establemente altos niveles de una enzima PDE4A de plena longitud, específica para el cAMP, con bajo valor de Km, que a su vez se ha usado para examinar potentes agentes inhibidores de las enzimas PDE4 y compara el orden de rango de sus potencias para elevar al cAMP en una formulación de células enteras con su capacidad para inhibir la actividad de fosfodiesterasa en una formulación de células rotas Se dice además que se había encontrado que el análisis de inhibición de enzimas solubles descrito en la técnica anterior no refleja el comportamiento de los agentes inhibidores que actuan *in vivo* Se describió entonces un análisis mejorado de células enteras con enzimas solubles, del que se afirma que refleja el comportamiento de los agentes inhibidores que actuan *in vivo* Se describe además que existen por lo menos cuatro distintas isoformas o subtipos de las PDE4, y se ha mostrado que cada subtipo da lugar a un cierto numero de variantes de empalme, que por sí mismas pueden exhibir diferente localización celular y diferentes afinidades para agentes inhibidores

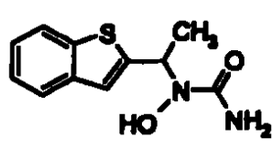
En lo que se refiere a las divulgaciones de las patentes y solicitudes de patente publicadas que antes se identifican, se apreciará que los compuestos implicados poseen la misma actividad biológica que los compuestos de Fórmula (1 0 0) Al mismo tiempo, sin embargo, el profesional observará que las estructuras químicas de dichos compuestos descritos en la técnica anterior no solamente son diversos unos de otros sino que son asimismo distintos de las de los nuevos compuestos del presente invento El estado de la técnica contiene todavía más información en relación con compuestos que son distintos en su estructura química de los de la Fórmula (1 0 0) y que, además, no poseen ninguna actividad inhibidora de las PDE4 similar a la de los compuestos de Fórmula (1 0 0) Dichos compuestos descritos en la técnica anterior no presentan sin embargo con frecuencia una utilidad terapéutica similar a la poseída por los compuestos de Fórmula (1 0 0), es decir en el tratamiento de enfermedades y condiciones inflamatorias, respiratorias y alérgicas En particular, esto es aplicable a ciertos agentes inhibidores de enzimas y agentes antagonistas de receptores en la denominada ruta de los leucotrienos Este es el caso especialmente con respecto a los leucotrienos LTB_4 y

LTD_4 Correspondientemente se describen seguidamente patentes y solicitudes de patente publicadas representativas, que describen más información acerca de este tipo

El ácido araquidónico es metabolizado por la ciclooxigenasa-1 y por la 5-lipoxigenasa La ruta de la 5-lipoxigenasa conduce a la producción de leucotrienos (LT's) que contribuyen a la respuesta inflamatoria por medio de su efecto sobre la aglomeración, la desgranulación y la quimiotaxis de neutrófilos, la permeabilidad vascular, la contractilidad de los musculos lisos y sobre los linfocitos Los cisteinil-leucotrienos, LTC_4, LTD_4 y LTE_4, desempeñan un cometido importante en la patogénesis del asma Los componentes de la ruta de los leucotrienos, que proporcionan dianas para una intervención terapéutica, se ilustran en el siguiente diagrama



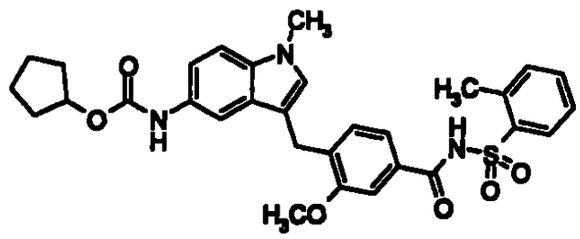
Correspondientemente los agentes que son capaces de intervenir en cualquiera de las etapas de la ruta de 5-lipoxigenasa proporcionan una oportunidad para un tratamiento terapéutico Un ejemplo de uno dichos agentes es el agente inhibidor de 5-lipoxigenasa, zileuton, que es un agente terapeutico identificado como ZYFLO®, que se puede representar por la Fórmula (0 1 14)



ZYFLO®

Zileuton (0 1 14)

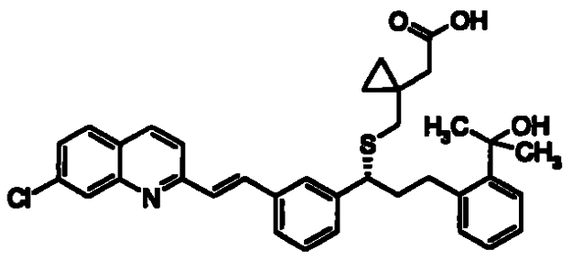
Otro de dichos agentes es el agente antagonista de receptores de LTD_4, zafirlukast, que es un agente terapéutico identificado como ACCOLATE® que se puede representar por la Fórmula (0 1 15)



ACCOLATE®

Zafirlukast (0 1 15)

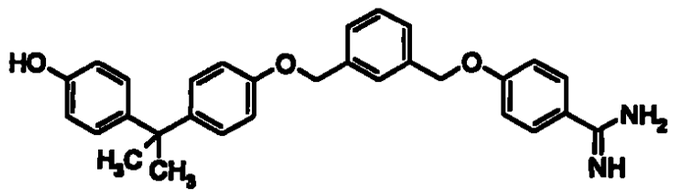
Otro de dichos agentes antagonistas de receptores de LTD_4 es el montelukast, que es un agente terapeutico identificado como SINGULAIR® que se puede representar por la Fórmula (0 1 16)



SINGULAIR®

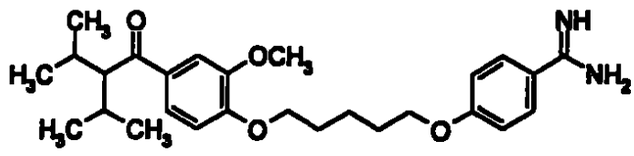
Montelukast (0 1 16)

Otro tipo de las dianas terapéuticas antes mencionadas es el receptor de LTB_4, y un ejemplo de un agente antagonista para dichos receptores es BIIL-260, un agente terapéutico que se puede representar por la Fórmula (0 1 17)



BIIL-260 (0 1 17)

Otro ejemplo de un agente terapéutico que es un agente antagonista de receptores de LTB_4 es el CGS-25019c que se puede representar por la Fórmula (0 1 18)



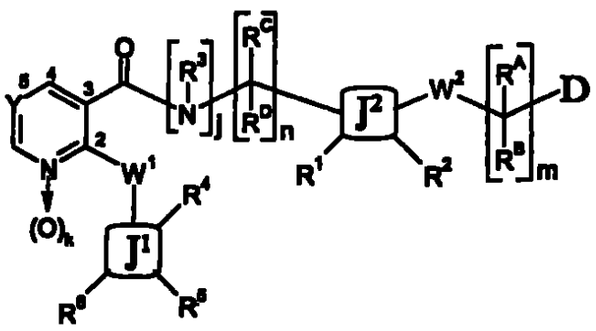
CGS-25019c (0 1 18)

Nada en el estado de la técnica que antes se ha descrito divulga o podría sugerir al profesional los nuevos compuestos del presente invento o su actividad inhibidora de las PDE4 y el resultante mejoramiento significativo en cuanto a la utilidad terapéutica y al índice terapéutico para el tratamiento de enfermedades y condiciones inflamatorias, respiratorias y alérgicas

4.0 SUMARIO DEL INVENTO

El presente invento se refiere a nuevos compuestos que tienen actividad biológica como agentes inhibidores de la fosfodiesterasa denominada isoenzima "Tipo IV" ("isozima PDE4") Formas de realización de los nuevos compuestos del presente invento son activas como agentes inhibidores no selectivos de la isozima PDE4 Otras formas de realización de dichos nuevos compuestos tienen especificidad para el substrato de las isozimas PDE4, especialmente para el subtipo D Dichos nuevos compuestos que tienen una actividad no selectiva o selectiva para la D del PDE4 son generalmente utiles en el tratamiento terapéutico de diversas enfermedades y condiciones inflamatorias, alérgicas y respiratorias, y proporcionan en particular un mejoramiento significativo en el tratamiento terapéutico de enfermedades respiratorias obstructivas, especialmente del asma y de la enfermedad pulmonar obstructiva crónica (COPD)

El presente invento se refiere a un compuesto de Fórmula (1 0 0)



(100)

- en la que -

-j es 0 ó 1 con la condición de que cuando j es 0, n debe ser 2,

-k es 0 ó 1

-m es 1, 2 ó 3,

-n es 1 ó 2,

-W^1 y W_2 son independientemente -O-, -$S(=O)_t$-, en que t es 0, 1 ó 2, o -$N(R^3)$- en que R^3 tiene el mismo significado que se define seguidamente,

-Y es $=C(R^1{}_a)$-, en que $R^1{}_a$ tiene los mismos significados que se definen seguidamente, o -$[N\rightarrow(O)_k]$- en que k es 0 ó 1,

- en que -

–$R^1{}_a$ es un miembro seleccionado entre el grupo que consta de -H, -F, -Cl -CN, -NO_2, alquilo C_1-C_4, alquinilo (C_2-C_4), alquilo (C_1-C_3) fluorado, alcoxi (C_1-C_3) fluorado -OR^{18}, y -$C(=O)NR^{22}{}_aR^{22}{}_b$,

- en que -

—$R^{22}{}_a$ y $R^{22}{}_b$ son cada uno de ellos independientemente -H, -CH_3, -CH_2CH_3, -CH_2CH_2 CH_3, -$CH_2(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, ciclopropilo ciclobutilo o ciclopentilo,

-R^A y R^B son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -CF_3, alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, y bencilo, en que dichos restos de cicloalquilo, fenilo y bencilo están sustituidos cada uno de ellos independientemente con 0 a 3 sustituyentes R^{10},

- en que -

–R^{10} es un miembro seleccionado entre el grupo que consta de fenilo, pirídilo, -F, -Cl, -CF_3, oxo (=O), -OR^{18}, -NO_2, -CN, -$C(=O)OR^{18}$, -$C(=O)R^{18}$, -$C(=O)NR^{18}R^{17}$, -O-$C(=O)NR^{18}R^{17}$, -$NR^{18}R^{17}$, -$NR^{18}C(=O)R^{17}$, -$NR^{18}C(=O)OR^{17}$, -$NR^{18}S(=O)_2R^{17}$, y -$S(=O)_2NR^{18}R^{17}$, en que dicho fenilo o pirídilo está sustituido con 0 a 3 R^{11},

- en que -

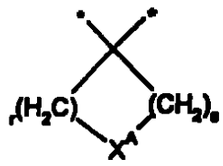
—R^{11} es -F, -Cl, -CF_3, -CN -NO_2 -OH, alcoxi (C_1-C_3), alquilo (C_1-C_3), ó -$NR^{16}R^{17}$,

- y -

—R^{16} y R^{17} son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, alquilo (C_1-C_4), alquenilo (C_2-C_4), cicloalquilo (C_3-C_6), fenilo, bencilo y piridilo, en que dicho alquilo, alquenilo, cicloalquilo, fenilo, bencilo o piridilo está sustituidos con 0 a 3 sustituyentes seleccionados entre el grupo que consta de -F, -Cl, -CF_3 -CN y alquilo (C_1-C_3),

- o -

-R^A y R^B se toman conjuntamente, pero solamente en el caso en el que m sea 1, para formar un resto de tipo espiro de Fórmula (1 2 0)



(1.2 0)

- en que -

—r y s son independientemente de 0 a 4, con la condición de que la suma de r + s ha de ser por lo menos 1 pero no mayor que 5,

- y -

—X^A se selecciona entre -CH_2- -$CH(R^{11})$- ó $C(R^{11})_2$-, en que cada R^{11} se selecciona de modo independiente de los otros y cada uno de ellos tiene el mismo significado que antes se define -NR^{15}-, en que R^{16} tiene el mismo significado que se define seguidamente, -O- y -$S(=O)_t$- en que t es 0, 1 ó 2,

- y -

dicho resto de tipo espiro de la Fórmula parcial (1 2 0) está sustituido como en uno cualquiera o más átomos de carbono de éste, distinto del que define a X^A, por 0 a 3 sustituyentes R^{14}, en que R^{14} tiene el mismo significado que se define seguidamente, en lo referente a un átomo de nitrógeno de éste por 0 a 1 sustituyente R^{15}, en que R^{15} tiene el mismo significado que se define seguidamente, y en lo referente a un átomo de azufre de éste por 0 a 2 átomos de oxígeno,

-R^C y R^D tienen los mismos significados que antes se definen para R^A y R^B excepto que uno de ellos debe ser -H y que éstos se seleccionan independientemente uno de otro y de R^A y R^B,

-R^1 y R^2 pueden aparecer individual o conjuntamente en cualquier anillo o en cualesquiera anillos que comprenden un significado del resto J^2 como se define seguidamente, y R^1 y R^2 son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -Cl, -CN, -NO_2, alquilo (C_1-C_4), alquinilo (C_2-C_4), alquilo (C_1-C_3) fluorado, -OR^{16}, y -$C(=O)NR^{22}_aR^{22}_b$, en que R^{16}, R^{22}_a y R^{22}_b tienen los mismos significados que antes se definen,

-R^3 es -H, alquilo (C_1-C_3), fenilo, bencilo, ó -OR^{16}, en que R^{16} tiene los mismos significados que antes se definen,

-R^4, R^5 y R^6 pueden aparecer individual o conjuntamente en cualesquiera anillo o anillos que constituyan un significado del resto J^1 que se define seguidamente, y R^4, R^5 y R^6 son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

-(*a*) -H, -F, -Cl, alquinilo (C_2-C_4) -R^{16}, -OR^{16}, -$S(O)_pR^{16}$, -$C(=O)R^{16}$, -$C(=O)OR^{16}$, -$OC(=O)R^{16}$, -CN -NO_2, -$C(=O)NR^{16}R^{17}$, -$OC(=O)NR^{16}R^{17}$, -$NR^{22}_aC(=O)NR^{16}R^{17}$, -$NR^{22}_aC(=NR^{12})NR^{16}R^{17}$, -$NR^{22}_aC(=NCN)NR^{16}R^{17}$, -$NR^{22}_aC(=N\text{-}NO_2)NR^{16}R^{17}$, -$C(=NR^{22}_a)NR^{16}R^{17}$, -$CH_2C(=NR^{22}_a)NR^{16}R^{17}$, -$OC(=NR^{22}_a)NR^{16}R^{17}$, -$OC(=N\text{-}NO_2)NR^{16}R^{17}$, -$NR^{16}R^{17}$, -$CH_2NR^{16}R^{17}$, -$NR^{22}_aC(=O)R^{16}$, -$NR^{22}_aC(=O)OR^{16}$, =$NOR^{16}$, -$NR^{22}_aS(O)_pR^{17}$, -$S(=O)_pNR^{16}R^{17}$, y -$CH_2C(=NR^{22}_a)NR^{16}R^{17}$,

- en la que -

–p es 0, 1 ó 2, y R^{22}_a, R^{16} y R^{17} tienen los mismos significados que se definen anteriormente,

-(*b*) alquilo (C_1-C_4), y alcoxi (C_1-C_4) en el caso de que uno o más de los R^4, R^5 ó R^6 tenga el significado de -OR^{16} en el párrafo (*a*) anterior y R^{16} sea definido como alquilo (C_1-C_4), en que dichos alquilo y alcoxi están sustituidos cada uno de ellos independientemente con 0 a 3 sustituyentes -F ó -Cl,
o bien 0 ó 1 sustituyente alcoxi (C_1-C_2)-carbonilo-, alquil (C_1-C_2)-carbonilo-, o alquil (C_1-C_2)-carboniloxi-

- y -

-(*c*) un resto anilo o heterociclilo seleccionado entre el grupo que consta de fenilo, bencilo, furanilo, tetrahidrofuranilo, oxetanilo, tienilo tetrahidrotienilo, pirrolilo, pirrolidinilo, oxazolilo, oxazolidinilo, isoxazolilo, isoxazolidinilo, tiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo pirazolilo, pirazolidinilo oxadiazolilo, tiadiazolilo, imidazolilo, imidazolidinilo, pindinilo, pirazinilo, pirimidinilo, pindazinilo, piperidinilo, piperazinilo, triazolilo, triazinilo tetrazolilo, piranilo, azetidinilo, morfolinilo, paratiazinilo, indolilo, indolinilo, benzo[*b*]furanilo, 2 3-dihidrobenzofuranilo, 2-*H*-cromenilo, cromanilo,

benzotienilo, 1-*H*-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, quinolinilo isoquinolinilo, ftalazinilo, quinazolinilo, quinoxalinilo y purinilo, en que dichos restos anlo y heterociclilo están sustituidos cada uno de ellos independientemente con 0 a 2 sustituyentes R^{14}

- en que -

--R^{14} es un miembro seleccionado entre el grupo que consta de alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, bencilo, piridilo, y quinolinilo, en que dicho alquilo, cicloalquilo, fenilo, bencilo, pindilo o quinolinilo está sustituido con 0, 1 ó 2 sustituyentes -F, -Cl, -CH_3, -OR^{16}, -NO_2, -CN, ó -$NR^{16}R^{17}$, y dicho grupo R^{14} consta adicionalmente de -F, -Cl, -CF_3, oxo (=O), -OR^{16}, -NO_2, -CN, -C(=O)OR^{16}, -O-C(=O)R^{16}, -C(=O)$NR^{16}R^{17}$, -O-C(=O)$NR^{16}R^{17}$, -$NR^{16}R^{17}$, -NR^{16}C(=O)R^{17}, -NR^{16}C(=O)OR^{17}, -NR^{16}S(=O_2)R^{17}, ó -S(=$O)_2NR^{16}R^{17}$, en que R^{16} y R^{17} tienen los mismos significados que antes se definen

- y además en que -

—R^{15} es un miembro seleccionado independientemente entre el grupo que consta de -H, -$NR^{16}R^{17}$, -C(=O)R^{16}, -OR^{16}, alquil (C_1-C_4)-OR^{16}, -C(=O)OR^{16}, alquil (C_1-C_2)-C(=O)OR^{16}, -C(=O)$NR^{16}R^{17}$, alquilo (C_1-C_4), alquenilo (C_2-C_4), -(CH_2)$_u$-cicloalquilo (C_3-C_7) en que u es 0, 1 ó 2, fenilo, bencilo, pindilo, y quinolinilo, en que dicho alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, bencilo, pindilo o quinolinilo está sustituido con 0 a 3 sustituyentes R^{12}, en que R^{16} y R^{17} tienen los mismos significados que antes se definen, y

- en que -

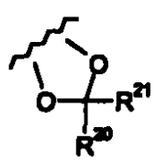
——R^{12} es un miembro seleccionado independientemente entre el grupo que consta de -F -Cl, -CO_2R^{18}, -OR^{18}, -CN, -C(=O)$NR^{18}R^{19}$, -$NR^{18}R^{19}$, -NR^{18}C(=O)R^{19}, -NR^{18}C(=O)OR^{19}, -NR^{18}S(=$O)_pR^{19}$ -S(=$O)_pNR^{18}R^{19}$, en que p es 1 ó 2, alquilo (C_1-C_4), y alcoxi (C_1-C_4) en el caso de que R^{12} tenga el significado de -OR^{16} anterior y R^{16} está definido como alquilo (C_1-C_4), en que dichos alquilo y alcoxi están sustituidos cada uno de ellos independientemente con 0 a 3 sustituyentes seleccionados independientemente entre -F, -Cl, alcoxi (C_1-C_2)-carbonilo, alquil (C_1-C_2)-carbonilo, y alquil (C_1-C_2)-carbonil-oxi, en que R^{18} tiene los mismos significados que antes se han definido, y

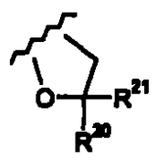
- en que -

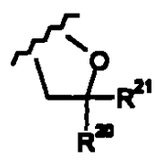
——R^{18} y R^{19} se seleccionan independientemente entre el grupo que consta de -H alquilo (C_1-C_4) y fenilo, en que dicho alquilo o fenilo está sustituido con 0-3 de -F, ó -Cl,

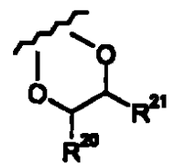
- o en el caso en el que J^1 es fenilo -

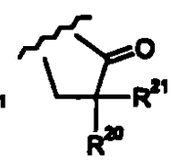
-(*d*) R^5 y R^6 se toman conjuntamente para formar un resto que es un miembro seleccionado entre el grupo que consta de las fórmulas parciales (1 3 1) hasta (1 3 15)

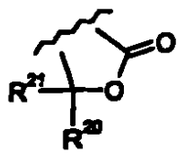

(1.3 1)

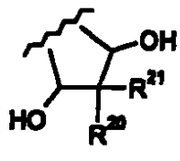

(1 3 2)

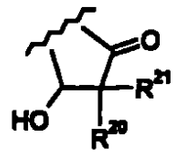

(1 3 3)

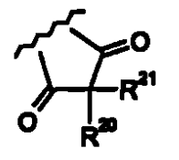

(1.3.4)

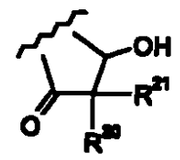

(1 3 5)

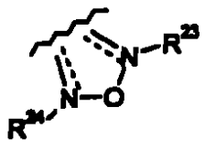

(1 3 6)

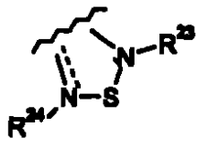

(1 3 7)

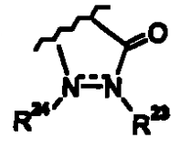

(1 3 8)

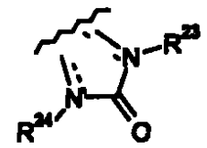

(1 3 9)

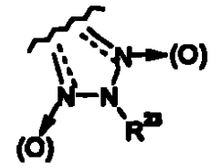

(1 3 10)


(1.3 11)


(1.3 12)


(1 3 13)


(1 3 14)


(1 3 15)

- en las que -

–R^{20} y R^{21} son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_3$, y $-OCF_3$,

–R^{23} y R^{24} son cada uno de ellos independientemente -H, $-CH_3$, $-OCH_3$, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, o están ausentes, en cuyo caso la línea de trazos - - - - representa un doble enlace,

-J^1 es un resto que comprende un sistema anular de carbonos, saturado o insaturado que es monocíclico de 3 a 7 miembros, o que es policíclico condensado de 7 a 12 miembros, con la condición de que J^1 no ha de ser un resto de bianlo discontinuo o restringido, y en el que opcionalmente un átomo de carbono de dicho sistema anular de carbonos puede estar reemplazado por un heteroátomo seleccionado entre N O y S, en el que opcionalmente un segundo átomo de carbono del mismo y opcionalmente además un tercer átomo de carbono del mismo puede estar reemplazado por N,

- en el que -

dicho resto que define J^1 está sustituido en cualesquiera anillo o anillos del mismo con R^4, R^5 y R^6, que tienen los mismos significados que antes se definen,

-J^2 es un resto que comprende un sistema anular de carbonos, saturado o

insaturado que es monocíclico de 3 a 7 miembros, o que es policíclico condensado de 7 a 12 miembros, con la condición de que J^2 no ha de ser un resto de bianlo discontinuo o restringido y en que opcionalmente un átomo de carbono de dicho sistema anular de carbonos puede estar reemplazado por un heteroátomo seleccionado entre N, O y S, en que opcionalmente un segundo átomo de carbono del mismo y además opcionalmente un tercer atomo de carbono del mismo puede estar reemplazado por N,

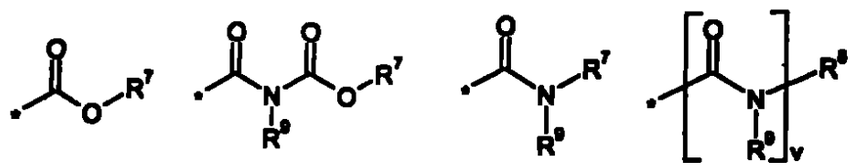
- en el que -

dicho resto que define J^2 está sustituido en cualesquiera anillo o anillos del mismo con R^1 y R^2, que tienen los mismos significados que antes se definen,

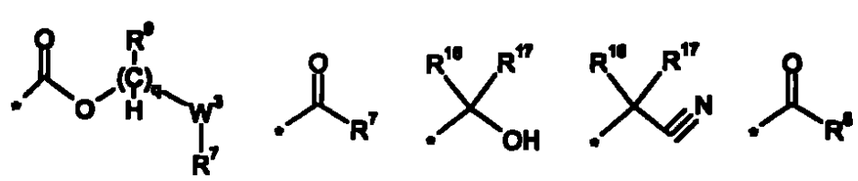
-D es un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

-(*a*) el grupo que consta de las Fórmulas parciales (1 1 1) hasta (1 1 9)



(1 1 1) (1 1 2) (1 1 3) (1 1.4)



(1 1.5) (1 1 6) (1 1 7) (1 1 8) (1 1 9)

- en las que -

–"*" indica el sitio de unión de cada Fórmula parcial (1 1 1) hasta (1 1 9) a la restante porción de la Fórmula (1 0 0),

–q es 1, 2 ó 3, con la condición de que cuando q es 2 ó 3, R^9 ha de tener el significado de -H en por lo menos un caso, o en dos casos, respectivamente,

–v es 0 ó 1,

–W^3 es -O-, -N(R^9)-, en que R^9 tiene el mismo significado que se define seguidamente, o -OC(=O)-,

–R^7 es un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

–(*1*) -H,

–(*2*) alquilo (C_1-C_8), alquenilo (C_2-C_8) o alquinilo (C_2-C_8), en que dicho alquilo, alquenilo o alquinilo está sustituido con 0 a 3 sustituyentes R^{10}, en que R^{10} tiene el mismo significado que se ha definido anteriormente,

–(*3*) -$(CH_2)_u$-cicloalquilo (C_3-C_7) en que u es 0, 1 ó 2, y además en que dicho cicloalquilo (C_3-C_7) está sustituido con 0 a 3 sustituyentes R^{10} en que R^{10} tiene los mismos significados que se han definido anteriormente,

- y -

–(*4*) fenilo o bencilo, en que dicho fenilo o bencilo está sustituido independientemente con 0 a 3 sustituyentes R^{10} en que R^{10} tiene el mismo significado que se ha definido anteriormente,

–R^8 es un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

–(*1*) *fenilo, tetrazol-5-ilo 1,2,4-triazol-3-ilo 1,2,4-triazol-3-on-5-ilo,* 1,2,3-triazol-5-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazolidin-2-on-4-ilo, 1,3,4-oxadiazolilo, 1,3,4-oxadiazol-2-on-5-ilo, 1,2,4-oxadiazol-3-ilo, 1,2,4-oxadiazol-5-on-3-ilo, 1,2 4-oxadiazol-5-ilo, 1,2,4-oxadiazol-3-on-5-ilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, morfolinilo, paratiazinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, pirrolilo, pirazolilo, succinimidilo, glutarimidilo, pirrolidinilo 2-pipendonilo, 2-pindonilo, 4-pindonilo, pindazin-3-onilo, pindilo pirimidinilo, pirazinilo, pindazinilo,

- y -

–(*2*) indolilo, indolinilo, isoindolinilo benzo[*b*]furanilo, 2,3-dihidrobenzofuranilo, 1,3-dihidroisobenzofuranilo, 2*H*-1-benzopiranilo, 2-*H*-cromenilo, cromanilo, benzotienilo, *1H*-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzotriazolilo, benzotriazinilo, ftalazinilo, 1,8-naftindinilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, pirazolo[3,4-*d*]pirimidinilo, pirimido[4,5-*d*]pirimidinilo imidazo[1,2-*a*]piridinilo, pindopindinilo, pteridinilo, y 1*H*-purinilo,

- en que -

cualquier resto citado en (*1*) ó (*2*) anteriormente está sustituido opcionalmente con respecto a (*i*) uno cualquiera o más átomos de carbono del mismo, opcionalmente con un sustituyente R^{14} en que R^{14} tiene el mismo significado que antes se ha definido, con respecto a (*ii*) uno cualquiera o más átomos de nitrógeno del mismo que no sea un sitio de unión de dicho resto, opcionalmente con un sustituyente R^{15} en que R^{15} tiene el mismo significado que antes se ha definido, y todas las formas tautómeras del mismo, y con respecto a (iii) cualquier átomo de azufre del mismo que no sea un sitio de unión de dicho resto, con 0, 1 ó 2 átomos de oxígeno,

–R^9 es un miembro seleccionado entre el grupo que consta de -H, alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, bencilo, pirídilo, -C(=O)OR^{16}, -C(=O)R^{16}, -OR^{16}, alquil (C_1-C_2)-OR^{16}, y alquil (C_1-C_2)-C(=O)OR^{16}, en que R^{16} tiene los mismos significados que antes se han definido,

- y D se selecciona adicionalmente entre -

-(*b*) un resto que comprende un miembro seleccionado entre el grupo que consta de -O-P(=O)$(OH)_2$ (fosfórico), -PH(=O)OH (fosfínico), -P(=O)$(OH)_2$ (fosfónico), -[P-(=O)(OH)-O-alquilo (C_1-C_4)] (alquil-fosfono), -P-(=O)(OH)-O-alquilo (C_1-C_4) (alquil-fosfinilo), -P-(=O)$(OH)NH_2$ (fosforamido), -P-(=O)(OH)NH-alquilo (C_1-C_4) y -P-(=O)(OH)NHR^{25} (fosforamido sustituido), -O-S(=O)$_2$OH (sulfúrico), -S(=O)$_2$OH (sulfónico), -S(=O)$_2$NHR^{25} ó -NHS(=O)$_2$$R^{25}$ (sulfonamido) en que R^{25} es -CH_3, -CF_3 ó o-tolilo, y acil-sulfonamido seleccionado entre el grupo que consta de -C(=O)NHS(=O)$_2$$R^{25}$, -C(=O)NHS(=O)$_2$$NH_2$, -C(=O)NHS(=O)$_2$-alquilo ($C_1$-$C_4$), -C(=O)NHS(=O)$_2$NH-alquilo ($C_1$-$C_4$), -C(=O)NHS(=O)$_2$N[alquilo ($C_1$-$C_4$)]$_2$, -S(=O)$_2$NHC(=O)alquilo ($C_1$-$C_4$), -S(=O)$_2$NHC(=O)$NH_2$, -S(=O)$_2$NHC(=O)NH-alquilo ($C_1$-$C_4$), -S(=O)$_2$NHC(=O)N[alquilo ($C_1$-$C_4$)]$_2$, -S(=O)$_2$NHC(=O)$R^{25}$ -S(=O)$_2$NHCN, -S(=O)$_2$NHC(=S)NH_2, -S(=O)$_2$NHC(=S)NH-alquilo (C_1-C_4), -S(O)$_2$NHC(=S)N[alquilo (C_1-C_4)]$_2$, y -S(=O)$_2$NHS(=O)$_2$$R^{25}$

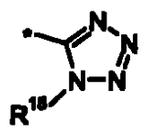
- en que -

–R^{25} es -H, alquilo (C_1-C_4), fenilo, ó -OR^{16}, en que R^{16} tiene los mismos significados que antes se han definido,

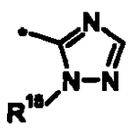
- o -

una sal farmacéuticamente aceptable del mismo

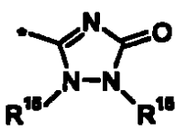
El presente invento se refiere en particular a un compuesto de la Fórmula (1 0 0) como antes se ha citado, en la que el resto D comprende, como un significado preferido de R^7, fenilo, bencilo o ciclohexilo ilustrado en las Fórmulas parciales (1 1 45) hasta (1 1 47) seguidamente o el resto D comprende un R^8 de Fórmula parcial (1 1 4) en el que v es 0 ó 1, que comprende un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (1 1 11) hasta (1 1 44) ilustradas seguidamente



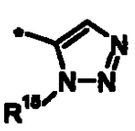
tetrazol-5-ilo
(1 1 11)



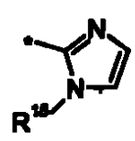
1,2,4-triazol-3-ilo
(1 1 12)



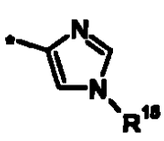
1,2 4-triazol-3-on-5-ilo
(1 1 13)



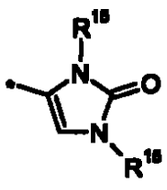
1 2 3-triazol-5-ilo
(1 1 14)



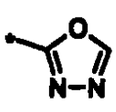
imidazol-2-ilo
(1 1 15)



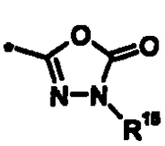
imidazol-4-ilo
(1 1 16)



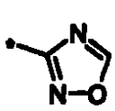
imidazolidin-2-on-4-ilo
(1 1 17)



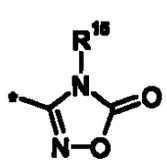
1,3,4-oxadiazolilo
(1 1 18)



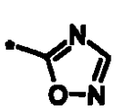
1,3,4-oxadiazol-2-on-5-ilo
(1 1 19)



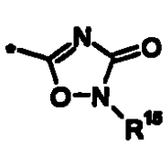
1,2,4-oxadiazol-3-ilo
(1 1 20)



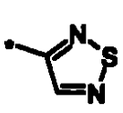
1,2,4-oxadiazol-5-on-3-ilo
(1 1 21)



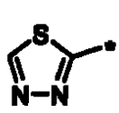
1,2,4-oxadiazol-5-ilo
(1 1 22)



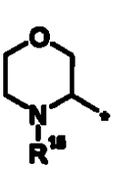
1,2,4-oxadiazol-3-on-5-ilo
(1 1 23)



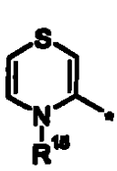
1,2,5-tiadiazol-2-ilo
(1 1 24)



1,3,4-tiadiazolilo
(1 1 25)



morfolin-3-ilo
(1 1 26)



paratiazin-3-ilo
(1 1 27)



oxazolilo
(1 1 28)



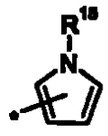
isoxazolilo
(1 1 29)



tiazolilo
(1 1 30)



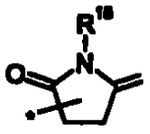
isotiazolilo
(1 1 31)



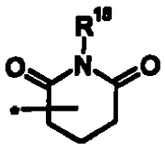
pirrolilo
(1 1 32)



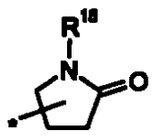
pirazolilo
(1 1 33)



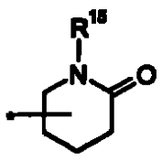
succinimidilo
(1 1 34)



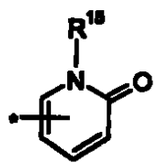
glutarimidilo
(1 1 35)



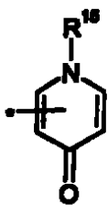
pirrolidonilo
(1 1 36)



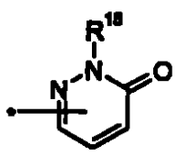
2-piperidonilo
(1 1 37)



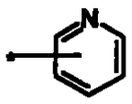
2-piridonilo
(1 1 38)



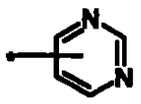
4-piridonilo
(1 1 39)



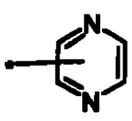
piridazin-3-onilo
(1 1 40)



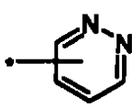
piridilo
(1 1 41)



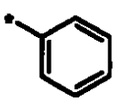
pirimidinilo
(1 1 42)



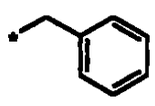
pirazinilo
(1 1 43)



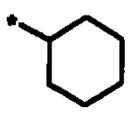
piridazinilo
(1 1 44)



fenilo
(1 1 45)



bencilo
(1 1 46)

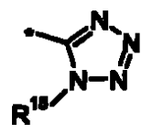


ciclohexilo
(1 1 47)

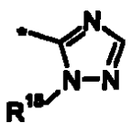
en que "*" indica el sitio de unión de cada Fórmula parcial (1 1 11) hasta (1 1 47) con la porción remanente de la Fórmula (1 0 0), y en que cada átomo de carbono de las Fórmulas parciales (1 1 11) hasta (1 1 44) está opcionalmente sustituido con un

sustituyente R^{14}, en que R^{14} y R^{15} tienen los mismos significados que se han definido anteriormente, y todas las formas tautómeras y opcionalmente las formas de N-óxidos, de los mismos, y además en que cada átomo de carbono de las Fórmulas parciales (1 1 45) hasta (1 1 47) está sustituido opcionalmente con un sustituyente R^{10}, en que R^{10} tiene los mismos significados que antes se han definido

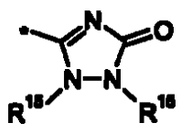
El presente invento se refiere además con mayor particularidad a un compuesto de la Fórmula (1 0 0) que antes se cita, en la que el resto D es especialmente el miembro seguidamente indicado, seleccionado entre el grupo antes citado que consta de las Fórmulas parciales (1 1 11) hasta (1 1 47)



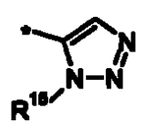
tetrazol-5-ilo
(1 1 11)



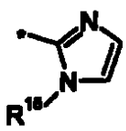
1,2,4-triazol-3-ilo
(1 1 12)



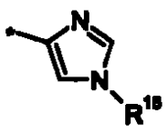
1,2,4-triazol-3-on-5-ilo
(1 1 13)



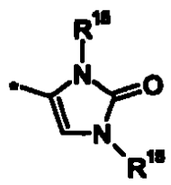
1,2,3-triazol-5-ilo
(1 1 14)



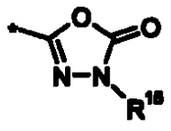
imidazol-2-ilo
(1 1 15)



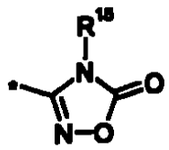
imidazol-4-ilo
(1 1 16)



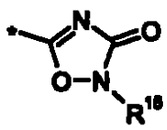
imidazolidin-2-on-4-ilo
(1 1 17)



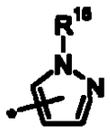
1,3,4-oxadiazol-2-on-5-ilo
(1 1 19)



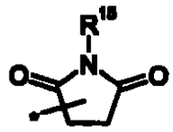
1,2,4-oxadiazol-5-on-3-ilo
(1 1 21)



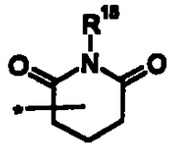
1,2,4-oxadiazol-3-on-5-ilo
(1 1 23)



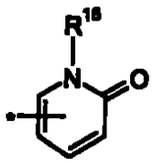
pirazolilo
(1 1 33)



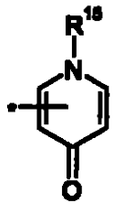
succinimidilo
(1 1 34)



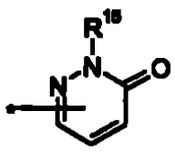
glutarimidilo
(1 1 35)



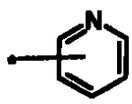
2-piridonilo
(1 1 38)



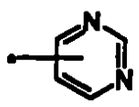
4-piridonilo
(1 1 39)



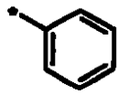
piridazin-3-onilo
(1 1 40)



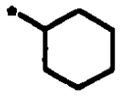
piridilo
(1 1 41)



pirimidinilo
(1 1 42)

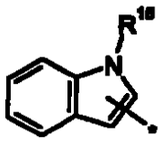


fenilo
(1 1 45)

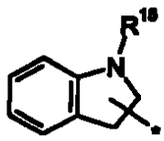


ciclohexilo
(1 1 47)

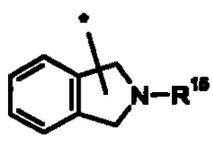
El presente invento está relacionado adicionalmente en particular con un compuesto de la Fórmula (1 0 0) que antes se ha citado, en la que el resto D comprende R^8 de la Fórmula parcial (1 1 4) en el que v es 0 ó 1, y R^8 de dicha Fórmula parcial (1 1 4) es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (1 4 1) hasta (1 4 28)



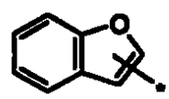
indolilo
(1 4 1)



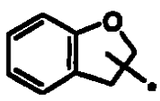
indolinilo
(1 4 2)



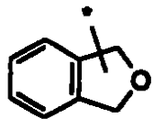
isoindolinilo
(1 4 3)



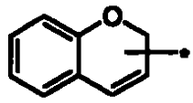
benzo[*b*]furanilo
(1 4 4)



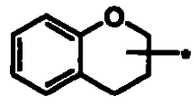
2,3-dihidro-benzofuranilo
(1 4 5)



1,3-dihidro-isobenzofuranilo,ftalanilo
(1 4 6)

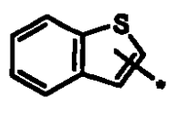


2H-1-benzopiranilo
(1 4 7)

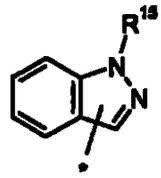


cromanilo
(1 4 8)

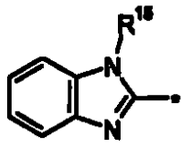
00343 339



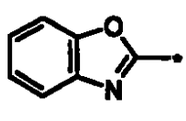
benzotienilo
(1 4 9)



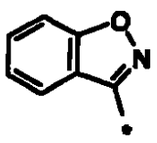
1*H*-indazolilo
(1 4 10)



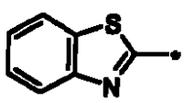
bencimidazolilo
(1 4 11)



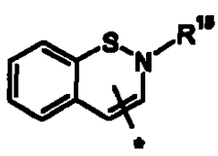
benzoxazolilo
(1 4 12)



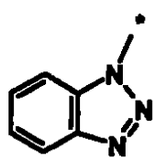
benzoisoxazolilo
(1 4 13)



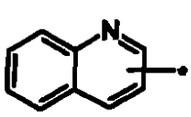
benzotiazolilo
(1 4 14)



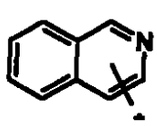
2*H*-1,2-benzotiazinilo
(1 4 15)



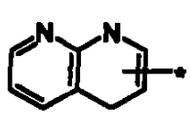
benzotriazolilo
(1 4 16)



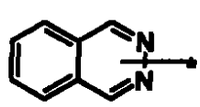
quinolinilo
(1 4 17)



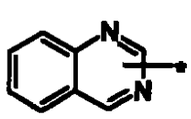
isoquinolinilo
(1 4 18)



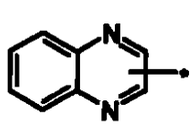
1,8-naftindinilo
(1 4 19)



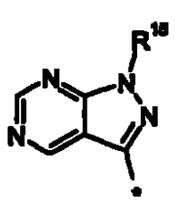
ftalazinilo
(1 4 20)



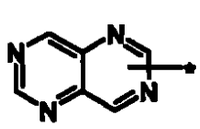
quinazolinilo
(1 4 21)



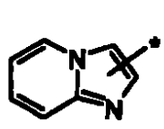
quinoxalinilo
(1 4 22)



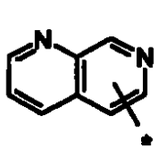
1H-pirazolo[3,4-*d*]-pirimidinilo
(1 4 23)



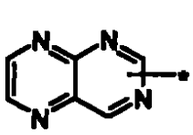
pirimido[5,4-*d*]-pirimidinilo
(1 4 24)



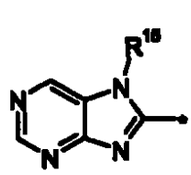
imidazo[1,2-*a*]-pindinilo
(1 4 25)



pindopindinilo
(1 4 26)



pteridinilo
(1 4 27)

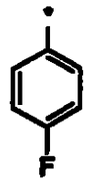


1H-purinilo
(1 4 28)

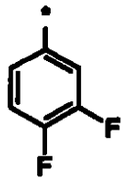
en que "*" indica el sitio de unión a la restante porción de la Fórmula (1 0 0), y en que cada átomo de carbono esta sustituido opcionalmente con un sustituyente R^{14}, y en que R^{14} y R^{15} tienen los mismos significados que antes se definen, y todas las formas tautómeras y opcionalmente las formas de N-óxidos de los mismos

El presente invento se refiere ademas a un compuesto de Fórmula (1 0 0) en el que J^1 comprende especialmente un miembro seleccionado entre el grupo que consta de fenilo pirrolilo, pirrolidinilo, furanilo tienilo, pindilo, pirimidinilo, pipendinilo, piperazinilo, imidazolilo, imidazolidinilo, oxazolilo, isoxazolilo, morfolinilo, tiazolilo, indolilo, quinolinilo, isoquinolinilo, bencimidazolilo benzoxazolilo quinuclidinilo, y azabiciclo[3 3 0]octanilo, un resto cicloalquilo (C_3-C_7) monocíclico un resto cicloalquenilo (C_5-C_7) monocíclico que es un miembro seleccionado entre el grupo que consta de ciclopentenilo, ciclohexenilo y cicloheptenilo, y un resto cicloalquilo (C_7-C_{10}) o cicloalquenilo (C_7-C_{10}) bicíclico que es un miembro seleccionado entre el grupo que consta de norbornanilo, norbornenilo, biciclo[2 2 2]octanilo, biciclo[3 2 1]octanilo biciclo[3 3 0]octanilo, biciclo[2 2 2]oct-5-enilo, biciclo[2 2 2]oct-7-enilo biciclo[3 3 1]nonanilo, ciclodecanilo y adamantanilo

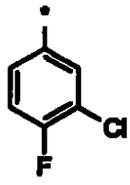
El presente invento se refiere todavia adicionalmente en especial a un compuesto de la Fórmula (1 0 0) en la que particularmente J^1 y los sustituyentes R^4, R^5 y R^6 se seleccionan de una manera tal que el extremo izquierdo de dicho compuesto de Fórmula (1 0 0) está representado por las siguientes Fórmulas parciales (2 0 1) hasta (2 0 72)



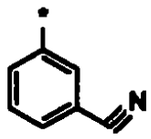
(2.0 1)



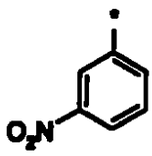
(2 0 2)



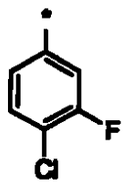
(2.0 3)



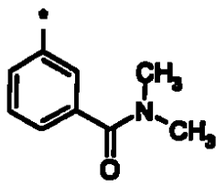
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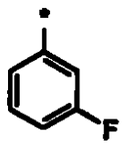
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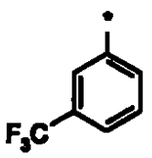
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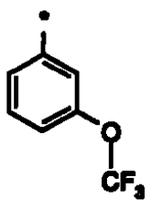
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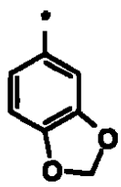
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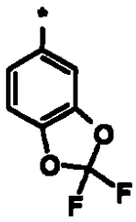
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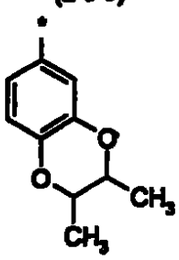
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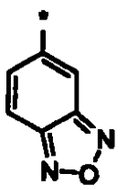
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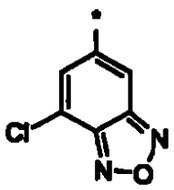
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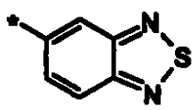
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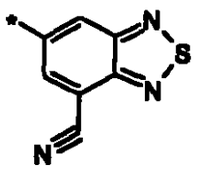
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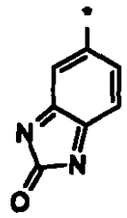
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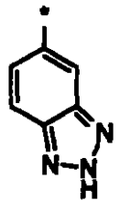
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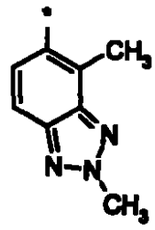
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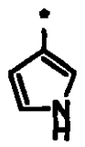
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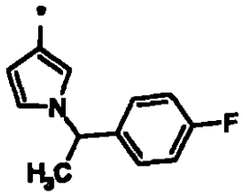
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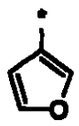
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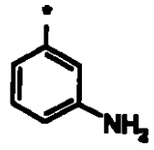
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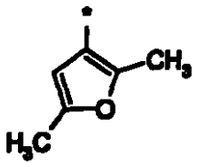
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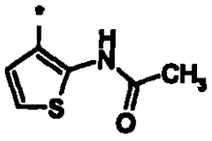
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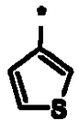
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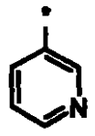
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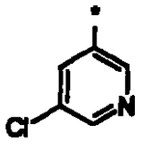
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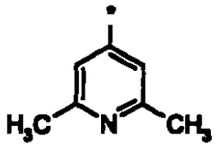
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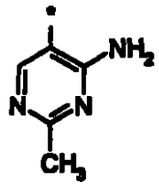
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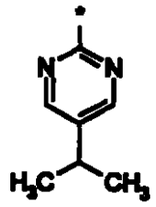
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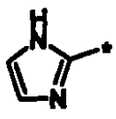
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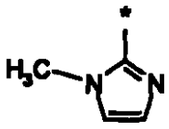
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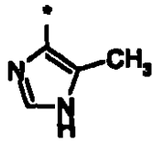
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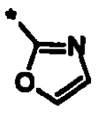
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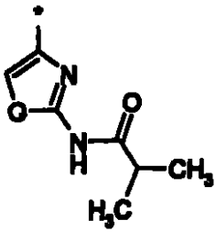
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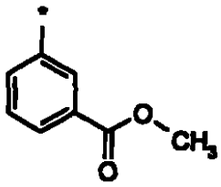
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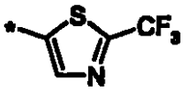
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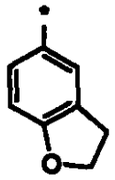
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(2 0 38)



(2 0 39)



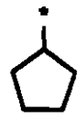
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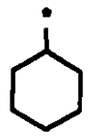
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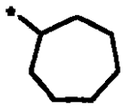
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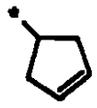
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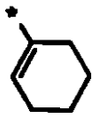
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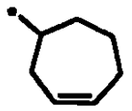
(2 0.45)



(2 0 46)



(2 0 47)



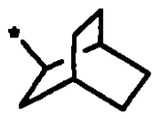
(2 0.48)



(2 0.49)



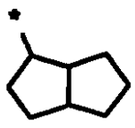
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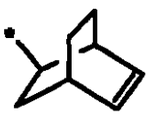
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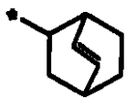
(2.0 52)



(2 0 53)



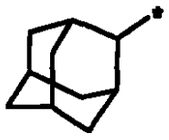
(2.0 54)



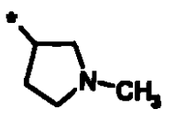
(2.0 55)



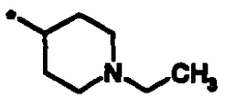
(2.0 56)



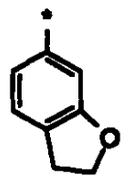
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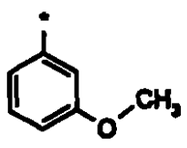
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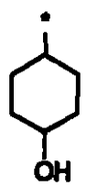
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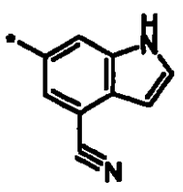
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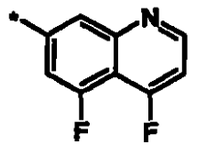
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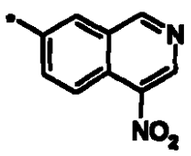
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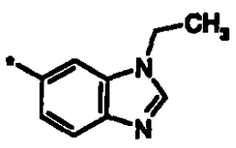
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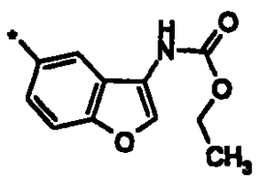
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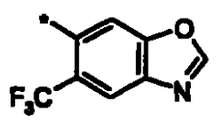
(2.0.65)



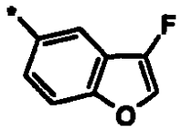
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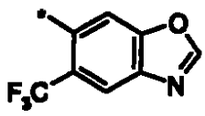
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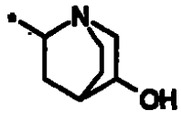
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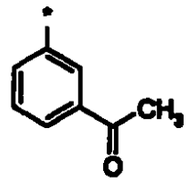
(2 0 69)



(2 0 70)



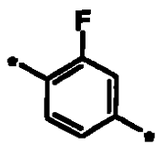
(2 0 71)



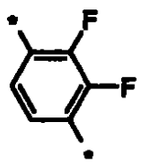
(2 0 72)

El presente invento se refiere adicionalmente a un compuesto de Fórmula (1 0 0) en el que J^2 comprende especialmente un miembro seleccionado entre el grupo que consta de fenilo, pirrolilo, pirrolidinilo, furanilo, tienilo, pirídilo, pirimidinilo, piperidinilo, piperazinilo, imidazolilo, imidazolidinilo, oxazolilo, isoxazolilo, tiazolilo, indolilo, quinolilo, isoquinolinilo, bencimidazolilo, benzoxazolilo, morfolinilo, quinuclidinilo, y azabiciclo-[3 3 0]octanilo, un resto cicloalquilo (C_3-C_7), un resto cicloalquenilo (C_5-C_7) monocíclico que es un miembro seleccionado entre el grupo que consta de ciclopentenilo, ciclohexenilo y cicloheptenilo, y un resto cicloalquilo (C_7-C_{10}) o cicloalquenilo (C_7-C_{10}) bicíclico que es un miembro seleccionado entre el grupo que consta de norbornanilo, norbornenilo biciclo[2 2 2]octanilo, biciclo[3 2 1]octanilo, biciclo[3 3 0]octanilo, biciclo-[2 2 2]oct-5-enilo, biciclo[2 2 2]oct-7-enilo, biciclo[3 3 1]nonanilo, ciclodecanilo y adamantanilo

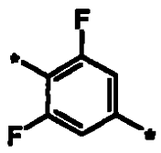
El presente invento se refiere adicionalmente en especial a un compuesto de Fórmula (1 0 0) en el que particularmente J^2 y los sustituyentes R^1 y R^2 se seleccionan de una manera tal que esta porción del extremo derecho de dicho compuesto de Fórmula (1 0 0) está representada por las siguientes Fórmulas parciales (2 5 1) hasta (2 5 50) presentadas seguidamente



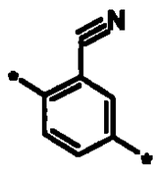
(2 5 1)



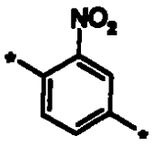
(2 5.2)



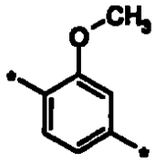
(2 5 3)



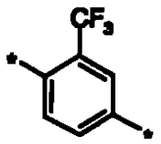
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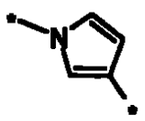
(2.5.5)



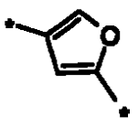
(2 5 6)



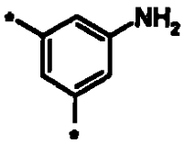
(2 5 7)



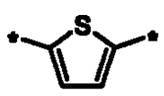
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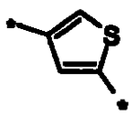
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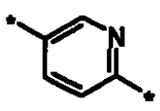
(2 5 10)



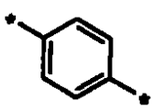
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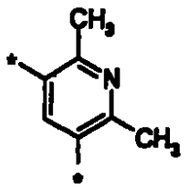
(2.5 12)



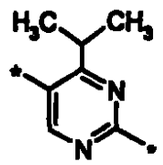
(2 5 13)



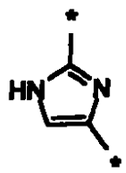
(2 5 14)



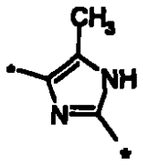
(2 5 15)



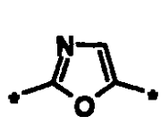
(2 5 16)



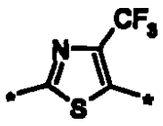
(2 5 17)



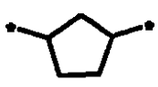
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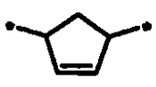
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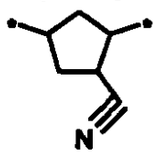
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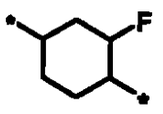
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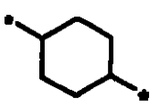
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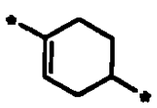
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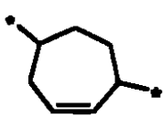
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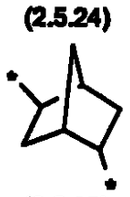
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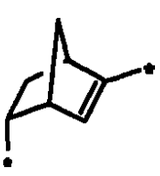
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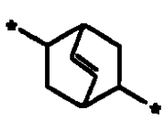
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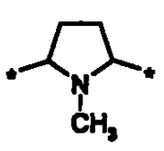
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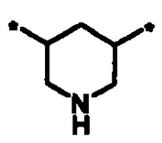
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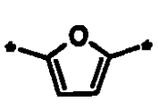
(2 5 30)



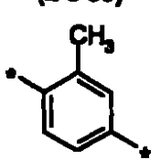
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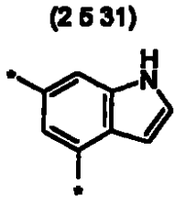
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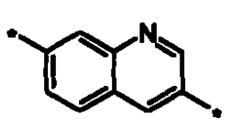
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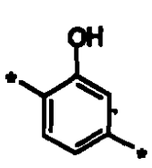
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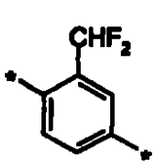
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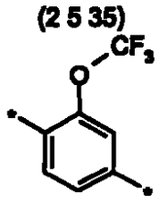
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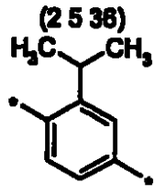
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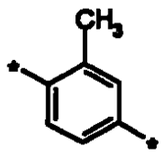
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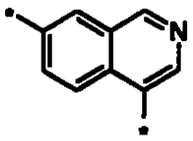
(2 5 39)



(2 5 40)



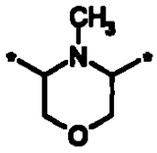
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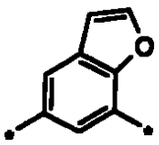
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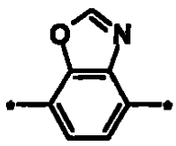
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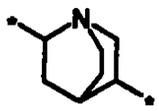
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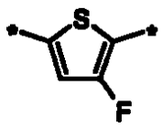
(2 5.45)



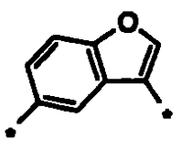
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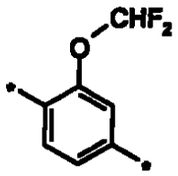
(2 5.47)



(2.5.48)

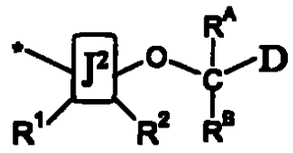


(2 5 49)



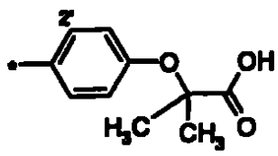
(2.5.50)

El presente invento se refiere todavía adicionalmente a un compuesto de Fórmula (1 0 0) caracterizado en lo que se refiere al lado derecho de la misma, cuando m es 1, por la Fórmula parcial (1 0 5)

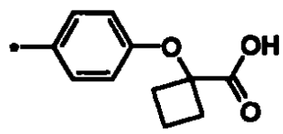


(1.0.5)

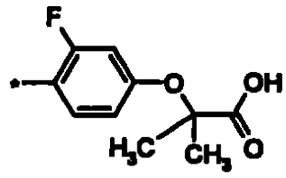
en la que "*" es un símbolo que representa el sitio de unión del grupo de Fórmula parcial (1 0 5) a la porción remanente de un compuesto de Formula (1 0 0), en que R^A y R^B son ambos -H, o uno de ellos es -H y el otro es $-CH_3$ o ambos son $-CH_3$, o ambos se toman conjuntamente para formar espiro-ciclopropilo o espiro-ciclobutilo, R^1 es -H, $-OCH_3$, ó 2'-F, R^2 es -H, y los restos J^2 y D se seleccionan de manera tal que dicho grupo de Fórmula parcial (1 0 5) es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (1 5 1) hasta (1 5 54) como se exponen seguidamente Cuando el resto J^2 es fenilo, la posición 2' del mismo está situada como se indica en la Fórmula parcial (1 5 1)



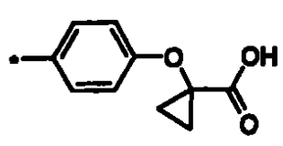
(1 5 1)



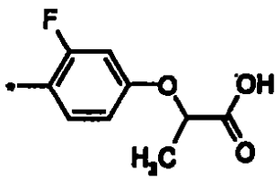
(1 5.2)



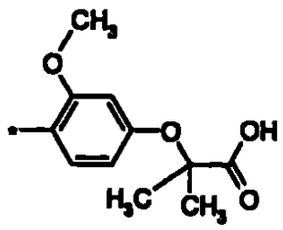
(1 5 3)



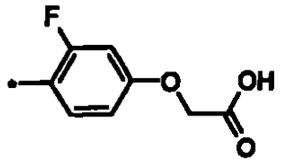
(1 5 4)



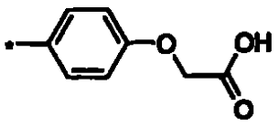
(1 5 5)



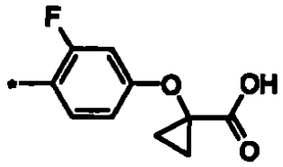
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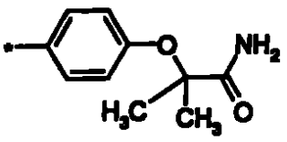
(1 5 7)



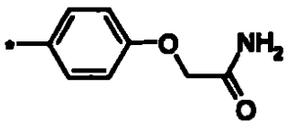
(1 5 8)



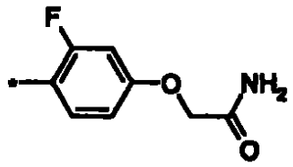
(1 5 9)



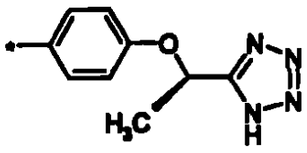
(1 5 10)



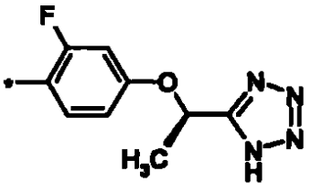
(1 5 11)



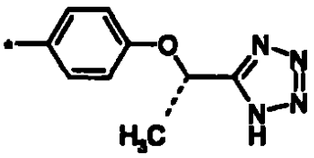
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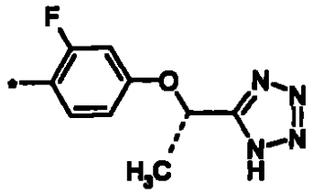
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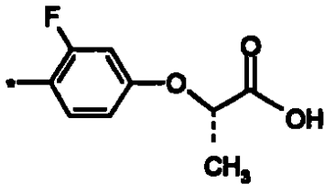
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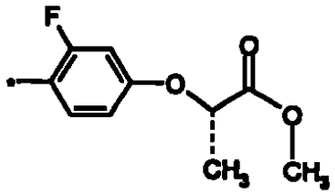
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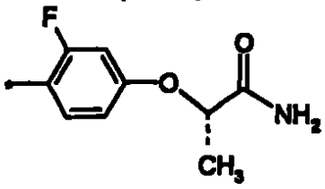
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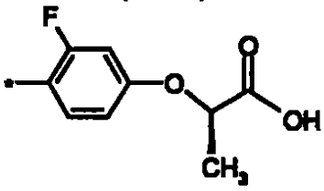
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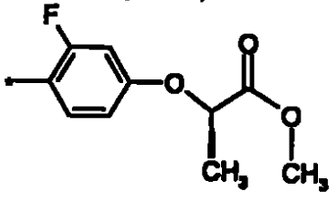
(1 5 18)



(1 5 19)

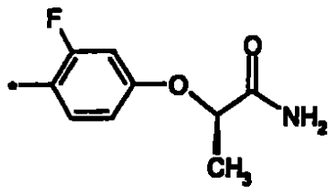


(1 5 20)

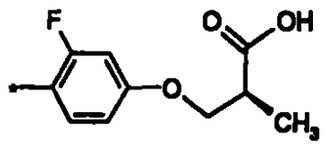


(1 5 21)

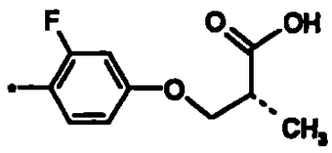
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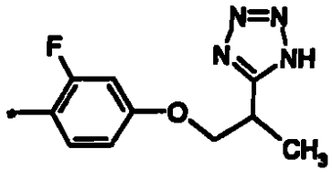
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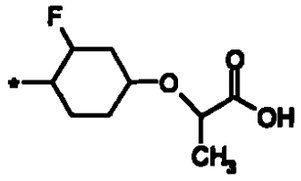
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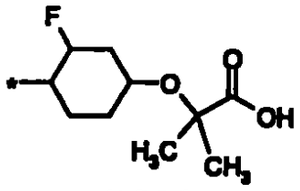
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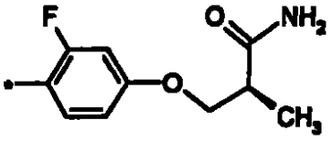
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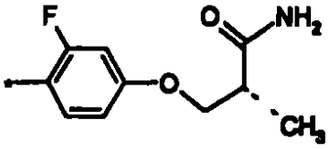
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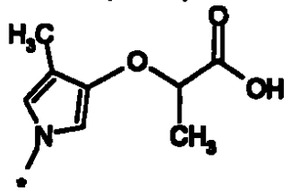
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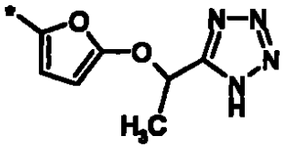
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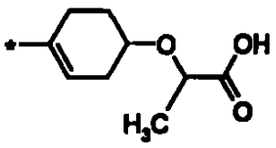
(1 5 29)



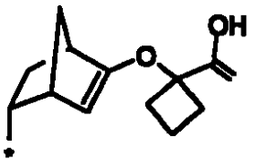
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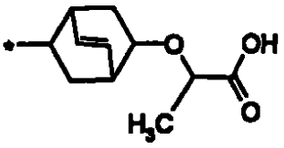
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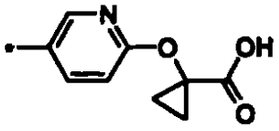
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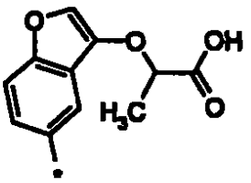
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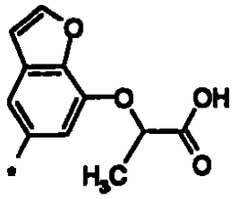
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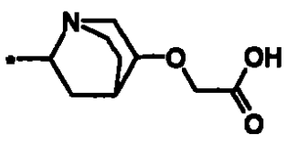
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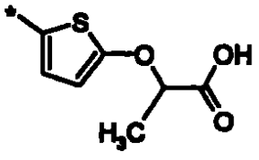
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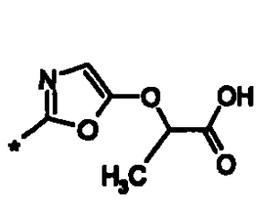
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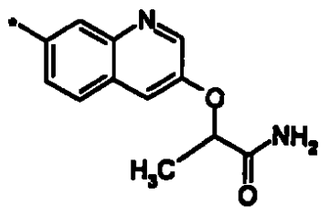
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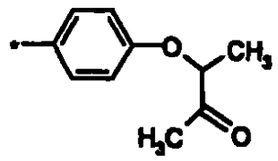
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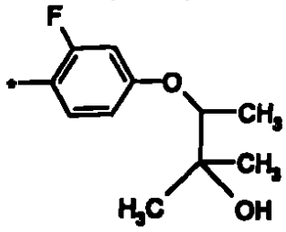
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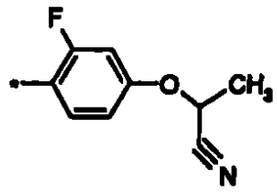
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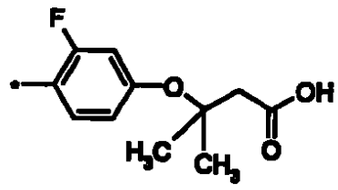
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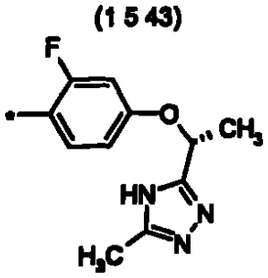
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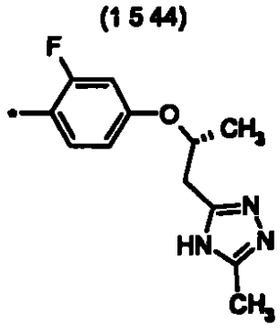
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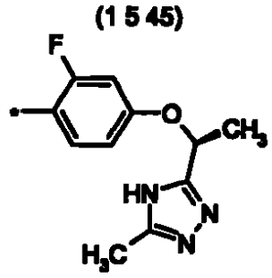
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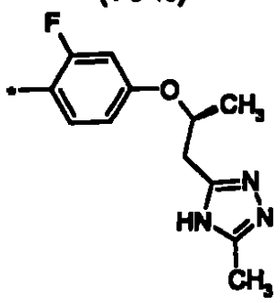
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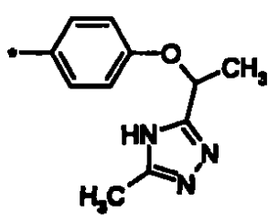
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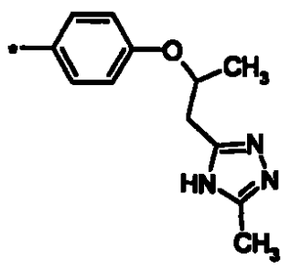
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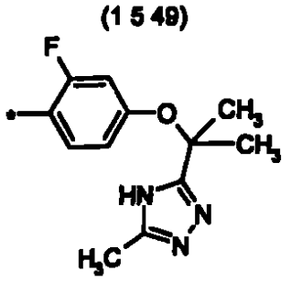
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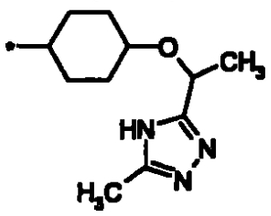
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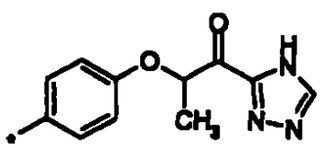
(1 5 51)



(1 5 52)



(1 5 53)



(1 5 54)

- en las que -

—[INH] indica el sitio de unión de cada uno de dichos grupos de Fórmula parcial (1 0 5),

representado por las Fórmulas parciales (1 5 1) hasta (1 5 54) con la porción remanente de la Fórmula (1 0 0)

El presente invento se refiere adicionalmente a un método para tratar a un individuo que padece de una enfermedad o condición mediada por la isozima de las PDE4 en su cometido de regular la activación y la desgranulación de eosinófilos humanos, que comprende administrar a dicho individuo que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de un compuesto de Fórmula (1 0 0) que antes se ha descrito Similarmente, el presente invento se refiere también a una composicion farmacéutica destinada a usarse en dicho tratamiento terapéutico, que comprende un compuesto de Fórmula (1 0 0) que antes se ha descrito juntamente con un vehículo farmacéuticamente aceptable

El presente invento se refiere a agentes inhibidores de las isozimas PDE4, que comprenden un compuesto de Fórmula (1 0 0) que se ha descrito anteriormente, que es util para tratar o prevenir uno o más miembros seleccionados entre el grupo de enfermedades, trastornos y condiciones que constan de

- un asma de cualquier tipo, etiología o patogénesis, o un asma que es un miembro seleccionado entre el grupo que consta de asma atópica, asma no atópica, asma alérgica, asma atópica bronquial, mediado por IgE, asma bronquial, asma esencial, asma verdadera, asma intrínseca causada por perturbaciones patofisiológicas asma extrinseca causada por factores ambientales, asma esencial de causa desconocida o no evidente, asma no atópica, asma bronquitica, asma enfisematosa, asma inducida por ejercicio, asma ocupacional, asma infecciosa causada por una infección bacteriana, fungica, protozoaria o vírica, asma no alérgico, asma incipiente, síndrome de niño que resuella con dificultad

- constricción crónica o aguda de los bronquios, bronquitis crónica, obstrucción de las vías respiratorias pequeñas, y enfisema,

- enfermedades obstructivas o inflamatorias de las vias respiratorias de cualquier tipo, etiología o patogénesis, o una enfermedad obstructiva o inflamatoria de las vías respiratorias que es un miembro seleccionado entre el grupo que consta de asma, neuomoconiosis, neumonía eosinofílica crónica, enfermedad pulmonar obstructiva crónica (COPD), una COPD que incluye bronquitis crónica, enfisema pulmonar o disnea asociada con ella, una COPD que está caractenzada por una obstrucción irreversible y progresiva de las vías respiratorias, síndrome de ahogo respiratorio de adultos (ARDS), y exacerbación de la hiper-reactividad de las vias respiratorias consiguiente a otra terapia con fármacos,

- una neumoconiosis de cualquier tipo, etiología o patogénesis, o una neumoconiosis que es un miembro seleccionado entre el grupo que consta de aluminosis o

enfermedad de obreros causada por bauxita, antracosis o asma de mineros, asbestosis o asma de instaladores de vapor de agua, calicosis o enfermedad del pedernal ptilosis causada por una inhalación del polvo fino procedente de las plumas de avestruz, siderosis causada por la inhalación de partículas de hierro, silicosis o enfermedad de los amoladores, bisinosis o asma causada por el polvo fino de algodón, y neumoconiosis causada por talco,

- una bronquitis de cualquier tipo, etiología o patogénesis, o una bronquitis que es un miembro seleccionado entre el grupo que consta de bronquitis aguda, bronquitis laringotraqueal aguda bronquitis araquídica (causada por cacahuete), bronquitis catarral, bronquitis crupal o garrotillo, bronquitis seca, bronquitis asmática infecciosa, bronquitis productiva, bronquitis causada por estafilococos o estreptococos, y bronquitis vesicular;

- una bronquiectasia de cualquier tipo, etiología o patogénesis, o una bronquitiectasia que es un miembro seleccionado entre el grupo que consta de bronquiectasia cilíndrica, bronquiectasia saculada, bronquiectasia fusiforme bronquiectasia capilar bronquiectasia cística bronquiectasia seca, y bronquiectasia folicular,

- rinitis alérgica estacional, o rinitis alérgica perenne, o una sinusitis de cualquier tipo, etiología o patogénesis, o una sinusitis que es un miembro seleccionado entre el grupo que consta de sinusitis purulenta o no purulenta, sinusitis aguda o crónica, y sinusitis del hueso etmoides, frontal, maxilar o esfenoides

- una artritis reumatoide de cualquier tipo, etiología o patogénesis, o una artritis reumatoide que es un miembro seleccionado entre el grupo que consta de artritis aguda, artritis gotosa aguda, artritis inflamatoria crónica, artritis degenerativa, artritis infecciosa, artritis de Lyme, artritis proliferante, artritis psoriásica, y artritis vertebral,

- gota, así como fiebre y dolor asociados con una inflamación,

- una enfermedad relacionada con eosinófilos de cualquier tipo, etiología o patogenesis, o una enfermedad relacionada con eosinófilos que es un miembro seleccionado entre el grupo que consta de eosinofilia, eosinofilia por infiltración pulmonar, síndrome de Loffler; neumonía eosinofílica crónica, eosinofilia pulmonar tropical, aspergilosis bronconeumónica, aspergiloma, granulomas que contienen eosinófilos, angitis granulomatosa alergica o síndrome de Churg-Strauss, poliarteritis nodosa (PAN), y vasculitis necrotizante sistémica,

- dermatitis atópica, o dermatitis alérgica, o eczema alérgico o atópico,

- una urticaria de cualquier tipo, etiología o patogénesis, o una urticaria que es un miembro seleccionado entre el grupo que consta de urticaria mediada por inmunidad, urticaria mediada por el complemento urticaria inducida por material urticariogénico, urticaria inducida por agentes físicos, urticaria inducida por estrés, urticaria idiopática, urticaria aguda, urticaria crónica, angioedema, urticaria colinérgica, urticaria al frío en la

forma dominante autosómica o en la forma adquirida, urticaria por contacto, urticaria gigante y urticaria papulosa,

- una conjuntivitis de cualquier tipo etiología o patogénesis, o una conjuntivitis que es un miembro seleccionado entre el grupo que consta de conjuntivitis actínica, conjuntivitis catarral aguda, conjuntivitis contagiosa aguda, conjuntivitis alérgica, conjuntivitis atópica, conjuntivitis catarral crónica, conjuntivitis purulenta, y conjuntivitis vernal,

- una uveítis de cualquier tipo etiología o patogénesis, o una uveítis que es un miembro seleccionado entre el grupo que consta de una inflamación de la totalidad o una parte de la uvea, uveitis anterior, iritis, ciclitis, iridociclitis, uveítis granulomatosa, uveítis no granulomatosa, uveítis facoantigénica uveitis posterior, coroiditis, y coriorretinitis,

- psoriasis,

- una esclerosis multiple de cualquier tipo, etiología o patogénesis, o una esclerosis multiple que es un miembro seleccionado entre el grupo que consta de esclerosis multiple progresiva primaria y esclerosis multiple en remisión y en relapso,

- enfermedades autoinmunitarias/inflamatorias de cualquier tipo, etiología o patogénesis, o una enfermedad autoinmunitaria/inflamatoria que es un miembro seleccionado entre el grupo que consta de trastornos hematológicos autoinmunitarios, anemia hemolítica anemia aplásica anemia de glóbulos rojos puros, purpura trombocitopénica idiopatica lupus eritematoso sistémico, policondritis, esclerodermia, granulomatosis de Wegner dermatomiositis, hepatitis activa crónica, miastenia grave, síndrome de Stevens-Johnson psilosis idiopática, enfermedades inflamatorias autoinmunitarias de los intestinos, colitis ulcerativa enfermedad de Crohn oftalmopatía endocrina, enfermedad de Grave sarcoidosis alveolitis neumonitis por hipersensibilidad crónica cirrosis biliar primaria diabetes juvenil o diabetes mellitus del tipo I, uveítis anterior, uveítis granulomatosa o posterior, queratoconjuntivitis seca, queratoconjuntivitis epidémica, fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial, fibrosis pulmonar idiopatica, fibrosis cistica artritis psoriásica, glomerulonefritis con y sin síndrome nefrótico glomerulonefritis aguda, síndrome nefrótico idiopático nefropatía por cambios mínimos, enfermedades inflamatorias/hiperproliferativas de la piel, psoriasis, dermatitis atópica, dermatitis por contacto, dermatitis alergica por contacto, pénfigo familiar benigno, pénfigo eritematoso, pénfigo foliáceo, y pénfigo vulgar;

- prevención del rechazo alogeneico de un injerto como continuación del transplante de un órgano,

- una enfermedad inflamatoria de los intestinos (IBD, de *inflammatory bowel disease*) de cualquier tipo, etiología o patogénesis, o una enfermedad inflamatoria de los intestinos que es un miembro seleccionado entre el grupo de consta de colitis ulcerativa

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(UC, de *ulcerative colitis*), colitis colagenosa colitis poliposa, colitis transmural, y enfermedad de Crohn (CD de *Crohn's disease*),

- un choque septico de cualquier tipo, etiologia o patogénesis, o un choque séptico que es un miembro seleccionado entre el grupo que consta de fallo renal, fallo renal agudo, caquexia, caquexia malánca caquexia de la hipófisis, caquexia urémica, caquexia cardiaca caquexia suprarrenal o enfermedad de Addison, caquexia cancerosa, y caquexia como consecuencia de una infección por el virus de la inmunodeficiencia humana (HIV de *human immunodeficiency virus*),

- lesión del hígado,

- hipertensión pulmonar; e hipertensión pulmonar inducida por hipoxia,

- enfermedades con pérdida de hueso, osteoporosis primana, y osteoporosis secundaria,

- trastornos del sistema nervioso central de cualquier tipo, etiología o patogénesis o un trastorno del sistema nervioso central que es un miembro seleccionado entre el grupo que consta de una depresión, la enfermedad de Parkinson, perjuicio del aprendizaje y de la memoria, discinesia tardía dependencia de drogas o fármacos, demencia arteroesclerótica, y demencias que acompañan a la corea de Huntington, la enfermedad de Wilson, parálisis agitante, y atrofias del tálamo,

- una infección, especialmente una infección causada por virus, en que dichos virus aumentan la producción de TNF-α en su hospedante, o en que dichos virus son sensibles a la regulación creciente del TNF-α en su hospedante de manera tal que se impacta desfavorablemente sobre su replicación u otras actividades vitales inclusive un virus que es un miembro seleccionado entre el grupo que consta de HIV-1, HIV-2 y HIV-3, citomegalovirus, CMV, los de influenza, los adenovirus, y los virus de Herpes, inclusive los de *Herpes zoster* y *Herpes simplex*,

- infecciones causadas por levaduras y hongos, en que dichas levaduras y dichos hongos son sensibles a la regulación creciente por TNF-α o provocan la producción de TNF-α en su hospedante p ej , meningitis fungica, particularmente cuando se administra en conjunción con otros fármacos selectos para el tratamiento de infecciones sistémicas causadas por levaduras y hongos, inclusive, pero sin limitarse a, polimixinas, p ej , Polimicina B, imidazoles, p ej , clotrimazol, econazol, miconazol y ketoconazol triazoles p ej , fluconazol e itranazol y anfotericinas, p ej , Anfotericina B y Anfotericina B liposomal,

- lesión por isquemia y reperfusión, diabetes autoinmunitaria, autoinmunidad de la retina, leucemia crónica de linfocitos, infecciones causadas por un HIV, lupus eritematoso, enfermedad de riñones y uréteres, trastornos urogenitales y gastrointestinales, y enfermedades de la próstata

En particular los compuestos de Fórmula (1 0 0) son utiles en el tratamiento de (1) enfermedades y condiciones inflamatorias que comprenden una inflamación de las articulaciones, artritis reumatoide, espondilitis reumatoide, osteoartritis enfermedad inflamatoria de los intestinos, colitis ulcerativa, glomerulonefritis crónica, dermatitis y enfermedad de Crohn, (2) enfermedades y condiciones respiratorias que comprenden asma, sindrome de ahogo respiratorio agudo, enfermedad inflamatoria pulmonar crónica, bronquitis, enfermedad obstructiva crónica de las vías respiratorias, y silicosis, (3) enfermedades y condiciones infecciosas que comprenden septicemia, choque séptico, choque endotóxico septicemia gram negativa, síndrome del choque tóxico, fiebre y mialgias debidas a infecciones causadas por bacterias, virus u hongos e influenza, (4) enfermedades y condiciones inmunitarias que comprenden diabetes autoinmunitaria, lupus sistémico eritematoso, reacción de injerto frente a hospedante rechazos de aloinjertos, esclerosis multiple psoriasis y rinitis alérgica, y (5) otras enfermedades y condiciones que comprenden enfermedades de resorción ósea lesión por reperfusión, caquexia secundaria a una infección o malignidad, caquexia secundaria al síndrome de inmunodeficiencia adquirida humana (SIDA), infección causada por un virus de inmunodeficiencia humana (HIV) o un complejo relacionado con el SIDA (ARC de *AIDS related complex*) formación de queloides, formación de tejido cicatricial, diabetes mellitus del tipo 1, y leucemia

El presente invento se refiere todavía adicionalmente a la combinación de un compuesto de Fórmula (1 0 0) juntamente con uno o más miembros seleccionados entre el grupo que consta de los siguientes (a) agentes inhibidores de la biosíntesis de leucotrienos agentes inhibidores de 5-lipoxigenasa (5-LO) y agentes antagonistas de la proteina activadora de 5-lipoxigenasa (FLAP) seleccionados entre el grupo que consta de zileuton ABT-761 fenleuton, tepoxalin, Abbott-79175, Abbott-85761, tiofeno-2-alquil-sulfonamidas (sustituidas en posición 5)en N de Fórmula (5 2 8), 2,6-di-*terc* -butil-fenol-hidrazonas de Fórmula (5 2 10), la clase de metoxi-tetrahidropiranos que incluye el Zeneca ZD-2138 de Fórmula (5 2 11), el compuesto SB-210661 de Fórmula (5 2 12) y la clase a la que éste pertenece, la clase de compuestos de 2-ciano-naftaleno sustituidos con pindinilo a los que pertenece el L-739,010, la clase de compuestos de 2-ciano-quinolina a los que pertenece el L-746,530, las clases de compuestos de indol y quinolina a los que pertenecen MK-591, MK-886 y BAY x 1005, (b) agentes antagonistas de receptores para leucotrienos LTB_4, LTC_4, LTD_4 y LTE_4 seleccionados entre el grupo de la clase de compuestos de fenotiazin-3-ona a los que pertenece el L-651,392, la clase de compuestos de amidino a los que pertenece el CGS-25019c, la clase de benzoxazol-aminas a la que pertenece el ontazolast la clase de benceno-carboximido-amidas a la que pertenece el BIIL 284/260, y las clases de compuestos a los que pertenecen

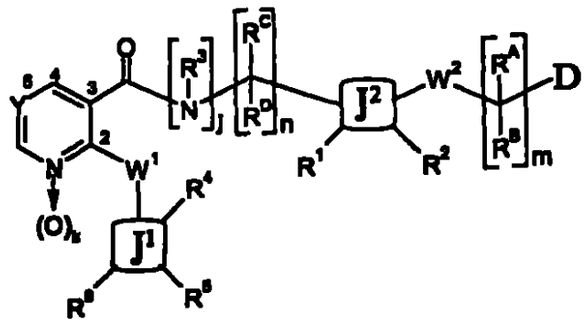
zafirlukast, ablukast montelukast pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A) y BAY x 7195, (c) agentes inhibidores de las PDE4, inclusive agentes inhibidores de la isoforma PDE4D, (d) agentes inhibidores de 5-lipoxigenasa (5-LO) o agentes antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP), (e) dobles agentes inhibidores de 5-lipoxigenasa (5-LO) y antagonistas del factor activador de plaquetas (PAF), (f) agentes antagonistas de leucotrienos (LTRA's) inclusive antagonistas de LTB_4, LTC_4, LTD_4 y LTE_4, (g) agentes antagonistas de receptores H_1 antihistamínicos inclusive cetirizina, loratadina, desloratadina, fexofenadina, astemizol, azelastina y clorofeniramina (h) agentes antagonistas de receptores H_2 protectores del estómago, (i) agentes simpatomiméticos vasoconstrictores agonistas de α_1- y α_2-adrenoceptores administrados por vía oral o tópica para uso descongestionante, inclusive propilhexedrina, fenilefrina, fenilpropanolamina, pseudoefedrina, hidrocloruro de nafazolina, hidrocloruro de oximetazolina, hidrocloruro de tetrahidrozolina, hidrocloruro de xilometazolina e hidrocloruro de etilnorepinefrina, (j) agentes agonistas de α_1- y α_2-adrenoceptores en combinación con agentes inhibidores de 5-lipoxigenasa (5-LO), (k) agentes anticolinérgicos inclusive bromuro de ipratropio bromuro de tiotropio bromuro de oxitropio, pirenzepina, y telenzepina (l) agentes agonistas de β_1- a β_4-adrenoceptores, inclusive metaproterenol, isoproterenol, isoprenalina, albuterol, salbutamol, formoterol, salmeterol, terbutalina, orciprenalina, mesilato de bitolterol y pirbuterol, (m) metil-xantaninas inclusive teofilina y aminofilina (n) cromoglicato de sodio, (o) agentes antagonistas de receptores muscarínicos (M1, M2 y M3), (p) agentes inhibidores de COX-1 (NSAID's), agentes inhibidores selectivos de COX-2 inclusive rofecoxib y NSAID's con óxido nítrico, (q) compuestos miméticos del factor de crecimiento del tipo I similar a insulina (IGF-1) (r) ciclesonida, (s) glucocorticoides inhalados con efectos colaterales sistémicos reducidos inclusive prednisona, prednisolona, flunisolida, acetonuro de triamcinolona, dipropionato de beclometasona, budesonida, propionato de fluticasona y furoato de mometasona, (t) agentes inhibidores de triptasas, (u) agentes antagonistas del factor activador de plaquetas (PAF), (v) anticuerpos monoclonales activos contra entidades inflamatorias endógenas, (w) IPL 576, (x) agentes contra el factor de necrosis de tumores (TNFα) inclusive Etanercept, Infliximab y D2E7, (y) DMARD's inclusive Leflunomida, (z) péptidos de TCR, (aa) agentes inhibidores de la enzima convertidora de interleucina (ICE), (bb) agentes inhibidores de IMPDH, (cc) agentes inhibidores de moléculas de adhesión inclusive agentes antagonistas de VLA-4, (dd) catepsinas, (ee) agentes inhibidores de cinasas de MAP, (ff) agentes inhibidores de la deshidrogenasa de glucosa-6-fosfato, (gg) agentes antagonistas B_1 y B_2 de receptores de cininas, (hh) oro en la forma de un grupo aurotio juntamente con diversos grupos hidrófilos, (ii) agentes supresores de inmunidad, p ej , ciclosporina, azatioprina y

metotrexato (jj) agentes contra la gota p ej , colquicina, (kk) agentes inhibidores de xantina-oxidasas p ej , alopurinol, (ll) agentes uricosuricos, p ej , probenecida, sulfinpirazona y benzobromarona, (mm) agentes antineoplásicos, especialmente fármacos antimitoticos inclusive los alcaloides de vinca tales como vinblastina y vincristina, (nn) secretagogos de hormonas del crecimiento, (oo) agentes inhibidores de metaloproteasas de matriz (MMP's) a saber, las estromelisinas, las colagenasas y las gelatinasas, así como agrecanasa especialmente colagenasa-1 (MMP-1), colagenasa-2 (MMP-8), colagenasa-3 (MMP-13), estromelisina-1 (MMP-3), estromelisina-3 (MMP-10) y estromelisina-3 (MMP-11) (pp) factor del crecimiento transformante (PGFβ), (qq) factor del crecimiento derivado de plaquetas (PDGF), (rr) factor del crecimiento de fibroblastos, p ej , factor de crecimiento de fibroblastos de carácter básico (bFGF), (ss) factor estimulador de colonias de macrófagos y granulocitos (GM-CSF), (tt) crema de capsaicina, (uu) agentes antagonistas de receptores de Taquicininas NK_1 u NK_3 seleccionados entre el grupo que consta de NKP-608C SB-233412 (talnetant) y D-4418 y (vv) agentes inhibidores de elastasas seleccionados entre el grupo que consta de UT-77 y ZD-0892

DESCRIPCIÓN DETALLADA DEL INVENTO

5 0 Compuestos

El presente invento se refiere a nuevos compuestos que se pueden representar por la Fórmula (1 0 0) que sigue



(1 0.0)

El alcance más amplio de los compuestos del presente invento se circunscribe con anterioridad dentro de la sección 4 0 relacionada con el Sumario del invento Una descripción adicional de dichos compuestos se proporciona seguidamente en términos de una gama de diferentes tipos y grupos de realizaciones, así como realizaciones específicas que caracterizan y ejemplifican a los compuestos de Fórmula (1 0 0) Realizaciones preferidas y más preferidas de dichos compuestos se exponen asimismo,

pero se entenderá que la citación de dichas preferencias no esta destinada de ninguna manera a limitar el alcance del presente invento en lo que se refiere a dichos compuestos, y no lo limita

Como se usa en el presente contexto, se pretende que las expresiones "alquilo (C_1-C_3)", "alquilo (C_1-C_4)" y "alquilo (C_1-C_8)" así como variaciones equivalentes de las mismas, incluyan conformaciones de cadena ramificada así como de cadena lineal de estos grupos alifáticos Por lo tanto, las expresiones antes señaladas incluyen, además de las entidades de cadena lineal metilo etilo, *n*-propilo, *n*-butilo, *n*-pentilo y *n*-hexilo las entidades de cadena ramificada iso-propilo, *iso*-butilo, *sec* -butilo, *terc* -butilo, *iso*-pentano (2-metil-butano), 2-metil-pentano, 3-metil-pentano, 1-etil-propano y 1-etil-butano Los significados de las expresiones antes señaladas están destinadas también a aplicarse a dichas expresiones, independientemente de que estas entidades estén o no sustituidas Por lo tanto la expresión "alquilo (C_1-C_3) fluorado" está destinada a abarcar las diversas especies fluoradas de los grupos alifáticos *n*-propilo e *iso*-propilo

Como se usa en el presente contexto, la expresión "sistema anular de carbonos, saturado o insaturado que es monocíclico de 3 a 7 miembros" se destina a incluir sistemas anulares de carbonos monocíclicos saturados tales como ciclopropano, ciclobutano ciclopentano, ciclohexano y cicloheptano La expresión antes señalada está destinada también a incluir sistemas anulares de carbono monocíclicos mono-insaturados, tales como ciclopenteno, ciclohexeno y cicloheptено, así como sistemas anulares de carbonos monocíclicos aromáticos tales como fenileno

Como se usan en el presente contexto las expresiones "policíclicos condensados o discontinuos" y "policíclicos condensados" están destinadas a significar en primer lugar un sistema anular de carbonos, que tiene dos o más anillos especialmente bicíclicos y tricíclicos, más especialmente bicíclicos, en los que los anillos están condensados, es decir en los que hay presentes por lo menos un par de átomos de carbono de cabeza de puente Estos sistemas de anillos policíclicos pueden ser saturados o insaturados En segundo lugar, la expresión antes señalada está destinada a significar un sistema anular de carbonos, que tiene dos o más anillos en que dichos anillos son discontinuos, es decir que están unidos uno con otro por un enlace covalente simple o doble y no hay presentes átomos de carbono de cabeza de puente, estos sistemas anulares policíclicos pueden ser también saturados o insaturados

El resto J^1 puede ser discontinuo mientras que el resto J^2 puede no ser discontinuo Se prevé también en el presente contexto que J^2 puede no tener el significado de un resto que es bianlo o discontinuo La expresión "bianlo" como se utiliza en el presente contexto, está destinada a significar un sistema anular policíclico

condensado como se define inmediatamente antes, en que (1) los átomos de carbono de cabeza de puente estan unidos por un enlace es decir, que no hay presentes átomos de carbono adicionales entre dichos atomos de carbono de cabeza de puente, y (2) los heteroátomos, si estan presentes, están contenidos solamente en un sistema anular condensado tricíclico o policíclico de orden superior Además, tal como ya se ha mencionado, J^2 puede no ser discontinuo, tal como se define esta expresión inmediatamente antes

Consiguientemente, los tipos de sistemas anulares bianlo y discontinuos que pueden constituir un significado de J^1, pero que pueden no constituir un significado de J^2 incluyen, entre otros los siguientes bifenilo, bifenileno, fluoreno 9H-carbazol fenantridina fenantreno, 2,2'-bipirdina, iminodibencilo, 2,2'-biquinolina, naftaleno, 2-fenil-naftaleno 1-fenil-naftaleno, difenil-metano, 1-fenil-pipendina, 1-fenil-piperazina, bibencilo, azuleno, 4,4'-difenil-2 2 -dipiridilo 1-(difenil-metil)azetidina, 4,5-difenil-oxazol, 2,5-difenil-oxazol, difenil-2-piridilmetano y difenil-4-piridilmetano, 3,6-difenil-1,2,4,5-tetrazina, 1-bencil-piperazina 1-bencil-pipendina, 2-bencil-pirdina, 3-bencil-pirdina y 4-bencil-pirdina, 4 5-difenil-imidazol fenotiazina, fenoxazina, fenazina, 1-fenil-3,4-dihidronaftaleno, 2-fenil-indeno, 2-fenil-indol, 4-fenil-morfolina, 2-fenil-benzotiazol 2-fenil-benzoxazol, y 2-fenil-bencimidazol

Los tipos antes citados de sistemas anulares de bianlo y discontinuos pueden constituir, por otro lado, un significado de J^1 Como una ilustración adicional se entenderá que p ej , un resto naftilo es bianlo como aquí se define, puesto que es un anillo bicíclico condensado con un enlace entre los átomos de carbono de cabeza de puente y no hay presentes heteroátomos Un resto de quinolinilo, por otro lado, mientras que también es un sistema bicíclico condensado con un enlace entre los átomos de carbono de cabeza de puente, no es bianlo como aquí se define, puesto que está presente también un heteroátomo de nitrógeno, y la definición de "bianlo" requiere que en dicho caso el sistema anular condensado sea tricíclico o policíclico de orden superior El resto bifenilo es un ejemplo de un sistema anular discontinuo que, correspondientemente, puede ser un significado de J^1 pero puede no ser un significado de J^2

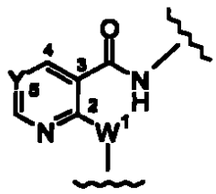
Como se usa en el presente contexto se pretende que la expresión "sistema anular de carbonos, saturado o insaturado que es de 7 a 12 miembros, condensado o discontinuo, policíclico" incluya los sistemas anulares de carbonos, bicíclicos y tricíclicos condensados saturados, tales como norbornano, biciclo[2 2 2]octanilo, biciclo[3 2 1]octanilo, biciclo[3 3 0]octanilo, biciclo[3 3 1]nonanilo, ciclodecanilo, y adamantanilo Se pretende también que la expresion antes señalada incluya sistemas

anulares de carbonos bicíclicos y tricíclicos tales como norbornenilo, biciclo[2 2 2]oct-5-enilo, y biciclo[2 2 2]oct-7-enilo, así como sistemas anulares de carbonos bicíclicos y tricíclicos aromáticos, tales como naftileno y bifenileno, se pretende además que la expresión antes señalada incluya sistemas anulares de carbonos bicíclicos discontinuos aromáticos tales como bifenileno

Los sistemas anulares de carbonos incluidos dentro del alcance de la expresion antes señalada y que antes se describen, incluyen también restos en los que opcionalmente uno de sus átomos de carbono se puede reemplazar por un heteroátomo seleccionado entre N O y S, y cuando se selecciona el N, opcionalmente un segundo átomo de carbono de los mismos se puede reemplazar por un heteroátomo seleccionado entre N O y S Los restos resultantes incluyen pirrolilo, pirrolidinilo furanilo, tienilo, pirídilo, pirimidinilo piperidinilo, piperazinilo, imidazolilo, imidazolidinilo, oxazolilo isoxazolilo, tiazolilo, indolilo, quinolinilo, isoquinolinilo bencimidazolilo, benzoxazolilo, morfolinilo, quinuclidinilo, y azabiciclo[3 3 0]octanilo

Como se usa en el presente contexto con respecto a los compuestos de Fórmula (1 0 0), así como otras fórmulas y fórmulas parciales relacionadas con ellas, en los que uno o mas componentes de atomos de nitrógeno de los mismos es o son representado(s) como [N⇨(O)], este o éstos comprende(n) una forma opcional de óxido de nitrógeno de dichos átomos de nitrógeno Cuando hay más de una de dichas formas de óxidos de nitrógeno, éstas se seleccionan independientemente unas de otras Además, se apreciará que dichas formas de óxidos de nitrógeno se pueden representar también como "[N⇨(O)$_u$]" en que u es 0 ó 1

Una porción del nucleo central de los compuestos de Fórmula (1 0 0) es la de una nicotinamida de Fórmula (1 0 1)



(1 0 1)

derivada de ácido nicotínico Esta porción del nucleo central es luego elaborada definiendo el resto Y como que es =C(R^1$_k$)-, o -[N⇨(O)$_k$]- en que k es 0 ó 1, y en que el símbolo ⇨(O) indica un heteroátomo de nitrógeno en la forma de su N-óxido cuando k es 1 Deberá señalarse que en los restos heterociclilo con un contenido de N, que definen a R^8 se prevé que opcionalmente uno o más de los heteroátomos N que comprenden dichos restos heterociclilo pueden estar en la forma del N-óxido de dichos

heteroátomos de N Correspondientemente, las consideraciones que implican a los N-óxidos que se acaban de describir se aplican también a dichos restos que contienen N-óxidos que definen a R^8

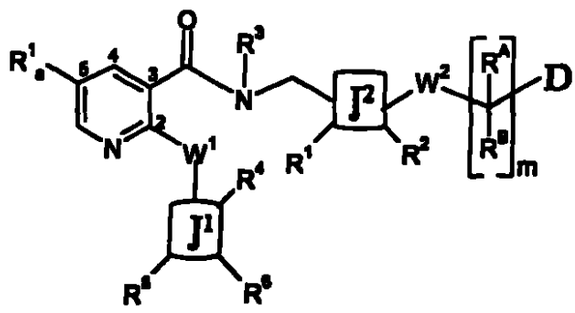
Cuando Y tiene el significado de -[N→(O)$_k$]- los compuestos del presente invento son pirimidinas El grupo pirimidino de compuestos de la Fórmula (1 0 0) es una parte importante del alcance del presente invento Se prefiere, no obstante, que los compuestos de Fórmula (1 0 0) tengan el resto Y definido como =C(R^1_a)- en que el sustituyente R^1_a se selecciona independientemente de los otros sustituyentes que forman los compuestos de Fórmula (1 0 0)

Ademas de -H, el R^1_a del resto =C(R^1_a)- es definido como un miembro seleccionado entre el grupo que consta de -F, -Cl, -CN, -NO_2, alquilo (C_1-C_4), alquinilo (C_2-C_4), alquilo (C_1-C_3) fluorado, alcoxi (C_1-C_3) fluorado, -OR^{16}, y -C(=O)$NR^{12}_aR^{12}_b$, en que R^{12}_a y R^{12}_b son, cada uno de ellos independientemente, -H -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_3$, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, ciclopropilo, ciclobutilo o ciclopentilo

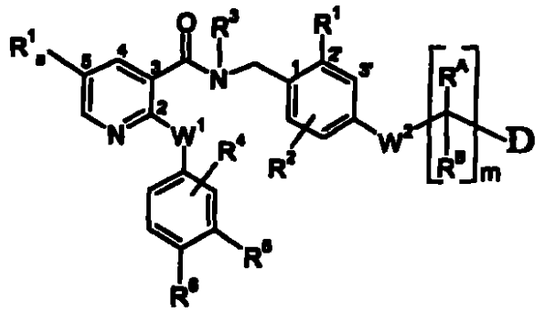
Sin embargo se prefiere que el sustituyente R^1_a del resto =C(R^1_a)- tenga el significado de -H, -F -Cl -CH_3 -OCH_3 o alquinilo (C_2-C_4), más preferiblemente R^1_a es -F ó -H

Se señalará que R^1_a tiene diversas definiciones de los sustituyentes, especialmente -F en comun con las de los sustituyentes R^1 y R^2 situados en el resto J^2 En las realizaciones de los compuestos de Fórmula (1 0 0) en que Y es =C(R^1_a)-, y tanto el resto J^1 como el resto J^2 tienen el significado preferido de fenilo, los sustituyentes situados en la posición 5 del nucleo central de la nicotinamida y en la posición 2' del grupo bencilo unido a porción amido del mismo, se seleccionan entre el mismo grupo de definiciones, aunque sobre una base independiente Las realizaciones del presente invento en las que están implicados dichos sustituyentes, y en las que j es 1, k es 0, n es 1, tanto R^C como R^D son -H, e Y es =C(R^1_a)-, se pueden ilustrar por la Fórmula genérica (1 0 2a) y la Fórmula sub-genérica (1 0 2b) que siguen

00267 363



(1 0.2a)



(1 0.2b)

En dichas realizaciones del presente invento los sustituyentes en posición 5 (R^1_a) y en posición 2' (R^1) sirven para la misma función de modular las propiedades del compuesto global de Fórmula (1 0 0) con respecto a sus propiedades farmacológicas y farmacocinéticas tales como potencia, especificidad (selectividad) para substratos y propiedades físico-químicas En realizaciones preferidas de los compuestos del presente invento de este tipo, tanto los sustituyentes R^1 como los R^1_a tendrán los mismos significados, que serán -H ó -F

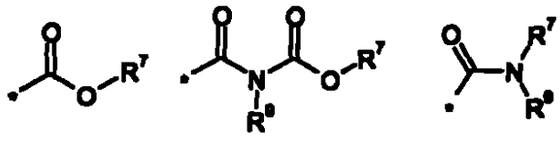
5 1.0 El resto terminal D es un resto de Fórmulas parciales (1.1 1)-(1 1.9)

D es un miembro seleccionado entre restos definidos por las Fórmulas parciales (1 1 1) hasta (1 1 9) que se ilustran más arriba Los restos de Fórmulas parciales (1 1 1) hasta (1 1 5) que definen al grupo D son típicamente, pero no necesariamente, ácidos, amidas y grupos heterocíclilo que actuan como compuestos miméticos de ácidos y amidas, pero no se limitan a estos tipos de grupos funcionales Los restos de Fórmulas parciales (1 1 6) hasta (1 1 9) que definen al grupo D son modo típicamente, pero no necesariamente, alcoholes terciarios y sus compuestos miméticos, especialmente restos

de acilo y nitrilo análogos, pero no están limitados a estos tipos de grupos funcionales Otros restos que aquí se describen se pueden emplear en el lado derecho de los compuestos de Formula (1 0 0) Estos restos son bioisostéricos puesto que permiten que los compuestos de Fórmula (1 0 0) que los contienen consigan una inhibición de las PDE4 esencialmente equivalente a la conseguida por otros restos, especialmente restos de ácidos, amidas y alcoholes

5 1 1 D es un resto de Fórmulas parciales (1 1 1), (1 1 2) ó (1 1 3)

Realizaciones del presente invento en las que la definición del grupo D es ilustrada por las Fórmulas parciales (1 1 1), (1 1 2) y (1 1 3), son como sigue



(1 1 1) (1 1 2) (1 1 3)

Un resto entre un cierto numero de restos preferidos para definir al grupo D es el de Fórmula parcial (1 1 1) en la que R^7 tiene el significado de -H, que es un significado preferido de este sustituyente Cuando R^7 es hidrógeno y m es 1, 2 ó 3 en la Fórmula (1 0 0), resulta un ácido carboxílico simple -COOH, y el grupo se convierte en un ácido alcanoico inferior El ácido benzoico como un significado del grupo D, sin embargo, constituye una realización menos preferida del presente invento

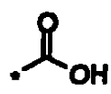
R^{10} es un sustituyente opcional de los restos que definen a R^7, y puede haber hasta tres de dichos sustituyentes, cuando estén presentes El significado del sustituyente R^{10} incluye fenilo o pirídilo, en que dicho fenilo o pirídilo está a su vez opcionalmente sustituido con hasta 3 sustituyentes R^{11}, en que R^{11} es -F, -Cl, -CN $-NO_2$, -OH, alcoxi (C_1-C_3) alquilo (C_1-C_3) o $-NR^{16}R^{17}$ En realizaciones preferidas que incluyen a dicha sustitución con R^{11}, habrá uno o dos sustituyentes R^{11} que tengan el significado de -F, -Cl, $-CH_3$, $-OCH_3$, -OH, -CN ó $-N(CH_3)_2$ Preferiblemente, hay 0 ó 1 de tal sustituyente R^{11} y, cuando está presente, éste es -F ó -Cl El significado del sustituyente R^{10} incluye además -F -Cl, $-CF_3$, oxo (=O), $-OR^{16}$ $-NO_2$, -CN, $-C(=O)OR^{16}$ $-O-C(=O)R^{16}$, $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$ ó $-S(=O)_2NR^{16}R^{17}$

Los sub-sustituyentes R^{16} y R^{17} comprenden -H alquilo (C_1-C_4), preferiblemente $-CH_3$, alquenilo (C_2-C_4), cicloalquilo (C_3-C_6), preferiblemente ciclopropilo, fenilo, bencilo

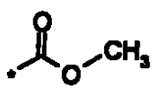
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o pirídilo Dichos grupos alquilo, alquenilo, cicloalquilo, fenilo, bencilo o pirídilo están a su vez opcionalmente sustituidos con hasta 3 sustituyentes -F, -Cl ó -CN Entre los significados adicionales antes citados de R^{10}, se prefiere que el sustituyente R^{10}, cuando este presente sea pirídilo opcionalmente sustituido con -F, -Cl, $-OCH_3$, -CN, $-NO_2$ ó $-NR^{16}R^{17}$, en que R^{16} y R^{17} son independientemente -H ó $-CH_3$, o que el sustituyente R^{10}, cuando esté presente, sea -F, -Cl, $-CF_3$, -CN, $-NO_2$, $-C(=O)OR^{16}$ ó $-NR^{16}R^{17}$, en que R^{16} y R^{17} son independientemente -H ó $-CH_3$

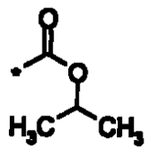
Estas y otras realizaciones preferidas de los compuestos de Fórmula (1 0 0) que comprenden los restos de Fórmula parcial (1 1 1) basados en los significados preferidos de R^7 y R^8 que antes se describen, incluyen, entre otros, los siguientes grupos ilustrados por las Fórmulas parciales (3 5 1) hasta (3 5 15)



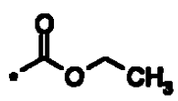
(3 5 1)



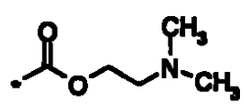
(3 5.2)



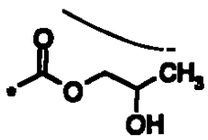
(3 5 3)



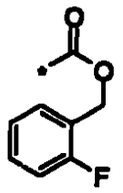
(3 5.4)



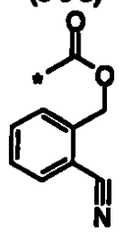
(3 5 5)



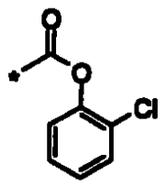
(3.5 6)



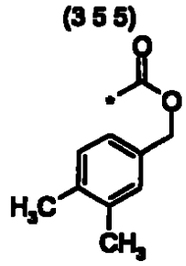
(3 5 7)



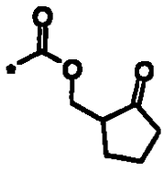
(3 5.8)



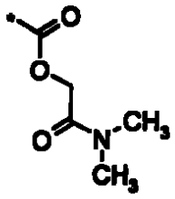
(3.5.9)



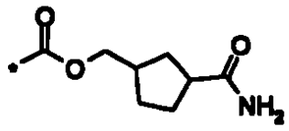
(3 5 10)



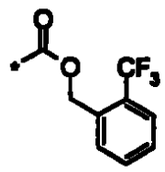
(3 5 11)



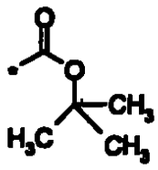
(3 5 12)



(3.5 13)



(3 5 14)



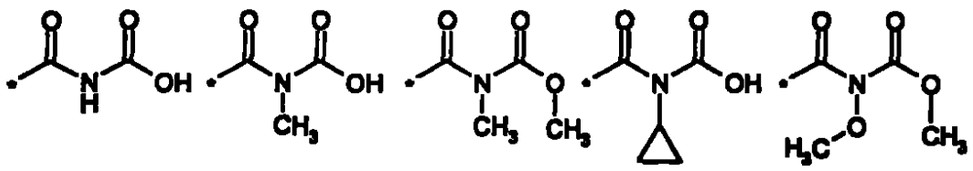
(3.5 15)

El grupo D es representado por la Formula parcial (1 1 2) en la que el átomo de nitrógeno está sustituido con R^9 en que R^9 tiene el significado de -H, alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, bencilo, $-C(=O)OR^{16}$, $-C(=O)R^{16}$, $-OR^{16}$, alquil (C_1-C_2)-OR^{16}, o

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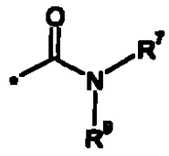
alquil $(C_1\text{-}C_2)$-C(=O)OR^{16}, en que R^{16} es -H o alquilo $(C_1\text{-}C_4)$, R^{16} es preferiblemente -H ó $-CH_3$

Correspondientemente realizaciones del presente invento en las que el grupo D está representado por la Fórmula parcial (1 1 2) se puede ilustrar como sigue por las Fórmulas parciales (4 1 1) hasta (4 1 5)



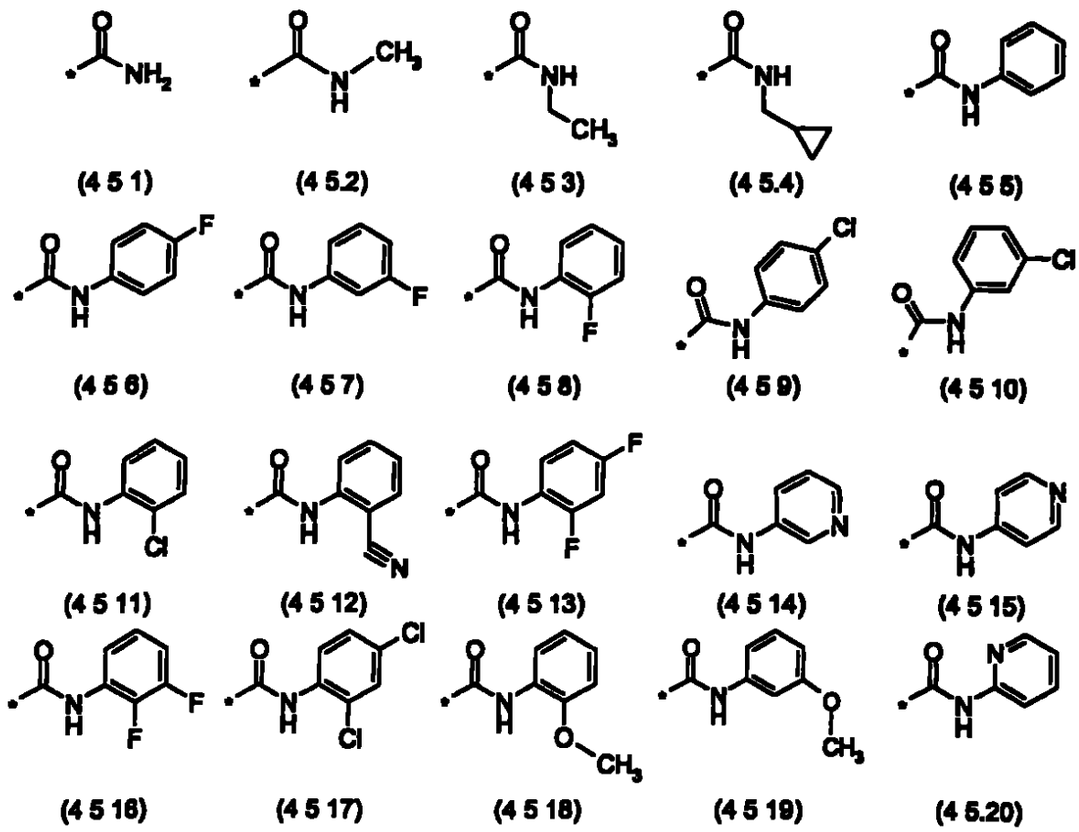
(4 1 1) (4 1.2) (4 1 3) (4 1 4) (4 1.5)

Estas realizaciones en las que la definición de D es la de un grupo amido, se ilustran por la Fórmula parcial (1 1 3)



(1 1 3)

Estas y otras realizaciones preferidas de los compuestos de Fórmula (1 0 0), que comprenden restos de Formula parcial (1 1 3) basados en los significados de R^7 y R^8 descritos anteriormente incluyen, entre otros, los siguientes grupos ilustrados por las Fórmulas parciales (4 5 1) hasta (4 5 20)



(4 5 1) (4 5.2) (4 5 3) (4 5.4) (4 5 5)

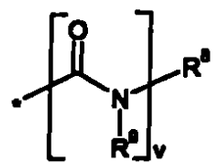
(4 5 6) (4 5 7) (4 5 8) (4 5 9) (4 5 10)

(4 5 11) (4 5 12) (4 5 13) (4 5 14) (4 5 15)

(4 5 16) (4 5 17) (4 5 18) (4 5 19) (4 5.20)

5 1 2 D es un resto de Fórmula parcial (1 1 4)

Realizaciones preferidas del presente invento comprenden también aquellos compuestos de Fórmula (1 0 0) en los que el resto terminal D cae dentro del alcance de la Fórmula parcial (1 1 4), es decir, realizaciones de este tipo están abarcadas dentro del alcance del resto D cuando éste tiene el significado de la Fórmula parcial (1 1 4)



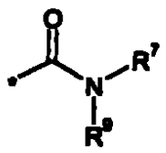
(1 1.4)

en la que R^8 es un heterociclilo monocíclico o bicíclico que es un miembro seleccionado entre el grupo que consta de tetrazol-5-ilo, 1,2,4-triazol-3-ilo, 1,2,4-triazol-3-on-5-ilo 1,2,3-triazol-5-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazolidin-2-on-4-ilo, 1,2,4-oxadiazol-3-

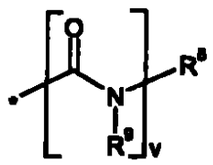
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ilo, 1,2,4-oxadiazol-5-on-3-ilo, 1,2,4-oxadiazol-5-ilo, 1,2,4-oxadiazol-3-on-5-ilo, 1,3,4-oxadiazolilo, 1,3,4-oxadiazol-2-on-5-ilo, oxazolilo, isoxazolilo, pirrolilo pirazolilo, succinimidilo glutarimidilo pirrolidonilo, 2-piperidonilo, 2-piridonilo, 4-pindonilo, pindazin-3-onilo pindazin-3-onilo, tiazolilo isotiazolilo, tiadiazolilo morfolinilo, paratiazinilo piridilo pirimidinilo, pirazinilo, piridazinilo, indolilo indolinilo, isoindolinilo, benzo[*b*]furanilo, 2,3-dihidro-benzofuranilo, 1,3-dihidro-isobenzofuranilo, 2*H*-1-benzopiranilo, 2-*H*-cromenilo, cromanilo, benzotienilo, *1H*-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzotriazolilo, benzotriazinilo, ftalazinilo, 1,8-naftiridinilo, quinolinilo, isoquinolinilo quinazolinilo quinoxalinilo, pirazolo[3,4-*d*]pirimidinilo pirimido[4 5-*d*]-pirimidinilo, imidazo[1,2-*a*]piridinilo, pindopindinilo, ptendinilo, y 1*H*-purinilo

Las Fórmulas parciales (1 1 3) y (1 1 4) son similares y se deberá señalar la distinción entre ellas Las Fórmulas parciales (1 1 3) y (1 1 4) son como sigue



(1 1.3)



(1 1.4)

Cuando v es 0 R^8 esta enlazado de una manera directa a la porción remanente de un compuesto de Fórmula (1 0 0) y es, de modo correspondiente, distinguible fácilmente con respecto de un resto de Fórmula parcial (1 1 3) en el que R^7 está enlazado a la porción remanente de un compuesto de Fórmula (1 0 0) a través del resto formador de puente de amida -C(=O)NR^8- Cuando v es 1, por otro lado los restos tanto R^8 como R^7 estan enlazados a la porcion remanente de un compuesto de Fórmula (1 0 0) a través del resto formador de puente de amida -C(=O)NR^8- En este caso, la distinción entre los restos de Fórmulas parciales (1 1 3) y (1 1 4) comprende la diferencia entre los significados de los restos R^8 y R^7 Esta diferencia ya ha sido descrita anteriormente con detalle

Con el fin de facilitar la descripción que sigue, los restos heterociclilo monocíclicos y los restos heterociclilo bicíclicos son en primer lugar tratados conjuntamente y después de ello se discuten como grupos separados

Uno cualquiera o más de los átomos de carbono del resto fenilo, bencilo o heterociclilo están sustituidos con 0 a 3 sustituyentes R^{14} en que R^{14} tiene los significados y los significados preferidos que ya se han descrito anteriormente con respecto a las Fórmulas parciales (1 1 1), (1 1 2) y (1 1 3) Uno cualquiera o más de los átomos de nitrógeno, que como se apreciará, se presentan solamente en el caso de los restos

heterociclilo, y que no son un sitio de unión de dicho resto heterociclilo, están opcionalmente sustituidos con hasta 3 sustituyentes R^{15} Cualquier átomo de azufre que pueda presentarse en un resto heterociclilo que no sea un sitio de unión de dicho resto heterociclilo, está sustituido con 0, 1 ó 2 átomos de oxigeno

El sustituyente heterociclilo con nitrógeno opcional, R^{15}, comprende -H, $-NR^{16}R^{17}$, $-C(=O)R^{16}$ $-OR^{16}$, preferiblemente $-OCH_3$, alquil (C_1-C_4)-OR^{16}, $-C(=O)OR^{16}$, alquil (C_1-C_2)-$C(=O)OR^{16}$ $-C(O)NR^{16}R^{17}$, alquilo (C_1-C_4), preferiblemente $-CH_3$, alquenilo (C_2-C_4), $-(CH_2)_u$-cicloalquilo (C_3-C_7) en que u es 0, 1 ó 2, preferiblemente ciclopropilo, fenilo, bencilo, piridilo, o quinolinilo Los grupos alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, bencilo, piridilo y quinolinilo incluidos de esta manera están opcionalmente sustituidos con hasta 2 sustituyentes R^{12}

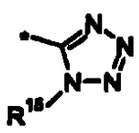
El sub-sustituyente R^{12} comprende -F, -Cl, $-CO_2R^{18}$, $-OR^{18}$, -CN, $-C(O)NR^{18}R^{19}$, $-NR^{18}R^{19}$ $-NR^{18}C(=O)R^{19}$ $-NR^{18}C(=O)OR^{19}$, $-NR^{18}S(=O)_pR^{19}$, $-S(=O)_pNR^{18}R^{19}$, en que p es 1 ó 2, preferiblemente 2, alquilo (C_1-C_4), preferiblemente $-CH_3$, y alcoxi (C_1-C_4), en que R^{12} tiene el significado de $-OR^{18}$ anterior y R^{18} es definido como alquilo (C_1-C_4), y preferiblemente R^{12} es $-OCH_3$, en que dichos alquilo y alcoxi están a su vez opcionalmente sustituidos con hasta 3 sustituyentes -F -Cl, alcoxi (C_1-C_2)-carbonilo, alquil (C_1-C_2)-carbonilo, y alquil (C_1-C_2)-carboniloxi Los sustituyentes R^{18} y R^{19} se seleccionan independientemente entre -H, alquilo (C_1-C_2), preferiblemente $-CH_3$, o fenilo, y están opcionalmente sustituidos con hasta 3 -F, o -Cl

No se muestran sustituyentes R^9 en las Fórmulas parciales (1 1 11) hasta (1 1 34) anteriores, así como dadas más adelante, puesto que el sustituyente R^9 está unido solamente a un átomo de nitrógeno que no forma una parte componente integral de un resto heterocíclico unido El sustituyente R^9 es de carácter opcional por el hecho de que "-H" está incluido como una definición del sustituyente R^9, y en muchas de las realizaciones de los compuestos de Fórmula (1 0 0) éste es el significado preferido de R^9 Otro significado preferido de R^9 es $-CH_3$

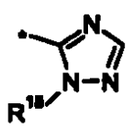
Se puntualiza también la distinción entre los sustituyentes R^9 y R^{15}, ambos de los cuales estan unidos solamente a átomos de nitrógeno en cualquiera de los significados del resto D El sustituyente R^{15} está unido solamente a un átomo de nitrógeno que es una parte componente integral de cualquier resto heterocíclico que puede ser definido a través del sustituyente R^8 de la Fórmula parcial (1 1 4) y en particular con referencia a los restos heterocíclicos más específicos de las Fórmulas parciales (1 1 11) hasta (1 1 34) que se muestran anteriormente así como también más adelante El sustituyente R^9, por otro lado, está unido solamente a un átomo de nitrógeno que a su vez está unido a, pero no es una parte componente integral de, cualquiera de los restos heterocíclicos que sea definido por las Fórmulas parciales (1 1 2), (1 1 3) y (1 1 5) El sustituyente R^{15}

puede estar unido a uno o mas átomos de nitrógeno y dichos átomos de nitrógeno pueden estar presentes en cualesquiera restos que caigan dentro del alcance de la Fórmula parcial (1 1 4), que puede ser caracterizado como que contiene o comprende un resto heterocíclico con un contenido de nitrógeno

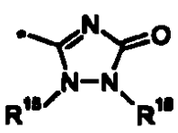
Como una ilustracion de realizaciones subgenericas preferidas del presente invento en las que el grupo D tiene el significado de un resto que cae dentro del alcance de la Fórmula parcial (1 1 4) se exponen seguidamente los grupos de Fórmulas parciales (1 1 11) hasta (1 1 44)



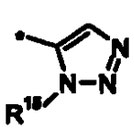
tetrazol-5-ilo (1 1 11)



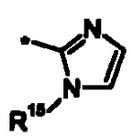
1,2,4-triazol-3-ilo (1 1 12)



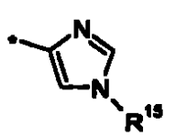
1,2,4-triazol-3-on-5-ilo (1 1 13)



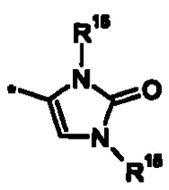
1,2,3-triazol-5-ilo (1 1 14)



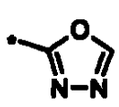
imidazol-2-ilo (1 1 15)



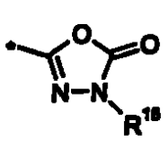
imidazol-4-ilo (1 1 16)



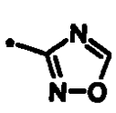
imidazolidin-2-on-4-ilo (1 1 17)



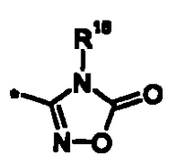
1,3,4-oxadiazolilo (1 1 18)



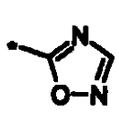
1,3,4-oxadiazol-2-on-5-ilo (1 1 19)



1,2,4-oxadiazol-3-ilo (1 1 20)

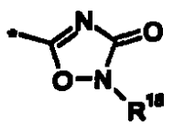


1,2,4-oxadiazol-5-on-3-ilo (1 1 21)



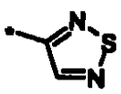
1,2,4-oxadiazol-5-ilo (1 1 22)

00375 371



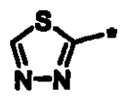
1 2,4-oxadiazol-3-on-5-ilo

(1 1 23)



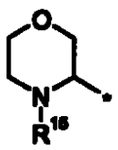
1,2,5-tiadiazol-2-ilo

(1 1 24)



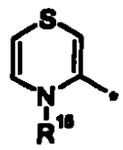
1 3,4-tiadiazolilo

(1 1 25)



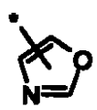
morfolin-3-ilo

(1 1 26)



paratiazin-3-ilo

(1 1 27)



oxazolilo

(1 1 28)



isoxazolilo

(1 1 29)



tiazolilo

(1 1 30)



isotiazolilo

(1 1 31)



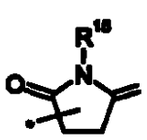
pirrolilo

(1 1 32)



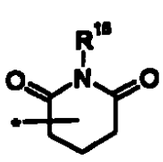
pirazolilo

(1 1 33)



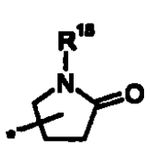
succinimidilo

(1 1 34)



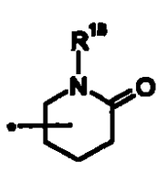
glutarimidilo

(1 1 35)



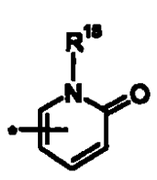
pirrolidonilo

(1 1 36)



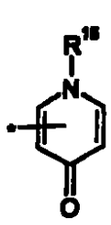
2-piperidonilo

(1 1 37)



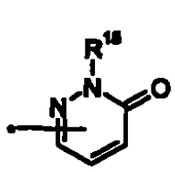
2-piridonilo

(1 1 38)



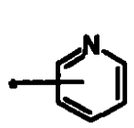
4-piridonilo

(1 1 39)



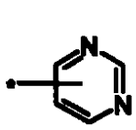
piridazin-3-onilo

(1 1 40)



piridilo

(1 1 41)

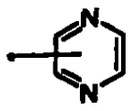


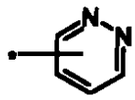
pirimidinilo

(1 1 42)

372

00576

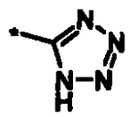


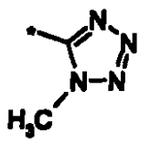


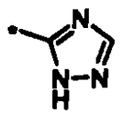
pirazinilo (1 1 43)

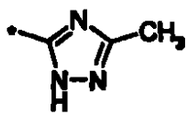
pindazinilo (1 1 44)

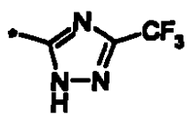
Con el fin de proporcionar otra demostración de realizaciones prefendas de los compuestos de Fórmula (1 0 0) con referencia al grupo D, en las que éste es un resto de Fórmula parcial (1 1 4) y v es 0 ó 1, y R^8 es un grupo heterocíclico monocíclico, se exponen seguidamente los grupos que constan de las Formulas parciales (4 8 1) hasta (4 8 80) de los que el resto D se selecciona entre dichas realizaciones prefendas

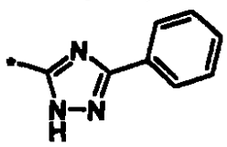

(4 8 1)

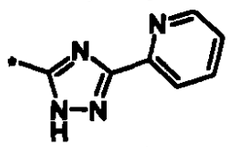

(4 8 2)

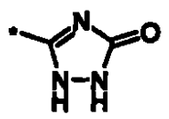

(4 8 3)

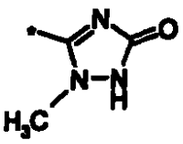

(4 8 4)

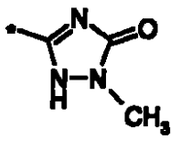

(4 8 5)

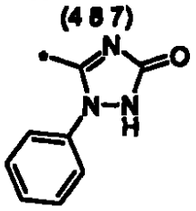

(4 8 6)

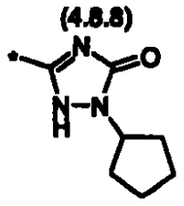

(4 8 7)

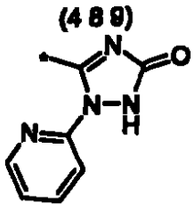

(4 8 8)

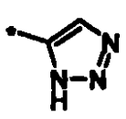

(4 8 9)

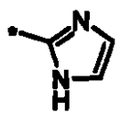

(4 8 10)

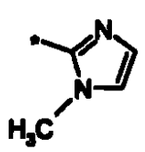

(4 8 11)

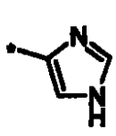

(4 8 12)

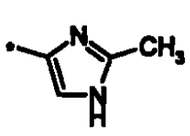

(4.8 13)

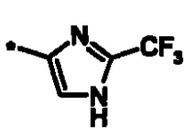

(4 8 14)

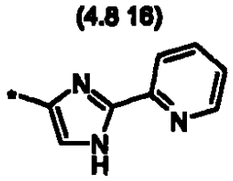

(4 8 15)

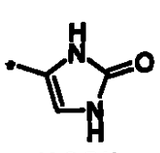

(4.8 16)

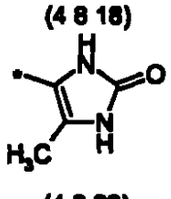

(4 8 17)

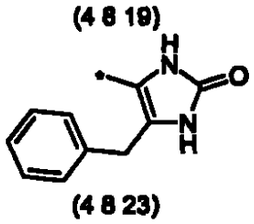

(4 8 18)

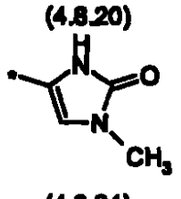

(4 8 19)

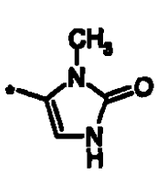

(4.8.20)

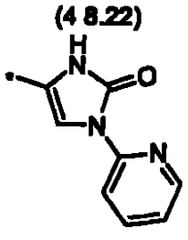

(4.8.21)

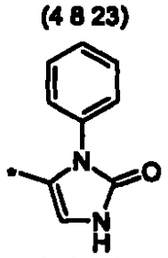

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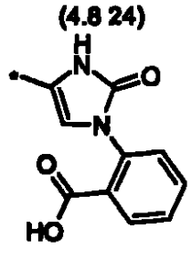

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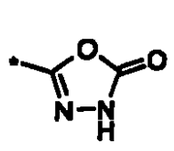

(4.8 24)


(4.8.25)

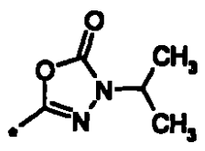

(4 8 26)


(4 8 27)

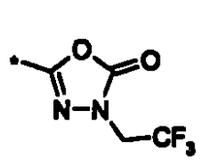

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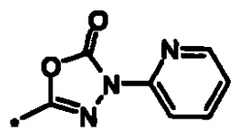
(4 8 29)



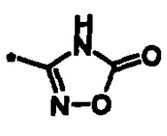
(4 8.30)



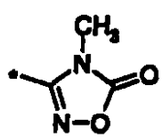
(4.8 31)



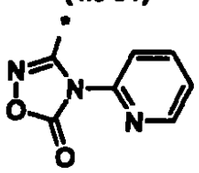
(4 8 32)



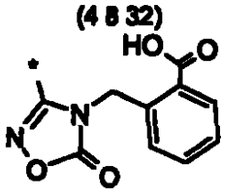
(4 8 33)



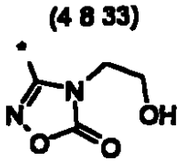
(4 8 34)



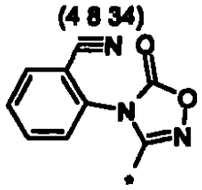
(4 8 35)



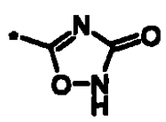
(4.8 36)



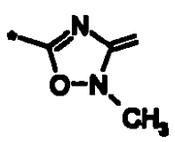
(4 8 37)



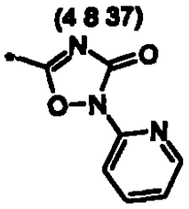
(4 8 38)



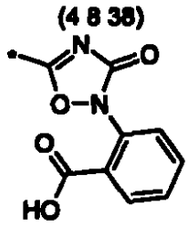
(4 8 39)



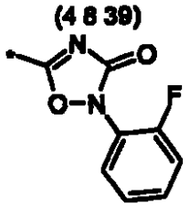
(4.8.40)



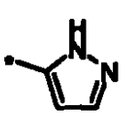
(4 8 41)



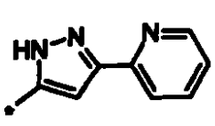
(4 8 42)



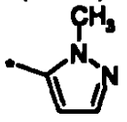
(4 8 43)



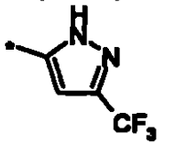
(4.8.44)



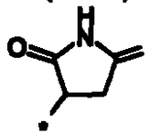
(4 8.45)



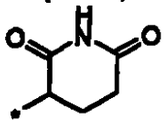
(4 8 46)



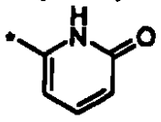
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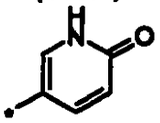
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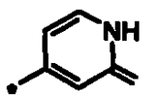
(4 8.49)



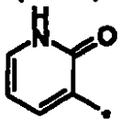
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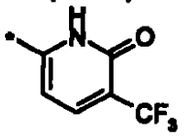
(4 8 51)



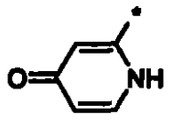
(4 8.52)



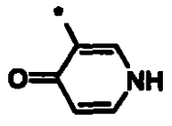
(4.8 53)



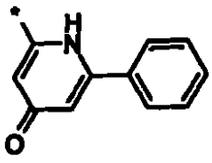
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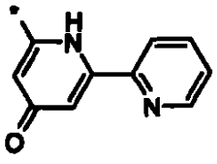
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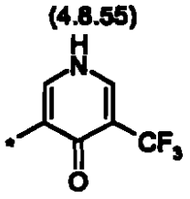
(4.8.56)



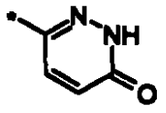
(4.8 57)



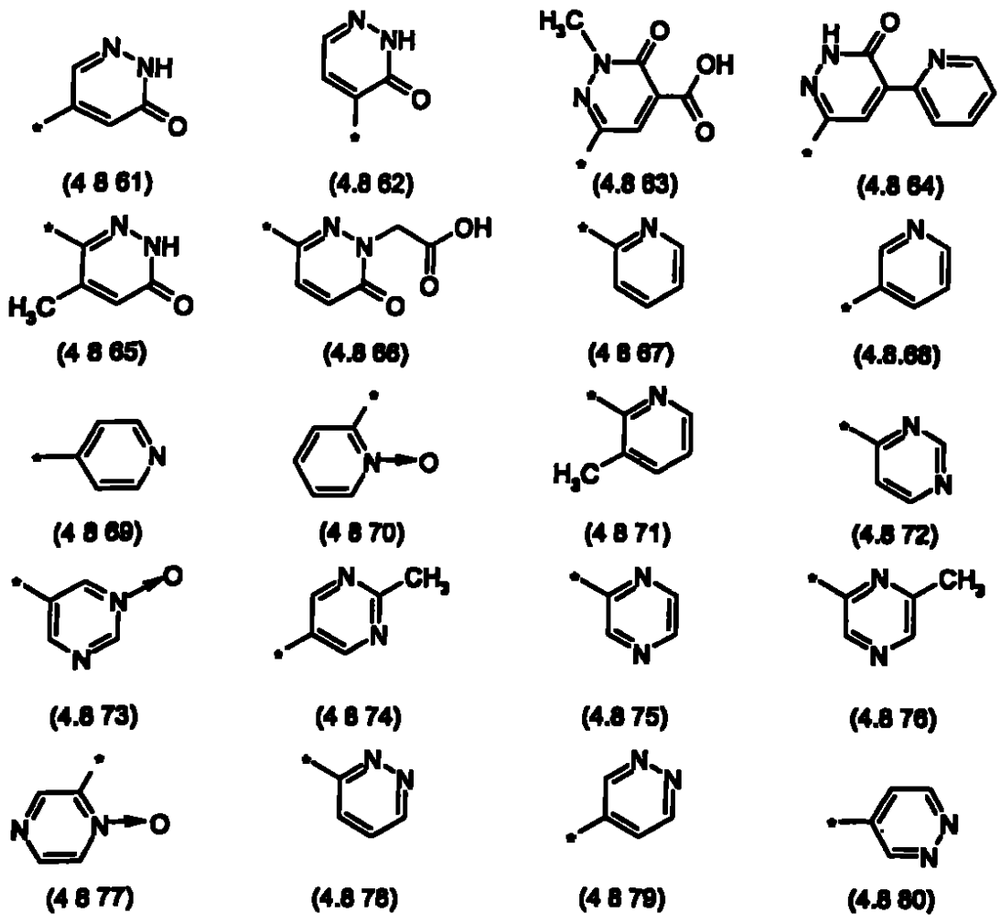
(4 8 58)



(4 8 59)



(4 8 60)

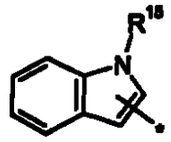


Realizaciones prefendas del presente invento en las que el grupo D es un resto de Fórmula parcial (1 1 4) y v es 0 ó 1, incluyen también aquéllas en las que el resto R^8 es un grupo heterocíclico bicíclico seleccionado entre el grupo que consta de indolilo, indolinilo isoindolinilo, benzo[*b*]furanilo, 2,3-dihidro-benzofuranilo, 1,3-dihidro-isobenzofuranilo, 2*H*-1-benzopiranilo, 2-*H*-cromenilo, cromanilo, benzotienilo, *1H*-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo, benzotriazolilo, benzotriazinilo, ftalazinilo, 1,8-naftindinilo quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo pirazolo[3,4-*d*]pirimidinilo, pirimido[4,5-*d*]pirimidinilo imidazo[1,2-*a*]pindinilo pindopindinilo ptendinilo, y *1H*-purinilo

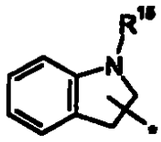
Con el fin de proporcionar una demostración todavía adicional de realizaciones prefendas de los compuestos de Fórmula (1 0 0) con referencia al grupo D en el que hay un resto de Fórmula parcial (1 1 4), v es 0 ó 1, y R^8 es un grupo heterocíclico bicíclico se exponen seguidamente los grupos que constan de las Fórmulas parciales

00330 376

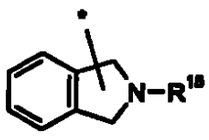
(5 0 1) hasta (5 0 28) de los que el resto D se selecciona entre dichas realizaciones preferidas



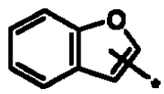
indolilo
(5 0 1)



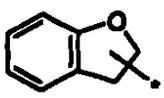
indolinilo
(5 0 2)



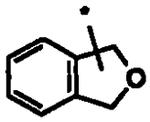
isoindolinilo
(5 0 3)



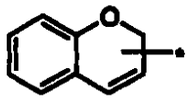
benzo[*b*]furanilo
(5 0 4)



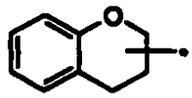
2,3-dihidrobenzofuranilo
(5 0 5)



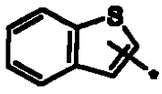
1,3-dihidro-isobenzofuranilo, ftalanilo
(5 0 6)



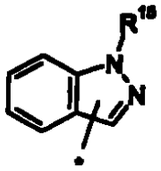
2*H*-1-benzopiranilo
(5 0 7)



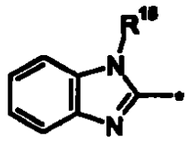
cromanilo
(5 0 8)



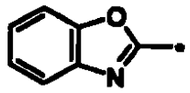
benzotienilo
(5 0 9)



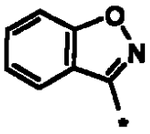
1H-indazolilo
(5 0 10)



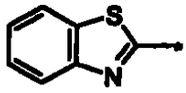
bencimidazolilo
(5 0 11)



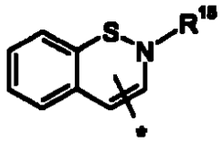
benzoxazolilo
(5 0 12)



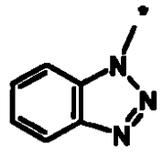
benzoisoxazolilo
(5 0 13)



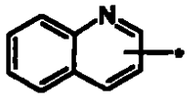
benzotiazolilo
(5 0 14)



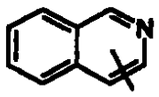
2*H*-1,2-benzotiazinilo
(5 0 15)



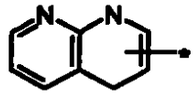
benzotriazolilo
(5 0 16)



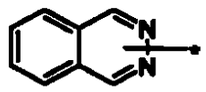
quinolinilo
(5 0 17)



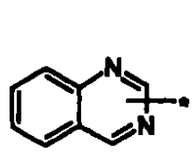
isoquinolinilo
(5 0 18)



1,8-naftiridinilo
(5 0 19)

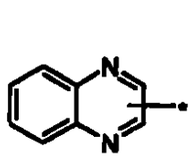


ftalazinilo
(5 0 20)



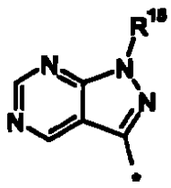
quinazolinilo

(5 0 21)



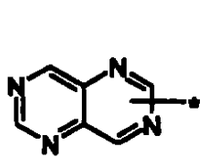
quinoxalinilo

(5 0 22)



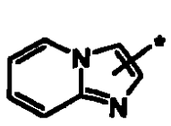
1H-pirazolo[3,4-*d*]-pirimidinilo

(5 0 23)



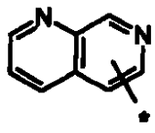
pirimido[5,4-*d*]-pirimidinilo

(5 0 24)



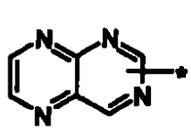
imidazo[1,2-*a*]-piridinilo

(5 0 25)



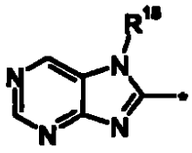
piridopirimidinilo

(5 0 26)



pteridinilo

(5 0 27)



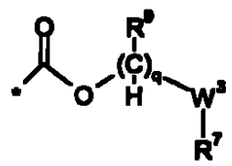
1H-purinilo

(5 0 28)

en las que "*" indica el sitio de unión a la porción remanente de la Fórmula (1 0 0), y en que cada átomo de carbono está opcionalmente sustituido con un sustituyente R^{14}, y en que R^{14} y R^{15} tienen los mismos significados que antes se han definido, y todas las formas tautómeras, y opcionalmente las formas de N-óxidos, de éstos

5.1.3 D es un resto de Fórmula parcial (1 1 5)

Hay otras realizaciones adicionales de los compuestos de Fórmula (1 0 0) en las que el resto D comprende un grupo que cae dentro del alcance de la Fórmula parcial (1 1 5)



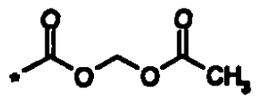
(1 1 5)

en que la que q es 1, 2 ó 3, con la condición de que cuando q es 2 ó 3 R^9 tiene el significado de -H en por lo menos un caso o en dos casos respectivamente, W^3 es -O-, -N(R^9)-, ó -OC(=O)- en que R^9 tiene los mismos significados que antes de han definido y R^7 tiene el mismo significado que antes se ha definido

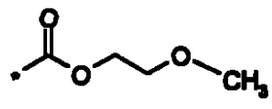
00352 378

En realizaciones preferidas de los compuestos de Fórmula parcial (1 1 5) q es 1 ó 2, R^9 es -H, ó $-CH_3$, W^3 es -O- -O(C=O)-, ó -NH-, y R^7 es uno de los restos preferidos que ya se han descrito anteriormente

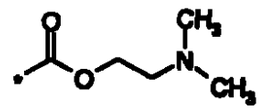
Realizaciones representativas de los compuestos de Fórmula (1 0 0) en las que el resto D cae dentro del alcance de la Fórmula parcial (1 1 5) son las ilustradas por las Fórmulas parciales (6 0 1) hasta (6 0 6)



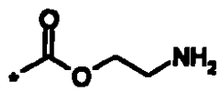
(6 0 1)



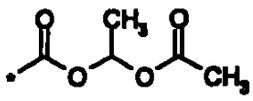
(6 0 2)



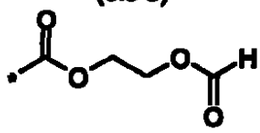
(6 0 3)



(6 0 4)



(6 0 5)



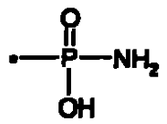
(6 0 6)

5 1 4 D es distinto de un ácido carboxílico

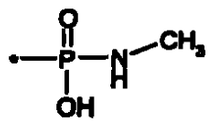
Las realizaciones de los compuestos de Fórmula (1 0 0) incluyen aquéllas en las que el resto D es distinto de un ácido carboxílico y es, en lugar de éste un ácido con fósforo o azufre o un derivado del mismo Hay un numero importante de dichos derivados entre los que el resto D se puede seleccionar, y éstos incluyen los siguientes

$-O-P(=O)(OH)_2$ (fosfonco) -PH(=O)OH (fosfinico), $-P(=O)(OH)_2$ (fosfónico), $-[P(=O)(OH)-O-$alquilo $(C_1-C_4)]$ (alquil-fosfono), $-P(=O)(OH)-O-$alquilo (C_1-C_4) (alquil-fosfinilo), $-P(=O)(OH)NH_2$ (fosforamido), $-P(=O)(OH)NH-$alquilo (C_1-C_4) y $-P(=O)(OH)NHR^{25}$ (fosforamido sustituido), $-O-S(=O)_2OH$ (sulfunco), $-S(=O)_2OH$ (sulfónico) $-S(=O)_2NHR^{26}$ ó $-NHS(=O)_2R^{26}$ (sulfonamido) en que R^{26} es $-CH_3$, $-CF_3$ o bien o-toluilo y acil-sulfonamido seleccionado entre el grupo que consta de $-C(=O)NHS(=O)_2R^{25}$ $-C(=O)NHS(=O)_2NH_2$, $-C(=O)NHS(=O)_2-$alquilo (C_1-C_4), $-C(=O)NHS(=O)_2NH-$alquilo (C_1-C_4) $-C(=O)NHS(=O)_2N[$alquilo $(C_1-C_4)]_2$, $-S(=O)_2NHC(=O)-$alquilo (C_1-C_4), $-S(=O)_2NHC(=O)NH_2$, $-S(=O)_2NHC(=O)NH-$alquilo (C_1-C_4) $-S(=O)_2NHC(=O)N[$alquilo $(C_1-C_4]_2$, $-S(=O)_2NHC(=O)R^{25}$, $-S(=O)_2NHCN$, $-S(=O)_2NHC(=S)NH_2$ $-S(=O)_2NHC(=S)NH-$alquilo (C_1-C_4) $-S(=O)_2NHC(=S)N[$alquilo $(C_1-C_4)]_2$, y $-S(=O)_2NHS(=O)_2R^{25}$, en que R^{25} es -H, alquilo (C_1-C_4), fenilo, o $-OR^{16}$ en que R^{16} tiene el mismo significado que antes se ha definido

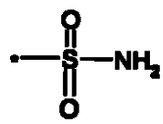
Realizaciones prefendas de los compuestos de Formula (1 0 0) en las que D es un ácido con fósforo o azufre o un denvado de éste, son aquéllas en las que D es -P(=O)(OH)NHR^{25} (fosforamido sustituido) -S(=O)$_2$NHR^{26} ó -NHS(=O)$_2$R^{26} (sulfonamido) o -C(=O)NHS(=O)$_2$R^{25} (acil-sulfonamido), en que R^{26} y R^{25} tienen los mismos significados que antes se han definido Algunas de estas realizaciones prefendas se pueden ilustrar por las Fórmulas parciales (6 5 1) hasta (6 5 9)



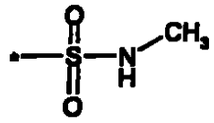
(6 5 1)



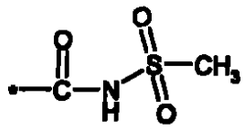
(6 5 2)



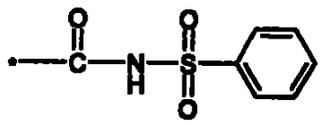
(6 5.3)



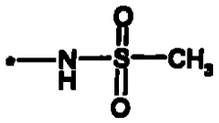
(6 5 4)



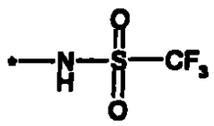
(6 5 5)



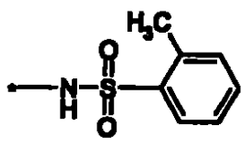
(6 5 6)



(6 5.7)



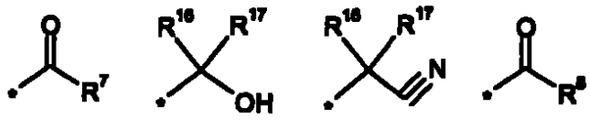
(6 5 8)



(6.5.9)

5 1 5 D es un resto de Fórmulas parciales (1 1 6) hasta (1 1.9)

Hay otras realizaciones adicionales de los compuestos de Fórmula (1 0 0) en las que el resto D comprende un grupo que cae dentro del alcance de las Fórmulas parciales (1 1 6) hasta (1 1 9)

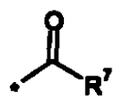


(1 1 6) (1 1 7) (1 1 8) (1 1 9)

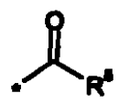
en las que R^7 R^8, R^{16} y R^{17} tienen los mismos significados que antes se han definido Por ejemplo, R^{16} y R^{17} se seleccionan cada uno de ellos independientemente entre -H, alquilo (C$_1$-C$_4$), alquenilo (C$_2$-C$_4$), cicloalquilo (C$_3$-C$_6$), fenilo, bencilo, y pindilo, en que dicho alquilo, alquenilo, cicloalquilo, fenilo, bencilo o pindilo está sustituido con 0 a 3

sustituyentes seleccionados entre el grupo que consta de -F, -Cl, -CF_3, -CN y alquilo (C_1-C_3)

Los grupos ceto de las Fórmulas parciales (1 1 6) y (1 1 9) son iguales con respecto a la entidad enlazadora de carbonilo pero difieren con respecto al grupo unido a ellos, R^7 ó R^8,



(1 1.6)



(1 1 9)

R^7 en el resto de Fórmula parcial (1 1 6) tiene el mismo significado que antes se ha definido adicionalmente, pero en realizaciones preferidas de los compuestos de Fórmula (1 0 0) R^7 tiene especialmente el significado de -H, alquilo (C_1-C_8), preferiblemente metilo, etilo, *iso*-propilo o *terc*-butilo, alquenilo (C_2-C_8), preferiblemente 2-propenilo, alquinilo (C_2-C_8), preferiblemente etinilo Cada uno de estos significados de R^7 está sustituido opcionalmente con hasta 3 sustituyentes R^{10} El significado de R^{10} es el mismo que antes se ha definido, pero preferiblemente es fenilo o pirídilo opcionalmente sustituido con hasta 3 R^{11} en que R^{11} es preferiblemente -F, -CF_3, -CN, -CH_3 ó -OCH_3 R^{10} tiene preferiblemente también los significados de -F -CF_3, -OR^{16}, -CN, -C(=O)OR^{16}, -C(=O)$NR^{16}R^{17}$, -$NR^{16}R^{17}$ ó -$NR^{16}S(=O)_2R^{17}$, en que R^{16} y R^{17} son preferiblemente -H, metilo, etilo ciclopropilo, fenilo, bencilo o pirídilo opcionalmente sustituido con hasta 3 de los -F, o con 1 de los -CF_3, -CN ó -CH_3

R^7 tiene también el significado de -$(CH_2)_u$-cicloalquilo (C_3-C_7) en que u es preferiblemente 0 ó 1 y en que cicloalquilo (C_3-C_7) es preferiblemente ciclopropilo, ciclopentilo o ciclohexilo sustituido opcionalmente con hasta 3 sustituyentes R^{10} en que R^{10} tiene los mismos significados preferidos que se han definido en el párrafo situado inmediatamente antes

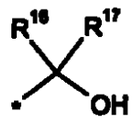
R^7 tiene también el significado de fenilo o bencilo, en que dicho fenilo o bencilo opcionalmente sustituido con hasta 3 sustituyentes R^{10} en que R^{10} tiene los mismos significados preferidos que se han definido en el párrafo situado inmediatamente antes

R^8 en el resto de Fórmula parcial (1 1 9) tiene el mismo significado que se ha definido adicionalmente con anterioridad, pero en realizaciones preferidas de los compuestos de Fórmula (1 0 0) R^8 tiene especialmente el significado de tetrazol-5-ilo, 1,2,4-triazol-3-ilo, 1 2,4-triazol-5-ilo imidazol-2-ilo imidazol-4-ilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazol-3-ilo, 1 2,4-oxadiazol-5-ilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, morfolinilo, oxazolilo, isoxazolilo tiazolilo, isotiazolilo pirrolilo, pirazolilo pirídilo, indolilo, benzo[*b*]fu-

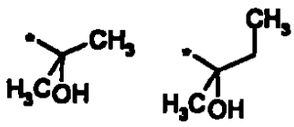
ranilo, 2,3-dihidro-benzofuranilo, 1*H*-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo benzotiazolilo, benzotriazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo

Cualquiera de los significados especialmente preferidos de R^8 que antes se citan está sustituido opcionalmente en un átomo de carbono con R^{14} en que R^{14} tiene el mismo significado que antes se ha definido, y en un átomo de nitrógeno con R^{15} en que R^{15} tiene el mismo significado que antes se ha definido Están incluidas especialmente en el caso de dichos sustituyentes con átomos de nitrógeno, todas las formas tautómeras de los restos de Fórmula parcial (1 1 9) Los átomos de azufre de dichos restos están opcionalmente sustituidos con 1 ó 2 átomos de oxígeno

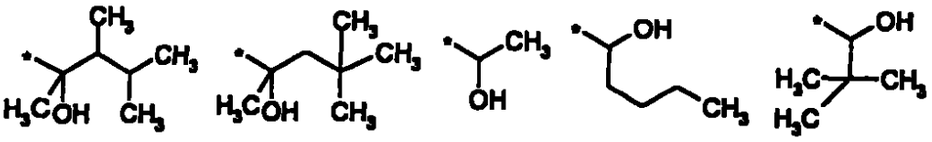
Con el fin de ilustrar significados adicionales de D que caen dentro del alcance de las Fórmulas parciales (1 1 6), (1 1 7), (1 1 8) y (1 1 9), se describen seguidamente restos de Fórmulas parciales (3 3 1) hasta (3 3 15) que representan significados diferentes que caen dentro del alcance de la Fórmula parcial (1 1 7)



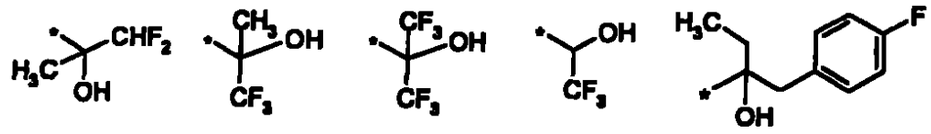
(1 1 7)



(3 3 1) (3 3 2) (3 3 3) (3 3 4) (3 3 5)



(3 3 6) (3.3 7) (3 3 8) (3 3 9) (3.3 10)



(3.3 11) (3 3 12) (3.3 13) (3 3 14) (3 3 15)

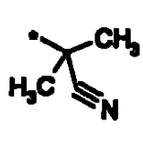
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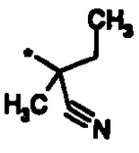
Significados adicionales de D son aquéllos que caen dentro del alcance de la Fórmula parcial (1 1 8), en los que un grupo de nitrilo, -C≡N, sirve como un reemplazo bioisostérico para el grupo hidroxilo de Fórmula parcial (1 1 7) Correspondientemente se describen seguidamente restos de Fórmulas parciales (3 8 1) hasta (3 8 10), que representan diferentes significados que caen dentro del alcance de la Fórmula parcial (1 1 8)



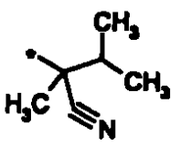
(1 1.8)



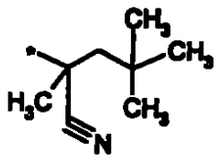
(3 8.1)



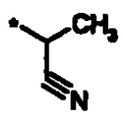
(3.8 2)



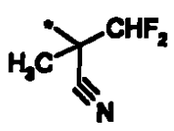
(3 8 3)



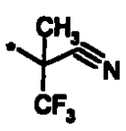
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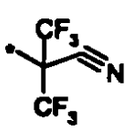
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(3.8 6)



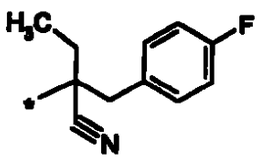
(3 8 7)



(3 8 8)



(3 8 9)

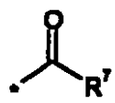


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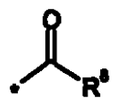
Con el fin de ilustrar significados adicionales de D que caen dentro del alcance de las Fórmulas parciales (1 1 6), (1 1 7), (1 1 8) y (1 1 9), se describen seguidamente restos de Fórmulas parciales (3 9 1) hasta (3 9 9) que representan diferentes significados que caen dentro del alcance de las Fórmulas parciales (1 1 6) y (1 1 9)

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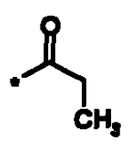
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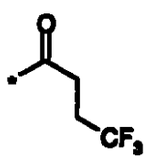
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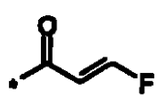
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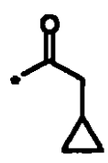
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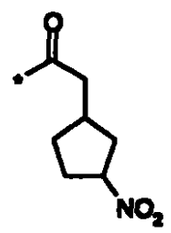
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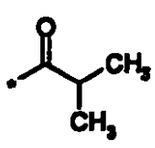
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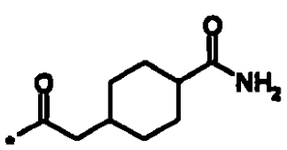
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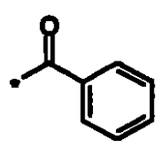
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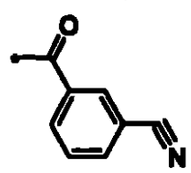
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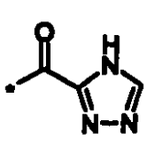
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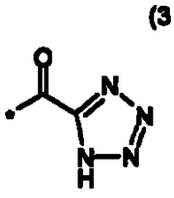
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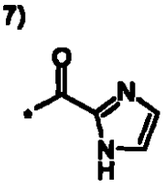
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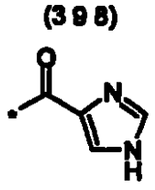
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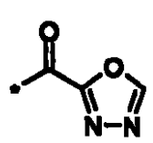
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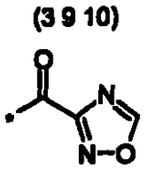
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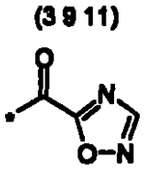
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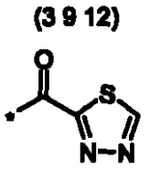
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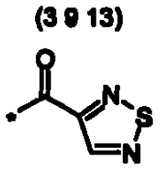
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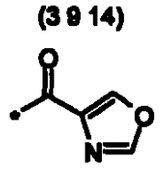
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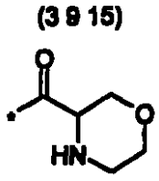
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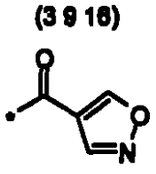
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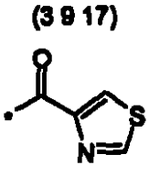
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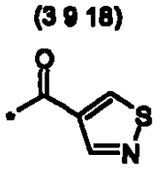
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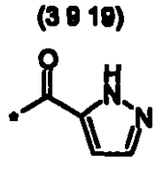
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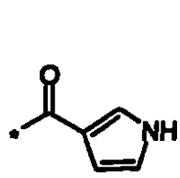
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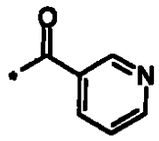
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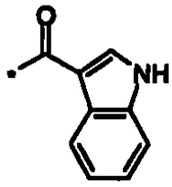
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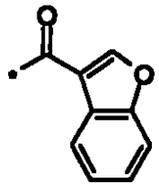
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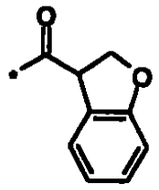
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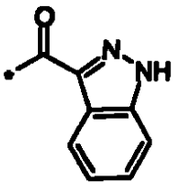
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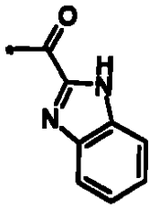
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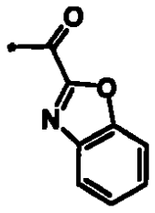
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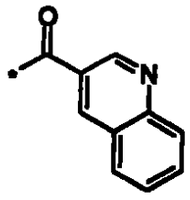
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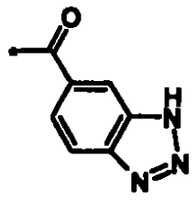
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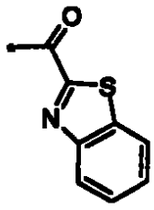
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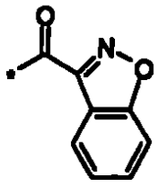
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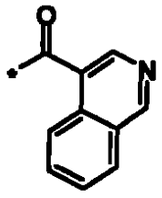
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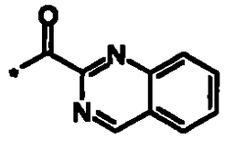
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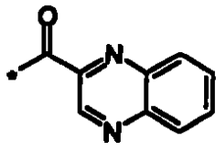
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(3 9 37)



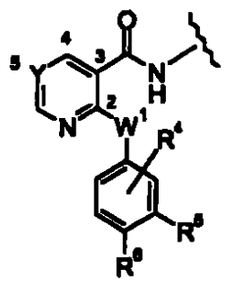
(3 9 38)



(3 9 39)

5.2 Resto J^1 sustituido con enlace W^1 y (R^4, R^5 y R^6)

El nucleo central de nicotinamida es elaborado adicionalmente dejando que el átomo de carbono en posicion 2 del anillo de pirdilo o pirimidinilo de dicho nucleo forme en enlace con un anillo que comprende el resto J^1 En realizaciones preferidas, el resto J^1 tiene el significado de un anillo de fenilo que está sustituido en *para* con un resto R^6, sustituido en *meta* por un resto R^5 o sustituido en cualquiera de las posiciones remanentes con un resto R^4, dando como resultado un resto de Fórmula parcial (1 0 3)



(1 0 3)

en que W^1 tiene el significado -O-, -S(=O)$_t$- en que t es 0, 1 ó 2, ó -N(R^3)- en que R^3 es -H, alquilo (C_1-C_3), fenilo, bencilo ó -OR^{16}, y es preferiblemente -H ó -CH_3

En otras realizaciones del presente invento, W^1 tiene el significado de -S(=O)$_t$- en que t es 0, 1 ó 2, y preferiblemente tiene el significado de -S- con lo que se forma un enlace de tioéter Cuando el átomo de azufre del enlace de tioéter está oxigenado, resulta un enlace de sulfinilo o de sulfonilo Todavía en otras realizaciones adicionales, cuando W^1 tiene el significado de -N(R^3)-, se forma un enlace de amino, que preferiblemente será -NH- No obstante, el átomo de nitrógeno puede estar sustituido, y cuando se da este caso se prefiere que dicho sustituyente sea -CH_3

Los significados de los sustituyentes R^4, R^5 y R^6 se seleccionan entre el mismo conjunto de definiciones pero se entenderá que dicho significado se selecciona sobre una base independiente de cada uno de otros R^5 y R^6 pueden también ser -H Correspondientemente, cuando el resto J^1 tiene el significado de un anillo de fenilo, la posición *para* (R^6), *meta* (R^5) u *orto* (R^4) del anillo de fenilo puede estar sustituida, o la totalidad de las tres posiciones pueden estar sustituidas, o cualquier combinación de dichas posiciones pueden estar sustituidas Se prefiere, sin embargo, en los compuestos de Fórmula (1 0 0) que estén sustituidas las posiciones *meta* y/o *para*, en vez de la posición *orto*

Cuando el resto J^1 tiene el significado preferido de un anillo de fenilo, R^5 y R^6 pueden ser tomados también conjuntamente para formar un miembro seleccionado entre un grupo de Fórmulas parciales descritas seguidamente de modo adicional con más detalle Algunos de estos significados de R^5 y R^6 tomados conjuntamente también constituyen realizaciones preferidas de los compuestos de Fórmula (1 0 0)

R^5 y R^6 pueden ser -H Además de -H R^5 y R^6 pueden ser entre otros -F, -Cl, -CN, -NO_2, -C(=O)R^{16} -OR^{16}, -C(=O)OR^{16}, ó $NR^{16}R^{17}$ Cuando R^5 es -H y R^6 es -F, resultan realizaciones preferidas del presente invento En una realización preferida adicionalmente del presente invento, R^5 y R^6 pueden ser también -OR^{16}, en que R^{16} es

hidrógeno alquilo (C_1-C_4), o cicloalquilo (C_3-C_8), en que dichos alquilo y cicloalquilo están sustituidos con 0 a 3 sustituyentes seleccionados entre el grupo que consta de -F y -Cl Otras realizaciones preferidas son aquellas en las que R^{16} es metilo, difluorometilo, etilo, o ciclopentilo

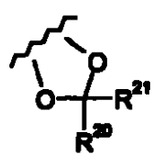
Un profesional químico medicinal apreciará que la elección de los sustituyentes entre los antes descritos será influenciada por el efecto que dichos sustituyentes tienen a su vez sobre las propiedades físico-químicas de las moléculas globales que resultan El presente estado de la técnica proporciona la capacidad de sintetizar con rapidez y facilidad un numero muy grande de compuestos muy similares desde el punto de vista químico, basados en las elecciones de sustituyentes que se bosquejan anteriormente, y después de ello de ensayar la eficacia relativa de las moléculas resultantes en rápidos métodos de ensayo *in vitro* Los procedimientos combinatorios de síntesis química y ensayo actualmente disponibles en el sector técnico han expandido considerablemente incluso todavía más el numero de combinaciones de sustituyentes que se pueden evaluar rápidamente La información que se ha producido de esta manera mediante el uso de estas técnicas permite una predicción razonable en el presente caso de ciertas preferencias que existen en cuanto a diversas realizaciones del presente invento Dichas realizaciones preferidas se describen aquí con detalle

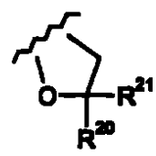
Realizaciones preferidas del presente invento incluyen además aquéllas en las que tanto R^5 como R^6 son ambos -F en que R^5 es -H y R^6 -F, y en que R^6 es -H y R^5 es -F, $-OR^{16}$ p ej , $-OCH_3$ $-OCH_2F$, $-OCHF_2$ ó $-OCF_3$, -CN, -COOH, $-COOCH_3$, $-CONH_2$ $-OCOCH_3$, ó $-NH_2$ Las realizaciones más preferidas son aquéllas en las que R^5 es -H y R^6 es -F R^5 es -CN y R^6 es -H y R^5 es $-NO_2$ $-NH_2$ -CN, $-OCH_3$ ó $-C(=O)CH_3$ y R^6 es -H

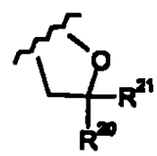
R^5 y R^6 se pueden seleccionar también entre sustituyentes que comprenden alquilo (C_1-C_4) y alcoxi (C_1-C_4) en que dichos alquilo y alcoxi están sustituidos con 0 a 3 sustituyentes -F ó -Cl o con 0 ó 1 sustituyente alcoxi (C_1-C_2)-carbonilo-, alquil (C_1-C_2)-carbonilo- o alquil (C_1-C_2)-carboniloxi-

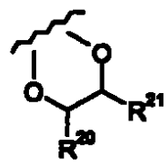
5 3 0 J^1 es fenilo y R^5 y R^6 se toman conjuntamente

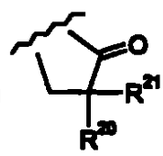
Cuando el resto J^1 tiene el significado preferido de un anillo de fenilo, R^5 y R^6 se pueden también tomar conjuntamente para formar un resto que es un miembro seleccionado entre el grupo que consta de la Fórmulas parciales (1 3 1) hasta (1 3 15)

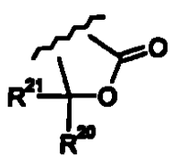

(1 3 1)

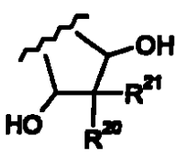

(1 3.2)

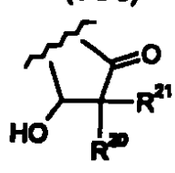

(1 3 3)

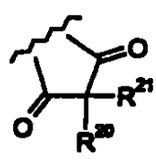

(1 3.4)

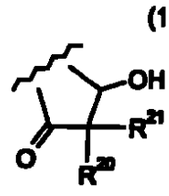

(1 3 5)

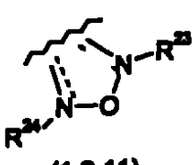

(1.3 6)

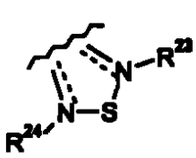

(1.3 7)

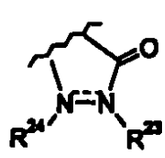

(1 3 8)

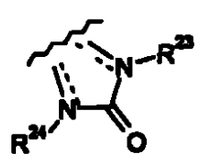

(1 3 9)

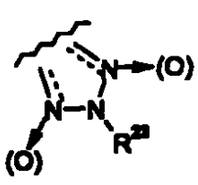

(1.3 10)


(1 3 11)


(1 3 12)


(1 3 13)


(1 3 14)

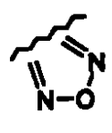

(1 3 15)

en las que R^{20} y R^{21} son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_3$, y R^{23} y R^{24} son cada uno de ellos independientemente -H, $-CH_3$, $-OCH_3$, $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)CH_2$, $-C(CH_3)_3$ o están ausentes, en cuyo caso la línea de trazos - - - - representa un doble enlace Para el resto de Fórmula parcial (1 3 13) los componentes con átomos de nitrógeno de ésta se representan como -[N(⇨O)]- y por lo tanto comprenden formas opcionales de óxidos de nitrógeno de dichos átomos de nitrógeno, seleccionadas independientemente unas de otras Se apreciará que dicha forma de óxido de nitrógeno se puede representar también como -[N(⇨O)$_j$]- en que j es 0 ó 1 como en la Fórmula (1 0 0)

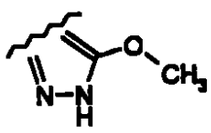
Cuando el resto J^1 tiene el significado preferido de un anillo de fenilo, y cuando R^5 y R^6 se toman conjuntamente para formar el resto de Fórmula parcial (1 3 1), y R^{20} y R^{21} son ambos hidrógeno, se forma, conjuntamente con el anillo de fenilo al que éste está unido, un grupo de 1,3-benzodioxol Análogamente, la estructura de Fórmula parcial (1 3 4) forma un grupo de 1,4-benzodioxano

Cuando el resto J^1 tiene el significado preferido de un anillo de fenilo, y cuando R^5 y R^6 se toman conjuntamente para formar los restos de Fórmulas parciales (1 3 1) hasta (1 3 15) y R^{23} y R^{24} son como se han definido benzofurazano benzotiazano triazol

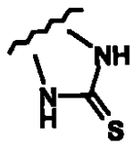
y otros grupos análogos así como derivados sustituidos de éstos, se forman, incluyendo, entre otros, los siguientes restos de Fórmulas parciales (2 1 1) hasta (2 1 20)



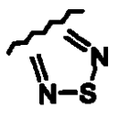
(2 1 1)



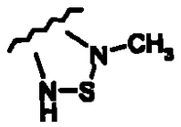
(2 1.2)



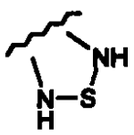
(2 1 3)



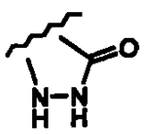
(2 1.4)



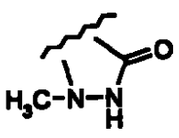
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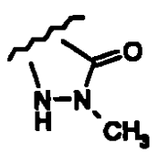
(2 1 6)



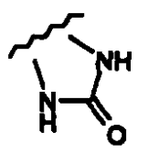
(2 1 7)



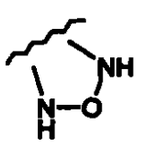
(2 1 8)



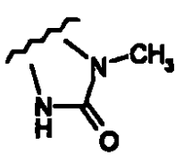
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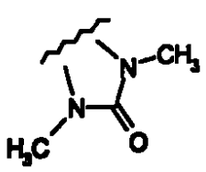
(2 1 10)



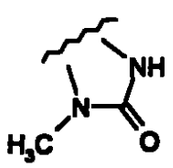
(2 1 11)



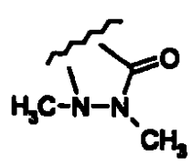
(2 1 12)



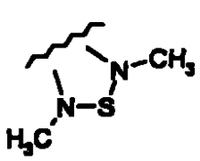
(2 1 13)



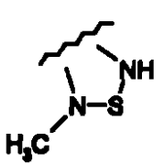
(2 1 14)



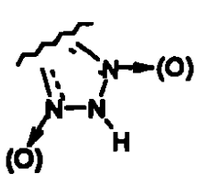
(2 1 15)



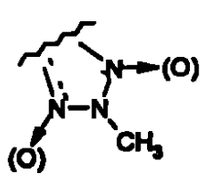
(2 1 16)



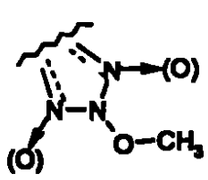
(2 1 17)



(2 1 18)



(2 1 19)



(2 1.20)

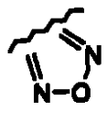
en que la línea de trazos - - - - en las Fórmulas parciales (2 1 18), (2 1 19) y (2 1 20) representa un doble enlace cuando ningún átomo de oxígeno está unido al correspondiente átomo de nitrógeno, y representa un enlace simple cuando un átomo de oxígeno está unido a dicho correspondiente átomo de nitrogeno

Un profesional con experiencia ordinaria en la preparación de moléculas orgánicas apreciará que los compuestos de Fórmula (1 0 0) en los que R^5 y R^6 se toman conjuntamente para formar restos de las Fórmulas parciales (2 1 2) (2 1 3), (2 1 7), (2 1 8), (2 1 10) (2 1 12) y (2 1 14) antes ilustradas existen en forma tautómera, y cada resto de dichas Fórmulas parciales (2 1 2), (2 1 3), (2 1 7), (2 1 8), (2 1 10), (2 1 12) y (2 1 14) tiene un compuesto contrapartida tautómero Estos tautómeros están relacionados por el desplazamiento de un nitrógeno y uno o más enlaces π, y cuando es

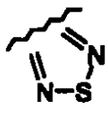
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necesario el profesional experto será capaz de discernir o determinar con facilidad cuál de las formas tautómeras está presente o es la más estable

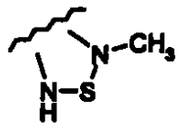
Realizaciones todavía más preferidas del tipo que comprende los restos de Fórmulas parciales (2 1 1) hasta (2 1 20) antes ilustradas, son aquéllas en las que R^5 y R^6 se toman conjuntamente para formar un resto que es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (2 1 1), (2 1 4) hasta (2 1 6), (2 1 11) y (2 1 16) hasta (2 1 20)



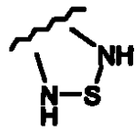
(2 1 1)



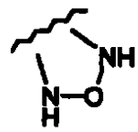
(2 1 4)



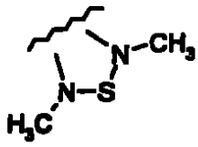
(2 1 5)



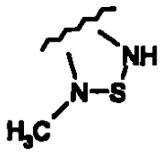
(2 1 6)



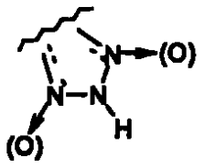
(2 1 11)



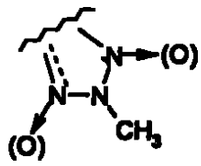
(2 1 16)



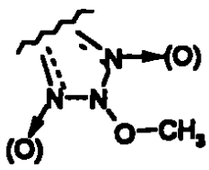
(2 1 17)



(2 1 18)



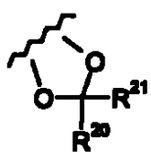
(2 1 19)



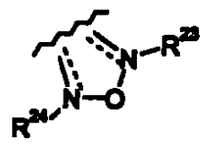
(2 1.20)

en que la línea de trazos - - - - en las Fórmulas parciales (2 1 18), (2 1 19) y (2 1 20) representan un doble enlace cuando ningún átomo de oxígeno está unido al correspondiente átomo de nitrógeno y representa un enlace simple cuando un átomo de oxígeno está unido a dicho correspondiente átomo de nitrógeno

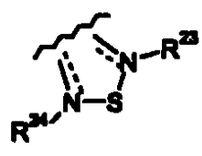
Realizaciones preferidas del presente invento resultan directamente a partir de la definición de R^5 y R^6 cuando se toman conjuntamente para formar un resto que es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (1 3 1), (1 3 11), (1 3 12) y (1 3 15)



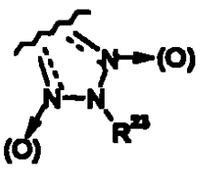
(1 3 1)



(1 3 11)

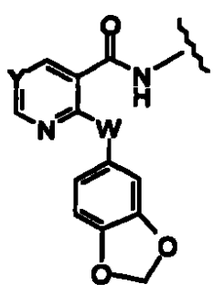


(1 3 12)

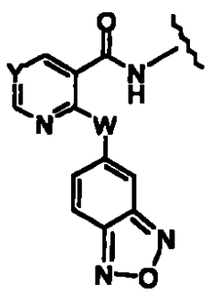


(1.3 15)

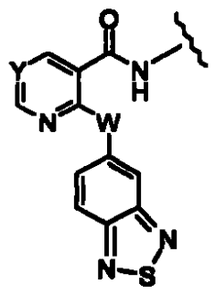
Correspondientemente, resultan adicionalmente los restos de Fórmulas parciales (1 0 15) hasta (1 0 18)



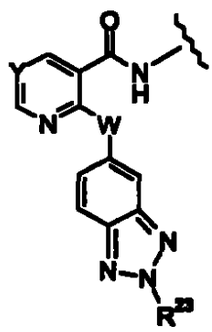
(1 0 15)



(1 0 16)



(1 0 17)



(1 0 18)

en las que R^{23} es -H ó $-CH_3$, y W tiene el significado de -O- $-S(=O)_t-$ en que t es 0, 1 ó 2, o $-N(R^3)-$ en que R^3 es como aquí se define y es preferiblemente -H ó $-CH_3$ En compuestos preferidos de Fórmula (1 0 0) W tiene el significado de -O- con lo que se crea un enlace de éter para unir el heterociclo bicíclico condensado con benzo al núcleo central de nicotinamida

En realizaciones preferidas de los compuestos de Fórmula (1 0 0) R^{23} y R^{24} están ambos ausentes, excepto en compuestos del tipo ilustrado por la Fórmula parcial (1 3 11) en la que puede estar ausente solamente uno de los R^{23} ó R^{24} Se reconocerá que cuando R^{23} y R^{24} están ambos ausentes y las líneas de trazos - - - - representan correspondientemente dobles enlaces que la porción de fenilo de los resultantes heterociclos bicíclicos condensados con benzo que se describen no pueden tener todos ellos los dobles enlaces descritos en dichas Fórmulas parciales puesto que el resultado sería entonces átomos de carbono pentavalentes prohibidos en dicha porción de fenilo

Correspondientemente cuando ambos R^{23} y R^{24} están ausentes, los resultantes compuestos son caracterizados por estructuras tal como las mostradas en las Fórmulas parciales (1 0 16) y (1 0 17) anteriores

En otras realizaciones de los compuestos de Fórmula (1 0 0) los sustituyentes R^{20} y R^{21} en los heterociclos bicíclicos condensados con benzo representados por la Fórmula parcial (1 3 1) son -H -F -Cl $-CH_3$ $-CH_2F$ $-CHF_2$ ó $-CF_3$ Preferiblemente R^{20} y R^{21} son ambos -H ó -F en cuyo caso los resultantes compuestos son caracterizados por la estructura mostrada en la Fórmula parcial (1 0 15) anterior, o su correspondiente compuesto análogo con difluoro (no mostrado) Los sustituyentes R^{23} y R^{24} en los heterociclos bicíclicos condensados con benzo representados por los restos de Fórmulas parciales (1 3 9) hasta (1 3 13) son cada uno de ellos independientemente -H, $-CH_3$, $-OCH_3$, o están ausentes en cuyo caso la línea de trazos - - - - representa un doble enlace Se entenderá desde luego, que cuando están ausentes R^{23} y R^{24}, no hay átomos de carbono pentavalentes en la porción de fenilo de dichos heterociclos bicíclicos

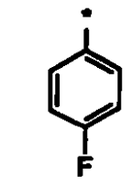
condensados con benzo Las resultantes estructuras heterocíclicas bicíclicas condensadas con benzo se muestran en las Fórmulas parciales (1 0 16) hasta (1 0 18) anteriores

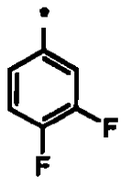
5 3.1 J^1 es distinto de fenilo

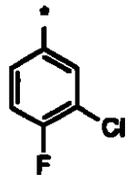
Además de las realizaciones del presente invento en las que J^1 tiene el significado preferido de fenilo, el presente invento también se ha definido anteriormente como estando implicado con un compuesto de Fórmula (1 0 0) en el que J^1 tiene el significado antes definido como un resto que comprende un sistema anular de carbonos, saturado o insaturado que es monocíclico de 3 a 7 miembros, o que es policíclico condensado o discontinuo de 7 a 12 miembros en que opcionalmente un átomo de carbono de éste puede ser reemplazado por un heteroátomo seleccionado entre N, O y S, y cuando se selecciona N, opcionalmente un segundo átomo de carbono de éste puede ser reemplazado por un heteroátomo seleccionado entre N, O ó S El presente invento concierne además a un compuesto de Fórmula (1 0 0) en que J^1 comprende especialmente un miembro seleccionado entre el grupo que consta de fenilo, pirrolilo, pirrolidinilo, furanilo tienilo, pindilo pirimidinilo, pipendinilo, piperazinilo, imidazolilo, imidazolidinilo, oxazolilo, isoxazolilo morfolinilo, tiazolilo, indolilo, quinolinilo, isoquinolinilo, bencimidazolilo, benzoxazolilo quinuclidinilo, y azabiciclo[3 3 0]octanilo, un resto cicloalquilo (C_3-C_7) monocíclico, un resto cicloalquenilo (C_5-C_7) monocíclico que es un miembro seleccionado entre el grupo que consta de ciclopentenilo ciclohexenilo y cicloheptenilo y un resto cicloalquilo (C_7-C_{10}) o cicloalquenilo (C_7-C_{10}) bicíclico que es un miembro seleccionado entre el grupo que consta de norbornanilo, norbornenilo, biciclo[2 2 2]octanilo, biciclo[3 2 1]octanilo biciclo[3 3 0]octanilo, biciclo[2 2 2]oct-5-enilo, biciclo[2 2 2]oct-7-enilo, biciclo[3 3 1]nonanilo, ciclodecanilo y adamantanilo

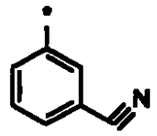
El presente invento concierne todavía adicionalmente de modo especial a un compuesto de Fórmula (1 0 0) en el que particularmente J^1 y los sustituyentes R^4, R^5 y R^6 se seleccionan de una manera tal que el extremo terminal izquierdo de dicho compuesto de Fórmula (1 0 0) está representado por las siguientes Fórmulas parciales (1 8 1) hasta (1 8 72)

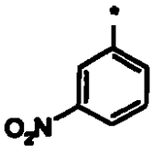
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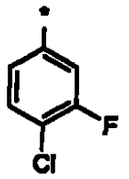

(1.8.1)

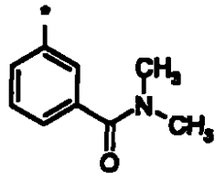

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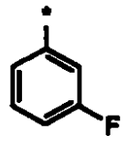

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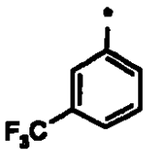

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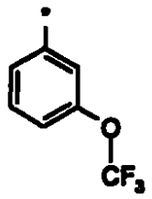

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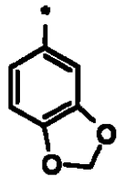

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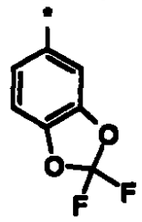

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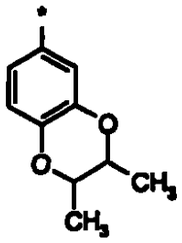

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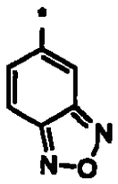

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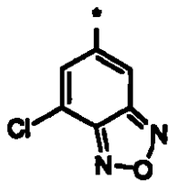

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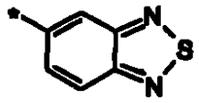

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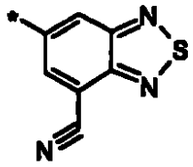

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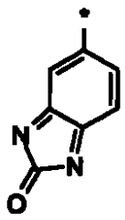

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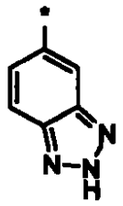

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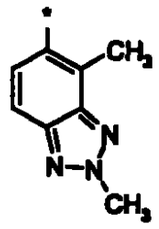

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(1.8.16)


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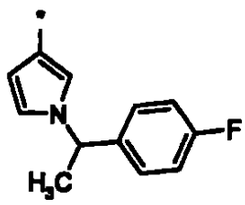

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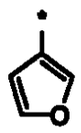

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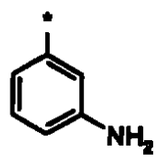
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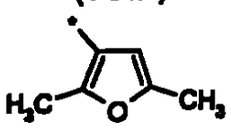
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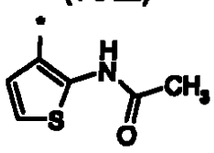
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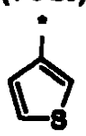
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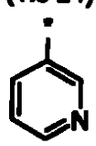
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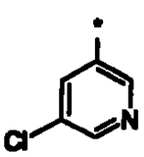
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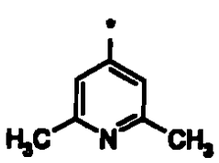
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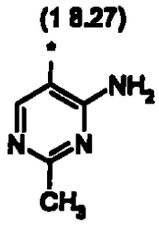
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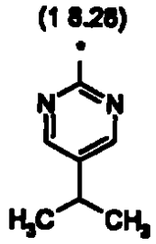
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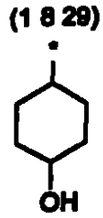
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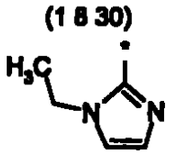
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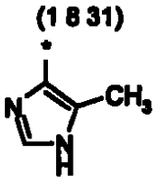
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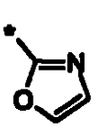
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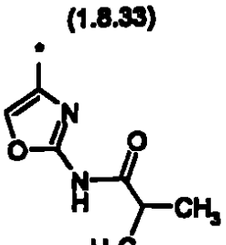
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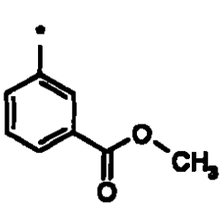
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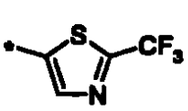
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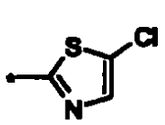
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(1 8 39)



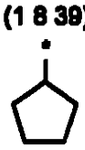
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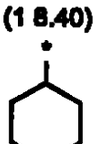
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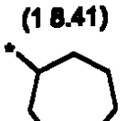
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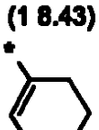
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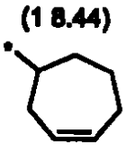
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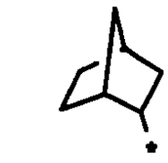
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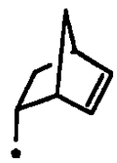
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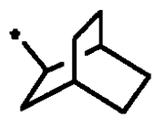
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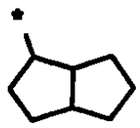
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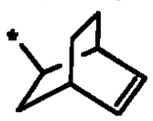
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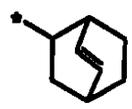
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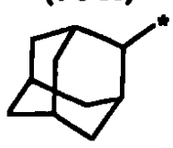
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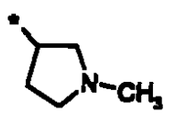
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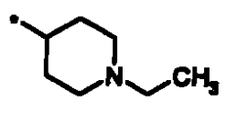
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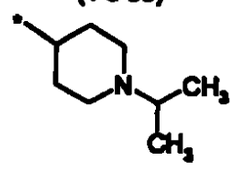
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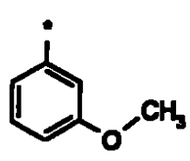
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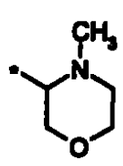
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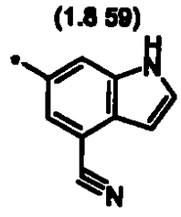
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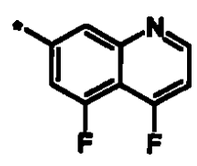
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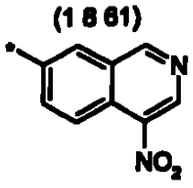
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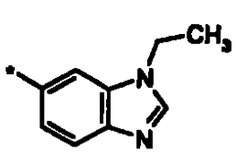
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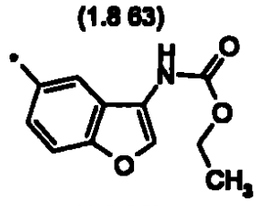
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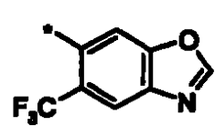
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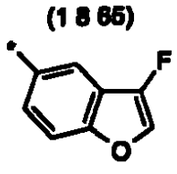
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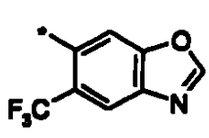
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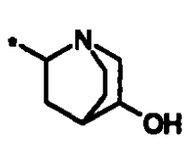
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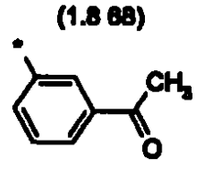
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(1 8 70)



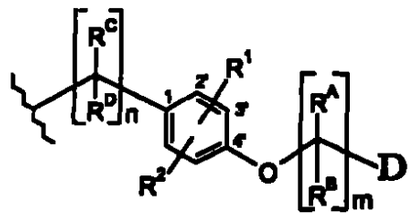
(1 8 71)



(1 8 72)

El carácter del nucleo nicotinamido con un enlace de éter, tioéter o sulfonilo a un grupo fenilo sustituido que forma el lado izquierdo del compuesto de Formula (1 0 0), ha sido descrito con anterioridad El lado derecho del compuesto de Fórmula (1 0 0) comprende, en realizaciones preferidas en las que J^2 tiene el significado preferido de fenilo, un grupo bencilo que está sustituido con los sustituyentes R^1 y R^2 Preferiblemente, sólo está presente un unico sustituyente, R^1 ó R^2, el unico sustituyente R^1 ó R^2 está en la posición 2', y el grupo bencilo está sustituido en la posición 4 con el resto que contiene los sustituyentes R^A, R^B y D Este lado derecho preferido del compuesto de Fórmula (1 0 0) puede ser representado por la Fórmula (1 0 4)

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(1.0.4)

5.4 0 J^2 es fenilo sustituido con R^1 y R^2

Los sustituyentes R^1 y R^2 son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -Cl, alquilo (C_1-C_3), alquilo (C_1–C_3) fluorado y/o clorado alcoxi (C_1-C_3) fluorado y/o clorado alquinilo (C_2-C_4), -CN, $-NO_2$, $-OR^{18}$ y $-C(=O)NH_2$ Cuando R^1 y/o R^2 son -H no habrá ningun sustituyente en ninguna de las posiciones especialmente en la posición 2 del grupo fenilo unido a la parte restante del lado izquierdo de la molécula de Fórmula (1 0 0) Dichas realizaciones no son tan preferidas como los compuestos del presente invento que tienen un sustituyente, especialmente uno en la posición 2 del grupo fenilo Por lo tanto, en algunas realizaciones preferidas de los compuestos del presente invento, los significados de R^1 y R^2 son definidos como -H -Cl -F alquilo (C_1-C_3) clorado y/o fluorado, alcoxi (C_1-C_3) clorado y/o fluorado, o alquinilo (C_2-C_4)

Cuando está implicado un sistema anular de carbonos de 6 miembros, p ej , como en el caso de ciclohexilo fenilo o piridilo se prefiere en particular que dicho resto que define a J^2 esté unido en sus posiciones 1 y 4 es decir que los puntos de unión de dicho resto estén en relación para unos con respecto a los otros Sin embargo otras configuraciones de dicho sistema anular de carbonos de 6 miembros que definen a J^2 están dentro del alcance de los compuestos de Fórmula (1 0 0), p ej , cuando los sitios de unión están en las posiciones 1 y 2 o en las posiciones 1 y 3 de dicho sistema anular de carbonos de 6 miembros

Se prefiere tener un grupo de halógeno en el sitio de la molécula que está ocupado por el sustituyente R^1 ó R^2, puesto que usualmente da como resultado un rendimiento mejorado Se considera que está dentro del alcance del presente invento el hecho de que R^1 ó R^2 sea un pequeño grupo lipófilo que comprende -Cl ó -F, alquilo (C_1–C_3) clorado y/o fluorado, o alcoxi (C_1-C_3) clorado y/o fluorado Por lo tanto, los significados del sustituyente R^1 ó R^2, así como de cualquier otro sustituyente de un compuesto de Fórmula (1 0 0) que incluye las definiciones que -Cl ó -F, alquilo (C_1-C_3) clorado y/o fluorado o alcoxi (C_1-C_3) clorado y/o fluorado se selecciona entre el grupo que consta de los siguientes

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—F	—CH_2F	—CHF_2	—CF_3	—CH_2CHF_2
—CH_2CHCF_2	—CH_2CF_3	-$CHFCH_2F$	-$CHFCHF_2$	—$CHFCF_3$
—$CF_2CF_2CF_3$	—O—CH_2F	—O—CHF_2	—O—CF_3	—O—CH_2CH_2F
—O—CH_2CHF_2	—O—CH_2CF_3	—O—$CHFCH_2F$	—O—$CHFCHF_2$	—O—$CHFCF_3$
—O—CF_2CH_2F	—O—CF_2CHF_2	—O—CF_2CF_3		

La selectividad de la molécula global que se consigue utilizando un resto de este tipo como el sustituyente R^1 y R^2 puede ser debida a la alineación en conformación del resto lipófilo con una correspondiente zona lipófila en el substrato de la enzima PDE4 o PDE40, o puede ser debida a un cambio en la lipofilia de la molécula global que resulta Cualquiera que sea el mecanismo real mediante el que se consigue dicha selectividad, todas dichas realizaciones están consideradas como encontrándose dentro del alcance del presente invento

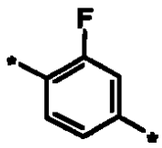
5 4.1 J^2 es distinto de fenilo

El presente invento se ha definido anteriormente también como estando relacionado con un compuesto de Fórmula (1 0 0) en el que J^2 tiene el significado antes definido como un resto que comprende un sistema anular de carbonos saturado o insaturado que es monocíclico de 3 a 7 miembros, o que es policíclico condensado o discontinuo de 7 a 12 miembros, en que opcionalmente un átomo de carbono de éste puede ser reemplazado por un heteroátomo seleccionado entre N, O ó S, y cuando se selecciona N, opcionalmente un segundo átomo de carbono de éste puede ser reemplazado por un heteroátomo seleccionado entre N, O ó S El presente invento concierne además a un compuesto de Fórmula (1 0 0) en que J^2 comprende especialmente un miembro seleccionado entre el grupo que consta de fenilo pirrolilo pirrolidinilo furanilo, tienilo, piridilo pirimidinilo, pipendinilo, piperazinilo, imidazolilo, imidazolidinilo, oxazolilo isoxazolilo, tiazolilo, indolilo, quinolinilo, isoquinolinilo, bencimidazolilo benzoxazolilo, morfolinilo, quinuclidinilo, y azabiciclo[3 3 0]octanilo, un resto cicloalquilo (C_3-C_7) monocíclico un resto cicloalquenilo (C_5-C_7) monocíclico que es un miembro seleccionado entre el grupo que consta de ciclopentenilo, ciclohexenilo y cicloheptenilo, y un resto cicloalquilo (C_7-C_{10}) o cicloalquenilo (C_7-C_{10}) que es un miembro seleccionado entre el grupo que consta de norbornanilo norbornenilo, biciclo-[2 2 2]octanilo, biciclo[3 2 1]octanilo, biciclo[3 3 0]octanilo, biciclo[2 2 2]oct-5-enilo, biciclo[2 2 2]oct-7-enilo, biciclo[3 3 1]nonanilo, ciclodecanilo y adamantanilo

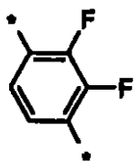
El presente invento concierne tambien adicionalmente de modo especial a un compuesto de Fórmula (1 0 0) en el que particularmente J^2 y los sustituyentes R^1 y R^2 se seleccionan de una manera tal que esta porción del extremo derecho de dicho compuesto de Fórmula (1 0 0) está representado por las siguientes Fórmulas parciales (3 0 1) hasta (3 0 47) que se exponen a continuación

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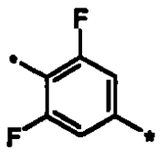
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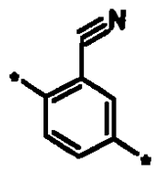
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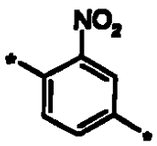
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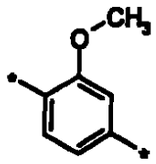
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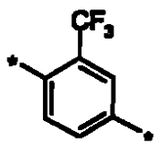
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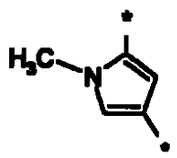
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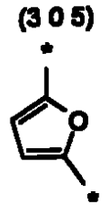
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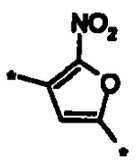
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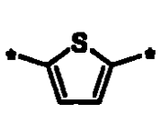
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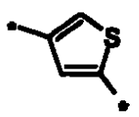
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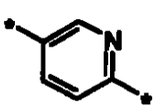
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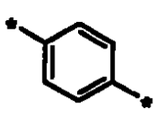
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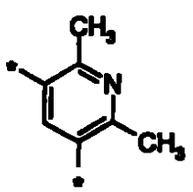
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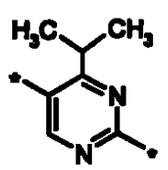
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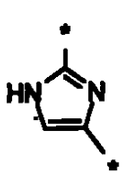
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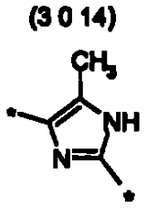
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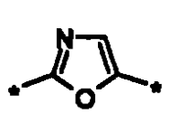
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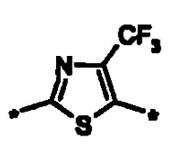
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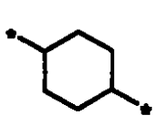
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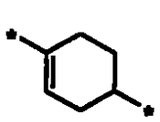
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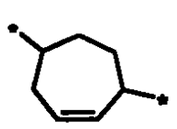
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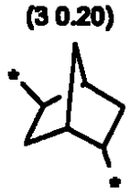
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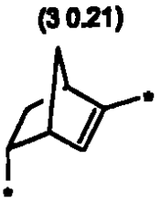
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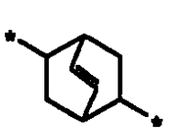
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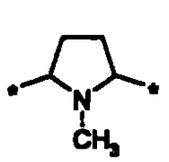
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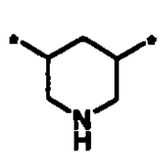
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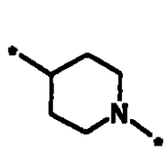
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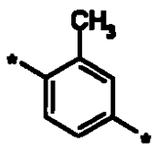
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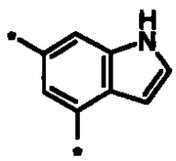
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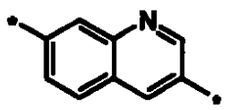
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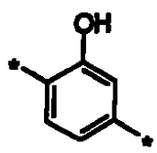
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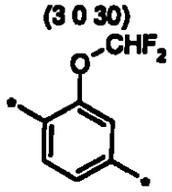
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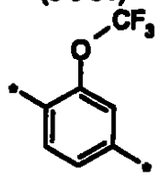
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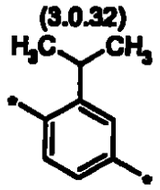
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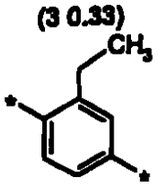
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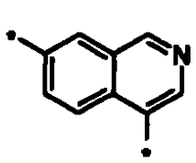
(3 0 35)



(3 0.36)



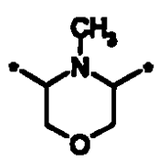
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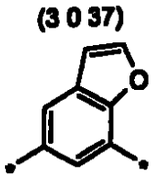
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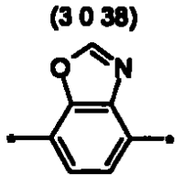
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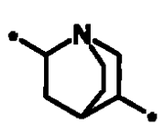
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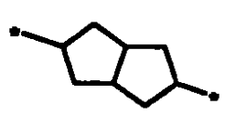
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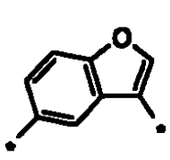
(3 0 42)



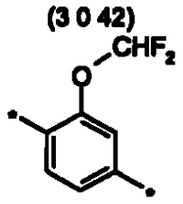
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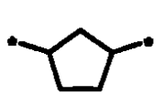
(3.0.44)



(3 0 45)



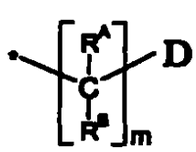
(3 0 46)



(3 0.47)

5.5 Los sustituyentes R^A y R^B

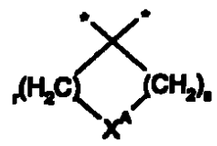
El grupo de Fórmula parcial (1 0 4) anterior está sustituido en la posición 4 con un resto que comprende los sustituyentes D, R^A y R^B, que se puede representar por la Fórmula parcial (1 1 8)



(1 1 8)

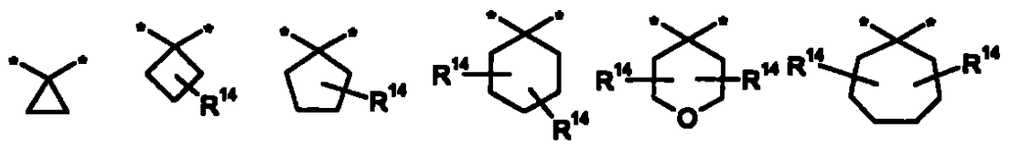
en la que m es 1 2 ó 3 En las realizaciones más preferidas de los compuestos del presente invento, m tiene el significado de 0 ó 1 Cuando m es 1, está presente el resto $-[R^A\text{-}C\text{-}R^B]_m-$, y R^A y R^B son preferiblemente cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H y alquilo (C_1-C_4), más preferiblemente -H y $-CH_3$

En otras realizaciones preferidas del presente invento, R^A y R^B se pueden tomar conjuntamente, pero solamente en el caso en que m sea 1, para formar un resto espiro de Fórmula (1 2 0)

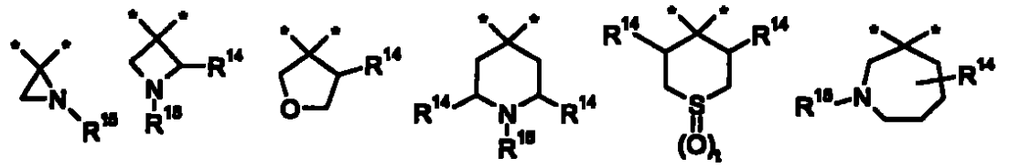


(1.2.0)

en la que r y s son independientemente de 0 a 4 con la condición de que la suma de r + s ha de ser por lo menos de 1, pero no mayor que 5, X^A es $-CH_2$, $-CHR^{11}$ ó $-C(R^{11})_2$- en que cada R^{11} se selecciona independientemente uno de otro y cada R^{11} tiene el mismo significado que aquí se define, $-NR^{15}$- en que R^{15} tiene el mismo significado que aquí se define, -O- ó $-S(=O)_t$ en que t es 0, 1 ó 2 y dicho resto espiro está sustituido como en uno cualquiera o más átomos de carbono de éste con 0 a 3 sustituyentes R^{14}, como en un átomo de nitrógeno de este con 0 o 1 sustituyente R^{15}, y como a un átomo de azufre de éste con 0 a 2 átomos de oxígeno Correspondientemente, resultan, entre otros, los restos ilustrados por las Fórmulas parciales (1 2 1) hasta (1 2 12)



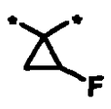
(1.2.1) (1.2.2) (1.2.3) (1.2.4) (1.2.5) (1.2.6)



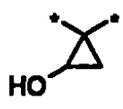
(1.2.7) (1.2.8) (1.2.9) (1.2.10) (1.2.11) (1.2.12)

en las que t es 0, 1 ó 2, y R^{14} y R^{15} tienen los mismos significados que aquí se definen

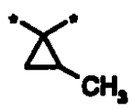
Significados prefendos del sustituyente R^{14} incluyen -F -Cl =O -OH, $-CH_3$, $-OCH_3$, -C(=O)OH $-C(=O)NH_2$ $-NH_2$, $-NHCH(CH_3)_2$, $-NHC(=O)CH_3$, $-NHC(=O)OCH_2CH_3$, $-NHS(=O)_2CH_3$, y $-S(=O)_2NH_2$, dando como resultado restos tales como los de las Fórmulas parciales (3 1 1) hasta (3 1 34)



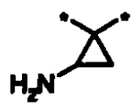
(3 1 1)



(3 1.2)



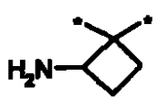
(3 1 3)



(3 1 4)



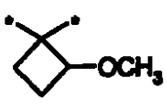
(3 1 5)



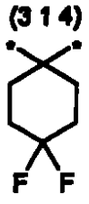
(3 1 6)



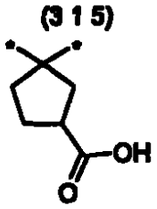
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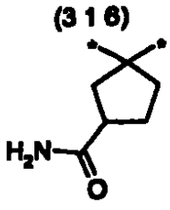
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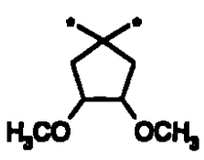
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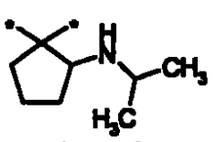
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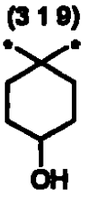
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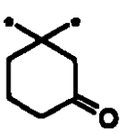
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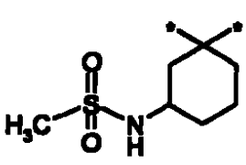
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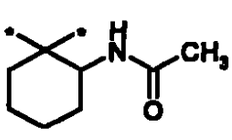
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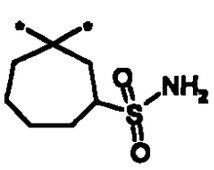
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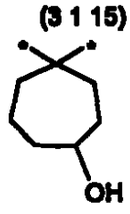
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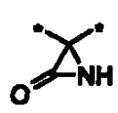
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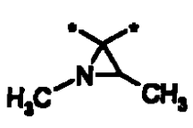
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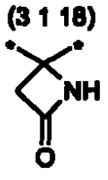
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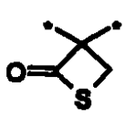
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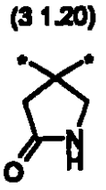
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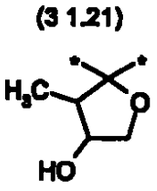
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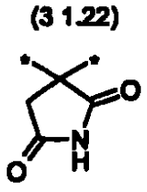
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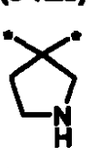
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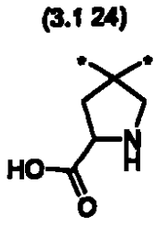
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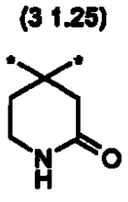
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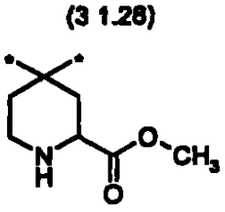
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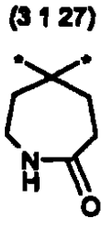
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(3 1.29)



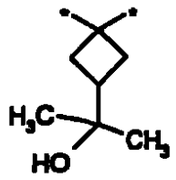
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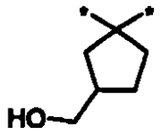
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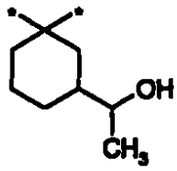
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(3 1 32)



(3 1.33)



(3 1.34)

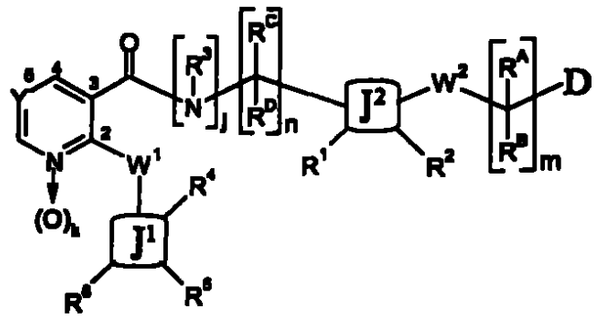
5 6 Los sustituyentes R^C y R^D

Como ya se ha descrito, R^C y R^D tienen los mismos significados que antes se han definido para R^A y R^B excepto que uno de ellos debe ser -H y que ellos se seleccionan independientemente unos de otros y de R^A y R^B Correspondientemente, todas las realizaciones particulares y preferidas de los compuestos de Fórmula (1 0 0), antes detallados con respecto a los sustituyentes R^A y R^B, son en su mayor parte también realizaciones particulares y preferidas de los compuestos de Formula (1 0 0) con respecto a los sustituyentes R^C y R^D

5 7 El resto -[N(R^3)]$_j$-

El subíndice j tiene el significado de 0 ó 1 Cuando j tiene el significado de 1, que es el significado preferido, está presente el resto -N(R^3)- y los compuestos de Fórmula (1 0 0) son esencialmente nicotinamidas en cuanto a su estructura con relación al lado izquierdo del nucleo central El sustituyente R^3 en el átomo de nitrógeno se selecciona preferiblemente entre -H, alquilo (C_1-C_3) y alcoxi (C_1-C_3), y más preferiblemente es -H, -CH_3, ó -OCH_3 En las realizaciones más preferidas de los compuestos de Fórmula (1 0 0), R^3 tiene el significado de -H

Cuando J^1 y J^2 ambos el significado preferido de fenilo, y j tiene el significado de 0, con un significado menos preferido que cuando j es 1, el resto -N(R^3)- está ausente y los compuestos de Fórmula (1 0 0) son esencialmente restos de nicotinoilo, es decir cetonas en cuanto a su estructura con respecto al lado izquierdo del nucleo central Dicha estructura de cetona en el lado izquierdo del nucleo central conjuntamente con bencilo como un significado preferido del resto J, se representa por la Fórmula (1 0 7)



(1.0 7)

en la que todos los sustituyentes y componentes de la misma, es decir, D, W, Y, k, m y n, R^1, R^2, R^4, R^5 y R^6 y R^A, R^B, R^C y R^D, tienen en su mayor parte los mismos significados particulares y preferidos que se describen aquí con detalle como en el caso en que j es 1 y el lado izquierdo del nucleo central de los compuestos tiene una estructura de nicotinamida

5 8 Realizaciones de subgéneros y subespecies preferidas de Fórmula (1 0 0)

En la descripción que antecede se han expuesto diversos aspectos preferidos de los compuestos de Fórmula (1 0 0) Como una demostración adicional del alcance y del contenido del presente invento se presentan realizaciones subgenéricas de los compuestos de Fórmula (1 0 0) Dichas realizaciones preferidas incluyen, pero no se limitan a, las citadas en los siguientes párrafos (i) hasta (viii)

(i) Un compuesto de acuerdo con la Fórmula (1 0 0) en el que cuando m es 1 ó 2, y n es 1 ♦ R^A y R^B son -H -CF_3 o alquilo (C_1-C_6) sustituido con 0 ó 1 de -F, -Cl, -CF_3, -CN, -NH_2 ó -C(=O)NH_2 o ambos tomados conjuntamente son espiro-cicloalquilo (C_3-C_6)- sustituido con 0 ó 1 de -F -Cl, -CF_3 ó -CN, ♦ uno de los R^C y R^D es -H y el otro es -H, alquilo (C_1-C_4) o fenilo, cada uno de ellos sustituido con 0 ó 1 de -F, -Cl ó -CN, ♦ W^1 es -O- ó -S-, ♦ W^2 es -O- ♦ Y es =C($R^1{}_a$)- en que $R^1{}_a$ es -H, -F, -Cl, -CN, -CH_3 ó -OCH_3, ♦ R^1 y R^2 son -H, -F, -Cl, -CN -NO_2, -OH, -CH_3, -OCH_3, -$OCHF_2$ ó -OCF_3, ♦ R^3 es -H ó -CH_3 ♦ R^4 es -H -F -CN, -NO_2 -OH -CH_3 ó -OCH_3, ♦ J^1 es fenilo ♦ R^5 y R^6 se toman conjuntamente para formar un resto de Fórmula parcial (1 3 1) en el que R^{20} y R^{21} son -H ó -CH_3, o un resto de Fórmula parcial (1 3 11), (1 3 12) ó (1 3 15) en el que R^{23} y R^{24} están ausentes o son -H ó -CH_3, ♦ J^2 es fenilo, norbornanilo, furanilo, tienilo pirimidinilo o ciclohexilo ♦ y D es -C(=O)OR^7 en que R^7 es -H ó -CH_3, -C(=O)NH_2 o tetrazol-5-ilo,

(ii) Un compuesto de acuerdo con el párrafo (i) en el que R^A y R^B son ambos

$-CH_3$, o uno de ellos es $-CH_3$ y el otro es $-CH(CH_3)_2$ ó $-C(CH_3)_3$, o uno de ellos es -H y el otro es $-CH_3$ o $-CF_3$, o ambos tomados conjuntamente son espiro-ciclopropilo o espiro-ciclobutilo, ♦ uno de los R^C y R^D es -H y el otro es -H ó $-CH_3$, W^1 es -O-, ♦ Y es $=C(R^1_a)-$ en que R^1_a es -H -F ó -Cl ♦ R^1 y R^2 son -H, -F ó -Cl, ♦ R^3 es -H ♦ R^4 es -H, ♦ R^5 y R^8 se toman conjuntamente para formar un resto de Fórmula parcial (1 3 1) o (1 3 11) en el que R^{23} y R^{24} estan ambos ausentes, ♦ J^2 es fenilo, tienilo o ciclohexilo, ♦ y D es $-C(=O)OR^7$ en que R^7 es -H ó $-CH_3$, $-C(=O)NH_2$, o tetrazol-5-ilo,

(iii) Un compuesto de acuerdo con el párrafo (ii) en el que R^A y R^B son ambos $-CH_3$, o ambos tomados conjuntamente son espiro-ciclopropilo, ♦ uno de los R^C y R^D es -H y el otro es -H ó $-CH_3$, ♦ Y es $=C(R^1_a)-$ en que R^1_a es -H, -F ó -Cl, ♦ R^1 y R^2 son -H, -F ó -Cl, ♦ R^3 es -H ♦ R^4 es -H ♦ R^5 y R^8 se toman conjuntamente para formar un resto de Fórmula parcial (1 3 11) en el que R^{23} y R^{24} están ambos ausentes, ♦ J^2 es fenilo, ♦ y D es $-C(=O)OR^7$ en que R^7 es -H ó $-CH_3$, $-C(=O)NH_2$ o tetrazol-5-ilo,

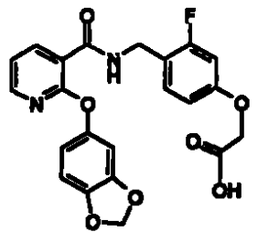
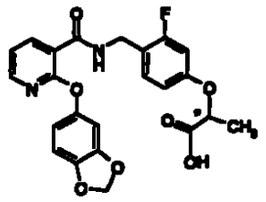
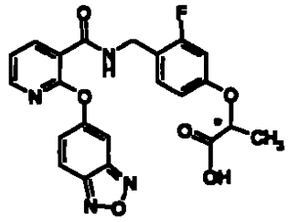
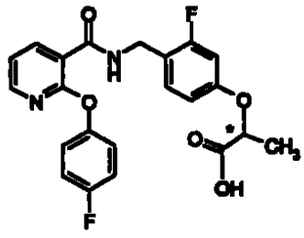
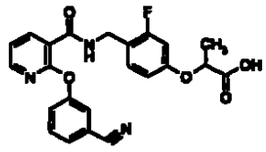
(iv) Un compuesto de acuerdo con el párrafo (iii) en el que R^A y R^B son ambos $-CH_3$, ♦ R^C y R^D son ambos -H, ♦ Y es $=C(R^1_a)-$ en que R^1_a es -H, ♦ y uno de los R^1 y R^2 es -H y el otro es -F,

(v) Un compuesto de acuerdo con el párrafo (iii) en el que Y es $=C(R^1_a)-$ en que R^1_a es -F ♦ y R^1 y R^2 son ambos -H,

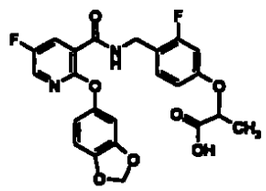
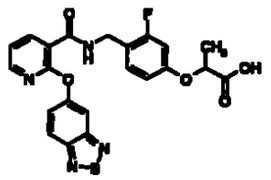
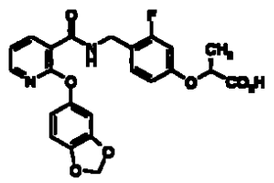
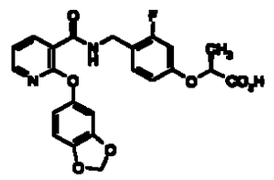
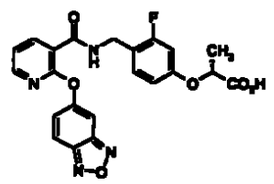
(vi) Un compuesto de acuerdo con el párrafo (ii) en el que R^A y R^B son ambos $-CH_3$ o ambos tomados conjuntamente son espiro-ciclopropilo, ♦ uno de los R^C y R^D es -H y el otro es -H ó $-CH_3$, ♦ Y es $=C(R^1_a)-$ en que R^1_a es -H, -F ó -Cl, ♦ R^1 y R^2 son -H, -F ó -Cl, ♦ R^3 es -H, ♦ R^4 es -H R^5 y R^8 se toman conjuntamente para formar un resto de Fórmula parcial (1 3 1) en el que R^{20} y R^{21} son ambos -H, ♦ J^2 es fenilo, ♦ y D es $-C(=O)OR^7$ en que R^7 es -H ó $-CH_3$, $-C(=O)NH_2$, o tetrazol-5-ilo,

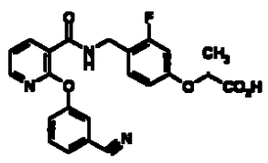
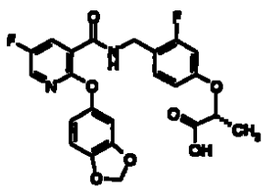
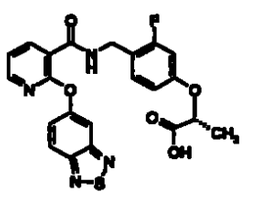
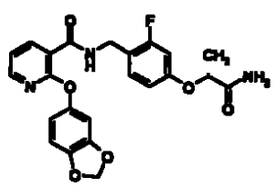
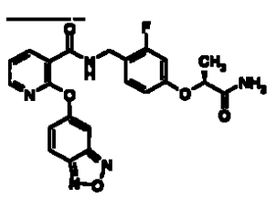
(vii) Un compuesto de acuerdo con el párrafo (vi) en el que R^A y R^B son ambos $-CH_2$, ♦ R^C y R^D son ambos -H, ♦ Y es $=C(R^1_a)-$ en que R^1_a es -H, ♦ y uno de los R^1 y R^2 es -H y el otro es -F, y

(viii) Un compuesto de acuerdo con el párrafo (vii) en el que Y es $=C(R^1_a)-$ en que R^1_a es -F, ♦ y R^1 y R^2 son ambos -H

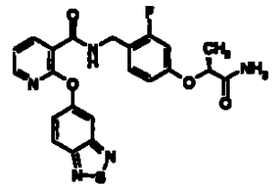
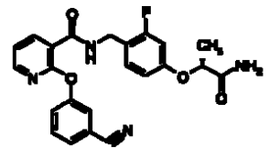
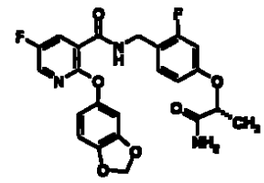
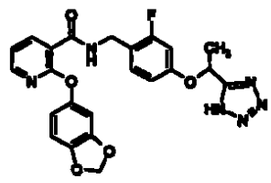
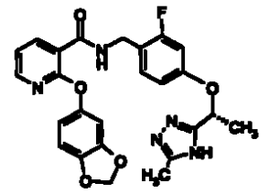
NOMENCLATURA	FÓRMULA ESTRUCTURAL
Ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético de Fórmula (5 5 1),	
(±)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 2),	
(±)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 3)	
(±)-Ácido 2-[3-fluoro-4-({[2-(4-fluoro-fenoxi)-pirdina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 4),	
(±)-Ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-pirdina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 5),	

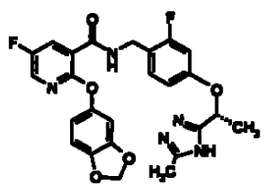
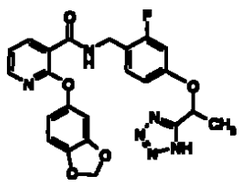
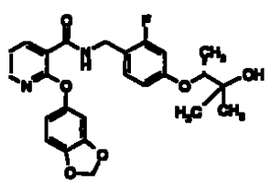
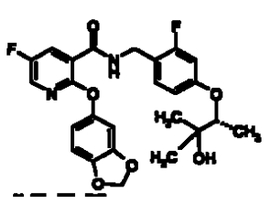
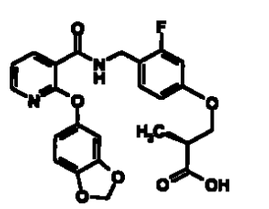
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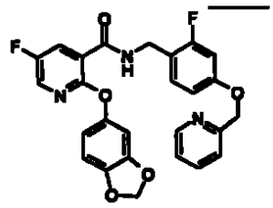
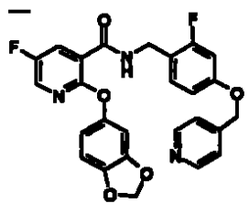
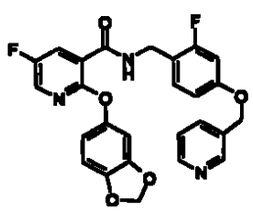
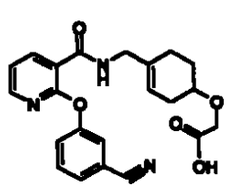
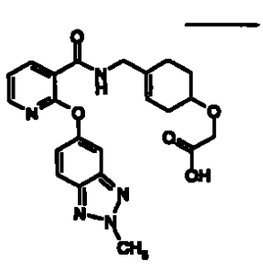
(±)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 6),	
(±)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 7),	
(R)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 8)	
(S)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 9),	
(R)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 10),	

(R)-Ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 11)	
(R)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 12),	
(R)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Formula (5 5 13),	
(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 14)	
(R)-2-(Benzo[2,1,3]oxadiazol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 15),	

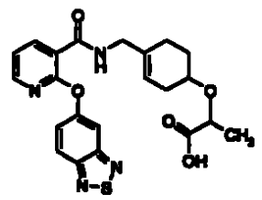
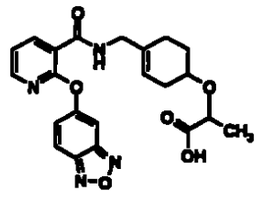
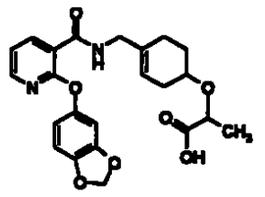
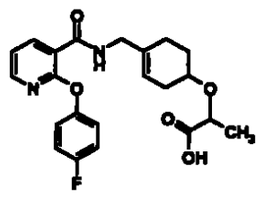
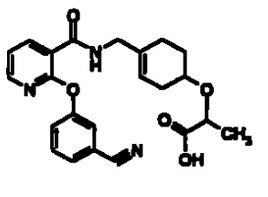
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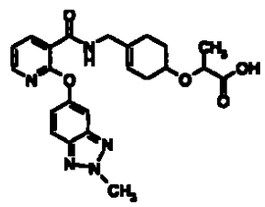
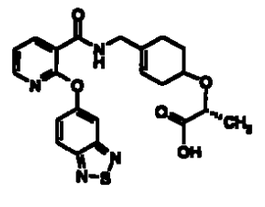
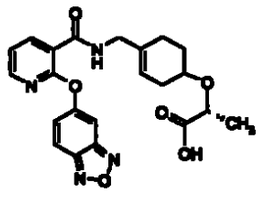
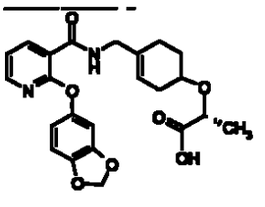
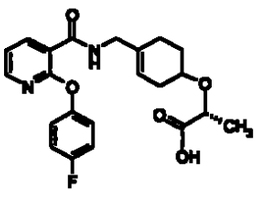
(R)-2-(Benzo[2,1,3]tiadiazol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 16),	
(R)-N-[4-(1-Carbamoil-etoxi)-2-fluoro-bencil]-2-(3-ciano-fenoxi)-nicotinamida de Fórmula (5 5 17),	
(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-5-fluoro-nicotinamida de Fórmula (5 5 18),	
(±)-2-(Benzo[1 3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(1*H*-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 19),	
(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 20),	

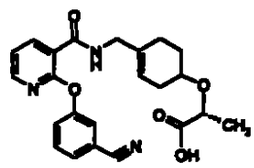
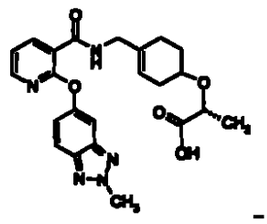
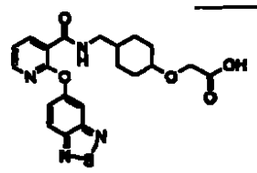
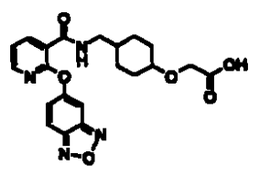
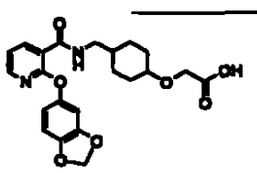
(R)-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-{2-fluoro-4-[1-(5-metil-4H-[1 2,4]triazol-3-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 21),	
(±)-2-(Benzo[1 3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(1*H*-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 22),	
(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[2-fluoro-4-(2-hidroxi-1,2-dimetil-propoxi)-bencil]-nicotinamida de Fórmula (5 5 23),	
(R)-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(2-hidroxi-1 2-dimetil-propoxi)-bencil]-nicotinamida de Fórmula (5 5 24),	
(S)-Ácido 3-[4-({(2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 25)	

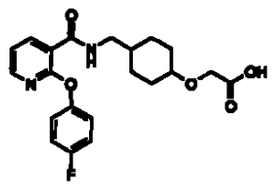
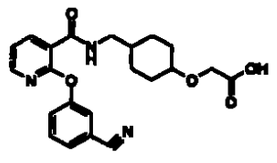
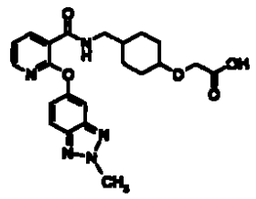
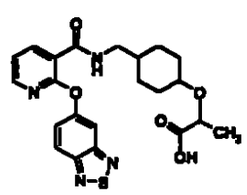
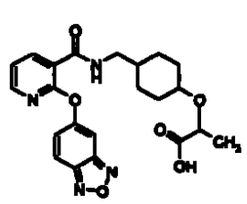
2-(Benzo[1 3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-2-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 28),	
2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-4-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 27),	
2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-3-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 28),	
Ácido [4-({[2-(3-ciano-fenoxi)-pirídina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Formula (5 5 29),	
Ácido [4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 30),	

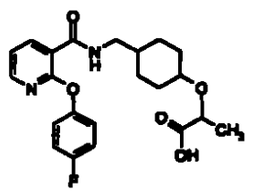
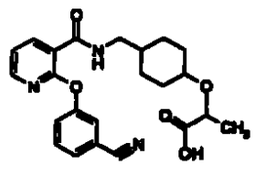
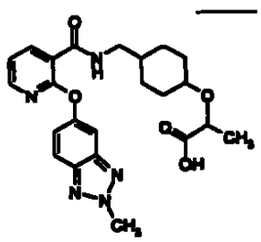
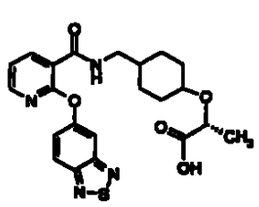
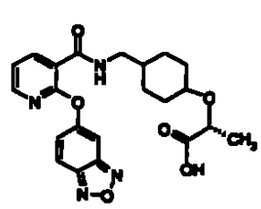
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(±)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 31),	
(±)-Ácido 2-[4-({[2-(benzo[2,1 3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 32),	
(±)-Ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 33)	
(±)-Ácido 2-[4-({[2-(4-fluoro-fenoxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 34),	
(±)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 35)	

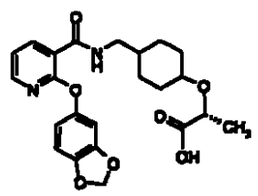
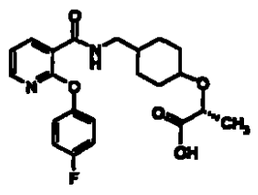
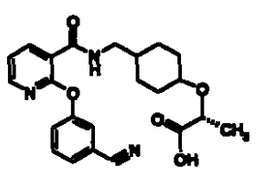
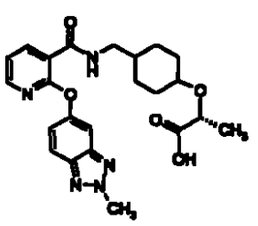
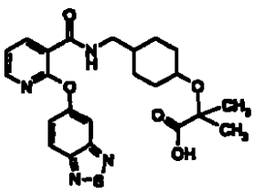
(±)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cıclohex-3-enıloxı]-propıónıco de Fórmula (5 5 36),	
(R)-Ácido 2-[4-({[2-(benzo[2,1,3]tıadıazol-5-iloxı)-pırıdına-3-carbonil]-amino}-metil)-cıclohexil-3-enıloxı]-propıónıco de Fórmula (5 5 37)	
(R)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadıazol-5-iloxı)-pırıdına-3-carbonil]-amino}-metil)-cıclohex-3-enıloxı]-propıónıco de Fórmula (5 5 38),	
(R)-Ácido 2-[4-({[2-(benzo[1,3]dıoxol-5-iloxı)-pırıdına-3-carbonil]-amino}-metil)-cıclohex-3-enıloxı]-propıónıco de Fórmula (5 5 39),	
(R)-Ácido 2-[4-({[2-(4-fluoro-fenoxı)-pırıdına-3-carbonil]-amino}-metil)-cıclohex-3-enıloxı]-propıónıco de Fórmula (5 5 40),	

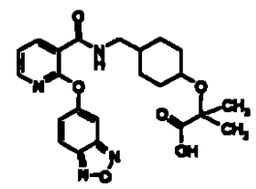
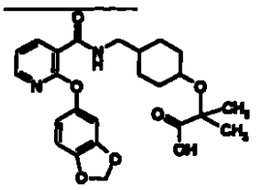
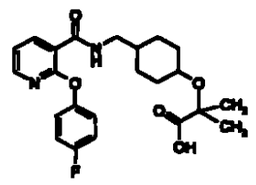
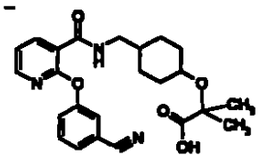
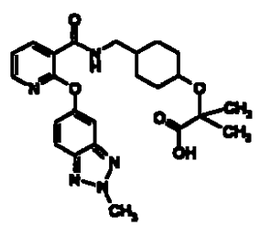
(R)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-pirídina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 41),	
(R)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 42),	
Ácido [4-({[2-(benzo[2,1 3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-acético de Fórmula (5 5 43),	
Ácido [4-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-acético de Fórmula (5 5 44),	
Ácido [4-({[2-(benzo[1 3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-acético de Fórmula (5 5 45),	

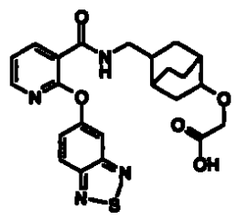
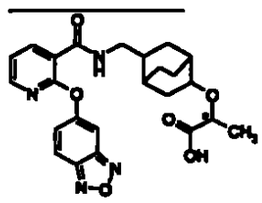
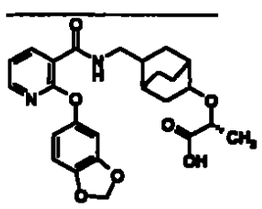
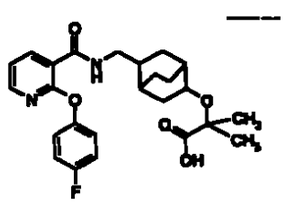
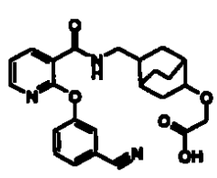
Ácido [4-({[2-(4-fluoro-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-acético de Fórmula (5 5 46),	
Ácido [4-({[2-(3-ciano-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-acético de Fórmula (5 5 47),	
Ácido [4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-acético de Fórmula (5 5 48),	
(±)-Ácido 2-[4-({[2-(benzo[2,1 3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 49),	
(±)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 50),	

(±)-Ácido 2-[4-({[2-(4-fluoro-fenoxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-propiónico de Fórmula (5 5 51)	
(±)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-propiónico de Fórmula (5 5 52),	
(±)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-propiónico de Fórmula (5 5 53),	
(R)-Ácido 2-[4-({[2-(benzo[2 1 3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-propiónico de Fórmula (5 5 54)	
(R)-Ácido 2-[4-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-propiónico de Fórmula (5 5 55),	

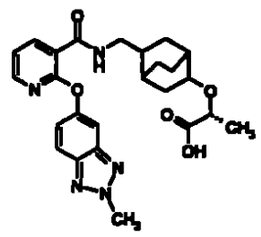
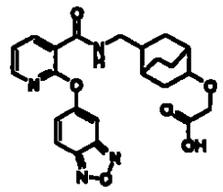
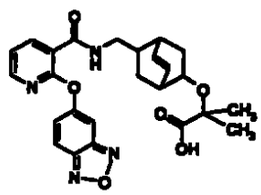
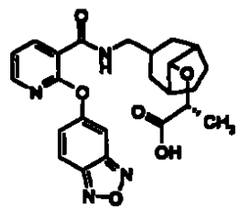
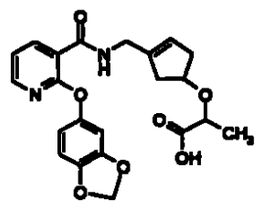
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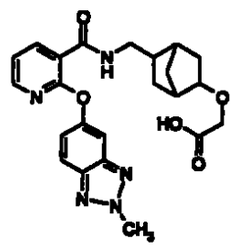
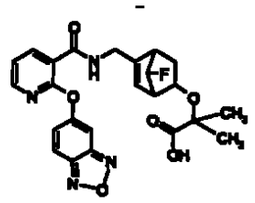
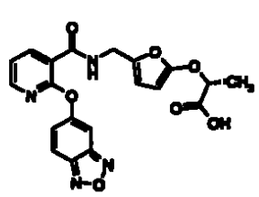
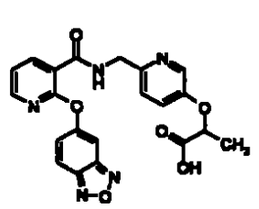
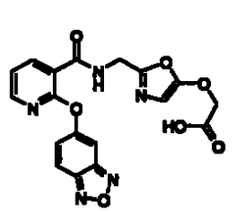
(R)-Ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 56),	
(R)-Ácido 2-[4-({[2-(4-fluoro-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 57),	
(R)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 58),	
(R)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 59),	
Ácido 2-[4-({[2-(benzo[2 1 3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-2-metil-propiónico de Fórmula (5 5 60),	

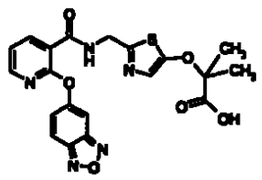
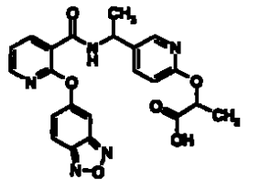
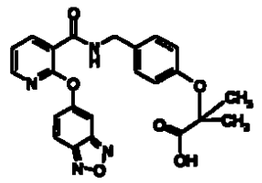
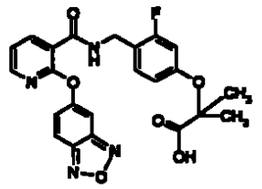
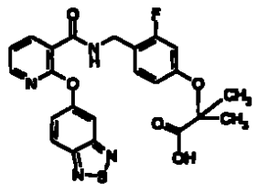
Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-2-metil-propiónico de Fórmula (5 5 61)	
Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-2-metil-propionico de Fórmula (5 5 62)	
Ácido 2-[4-({[2-(4-fluoro-fenoxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-2-metil-propiónico de Fórmula (5 5 63)	
Ácido 2-[4-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-2-metil-propiónico de Fórmula (5 5 64),	
Ácido 2-metil-2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohexiloxi]-propiónico de Fórmula (5 5 65),	

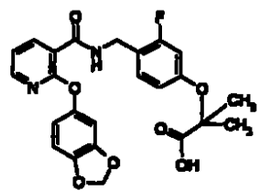
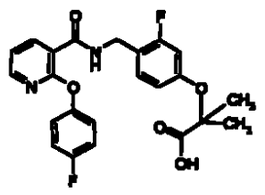
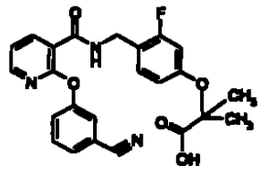
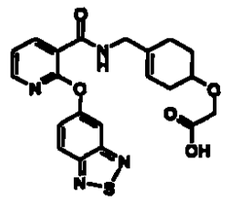
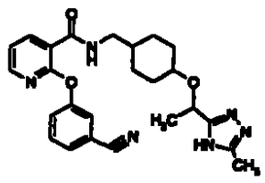
Ácido [5-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-acético de Fórmula (5 5 66)	
(±)-Ácido 2-[5-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-biciclo-[2 2 2]oct-2-iloxi]-propiónico de Fórmula (5 5 67)	
(R)-Ácido 2-[5-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-propiónico de Fórmula (5 5 68),	
Ácido 2-[5-({[2-(4-fluoro-fenoxi)-piridina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-2-metil-propionico de Fórmula (5 5 69),	
Ácido 2-[5-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-2-metil-propiónico de Formula (5 5 70),	

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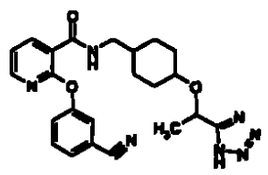
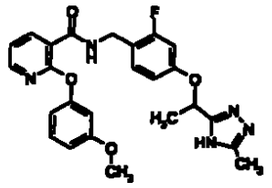
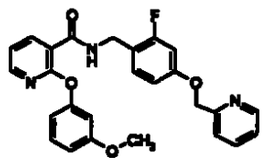
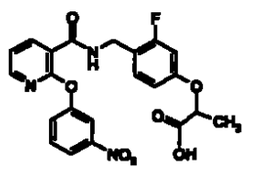
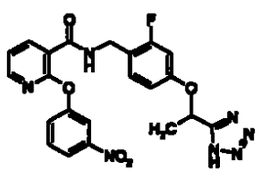
(R)-Ácido 2-[5-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-biciclo-[2 2 2]oct-2-iloxi]-propiónico de Fórmula (5 5 71)	
Ácido [5-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-acetico de Fórmula (5 5 72)	
Ácido 2-[8-({[2-(benzo[2,1 3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-5-en-2-iloxi]-2-metil-propiónico de Fórmula (5 5 73)	
(R)-Ácido 2-[3-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-biciclo-[3 2 1]oct-8-iloxi]-propiónico de Fórmula (5 5 74),	
Ácido 2-[3-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclopent-3-eniloxi]-propiónico de Fórmula (5 5 75)	

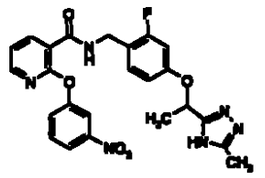
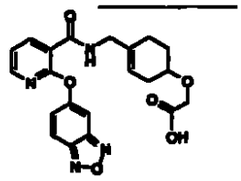
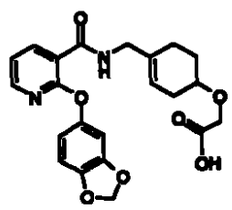
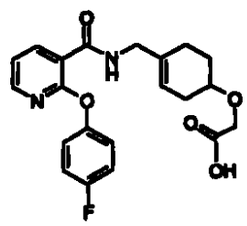
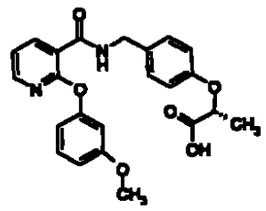
Ácido [5-({[2-(2-metil-2H-benzotriazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-biciclo-[2 2 1]hept-2-iloxi]-acetico de Fórmula (5 5 76),	
Ácido 2-[5-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-7-fluoro-biciclo[2 2 1]hept-5-en-2-iloxi]-2-metil-propiónico de Formula (5 5 77)	
(R)-Ácido 2-[5-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-furan-2-iloxi]-propiónico de Formula (5 5 78)	
(±)-Ácido 2-[6-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-piridin-3-iloxi]-propionico de Fórmula (5 5 79),	
Ácido [2-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-oxazol-5-iloxi]-acético de Fórmula (5 5 80),	

Ácido [2-({[2-(benzo[2,1 3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-tiazol-5-iloxi]-2-metil-propiónico de Fórmula (5 5 81),	
(±)-Ácido 2-[5-(1-{[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-etil)-pirıdin-2-iloxi]-propiónico de Fórmula (5 5 82),	
Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-fenoxi]-2-metil-propiónico de Fórmula (5 5 83),	
Ácido 2-[4-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 84)	
Ácido 2-[4-({[2-(benzo[2 1,3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 85),	

Ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 86),	
Ácido 2-[3-fluoro-4-({[2-(4-fluoro-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-fenoxi]-2-metil-propiónico de Fórmula (5 5 87),	
Ácido 2-[4-({[3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 88)	
Ácido [4-({[2-benzo[2 1,3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 89)	
(±)-2-(3-Ciano-fenoxi)-N-{4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-ciclohexilmetil}-nicotinamida de Fórmula (5 5 90),	

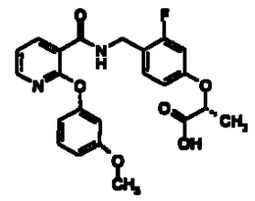
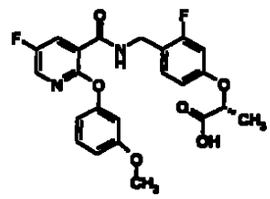
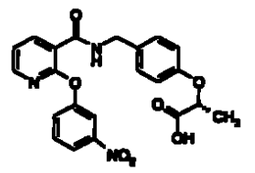
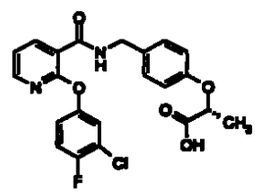
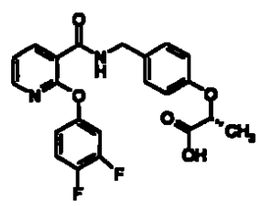
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(±)-2-(3-Ciano-fenoxi)-N-{4-[1-(1H-tetrazol-5-il)-etoxi]-ciclohexilmetil}-nicotinamida de Fórmula (5 5 91),	
(±)-N-{2-Fluoro-4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-bencil}-2-(3-metoxi-fenoxi)-nicotinamida de Fórmula (5 5 92)	
N-[2-Fluoro-4-(piridin-2-ilmetoxi)-bencil]-2-(3-metoxi-fenoxi)-nicotinamida de Fórmula (5 5 93),	
(±)-Ácido 2-[3-fluoro-4-({[2-(3-nitro-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 94)	
(±)-N-{2-Fluoro-4-[1-(1H-tetrazol-5-il)-etoxi]-bencil}-2-(3-nitro-fenoxi)-nicotinamida de Fórmula (5 5 95)	

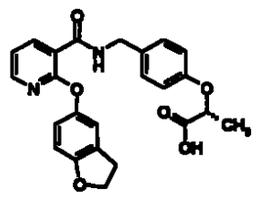
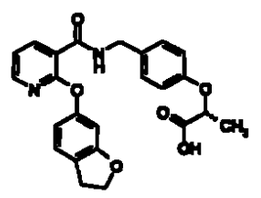
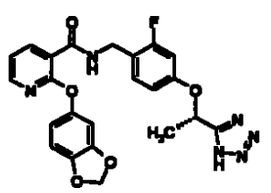
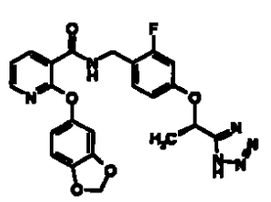
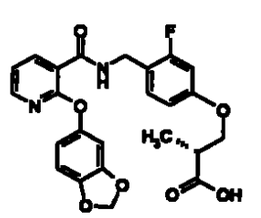
(±)-N-{2-Fluoro-4-[1-(5-metil-4H-[1 2,4]triazol-3-il)-etoxi]-bencil}-2-(3-nitro-fenoxi)-nicotinamida de Fórmula (5 5 96),	
Ácido [4-({[2-(benzo[2 1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 97),	
Ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 98),	
Ácido [4-({[2-(4-fluoro-fenoxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 99),	
(R)-Ácido 2-[4-({[2-(3-metoxi-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 100),	

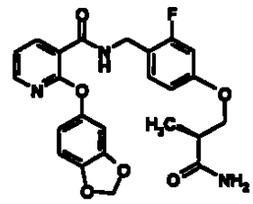
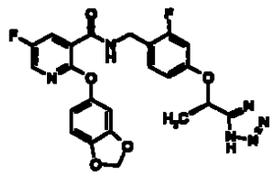
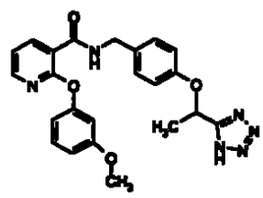
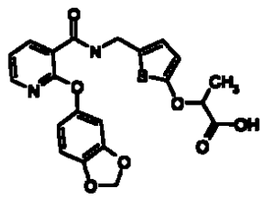
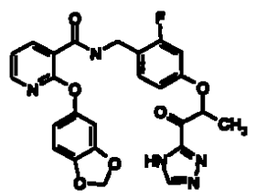
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(R)-Ácido 2-[3-fluoro-4-({[2-(3-metoxi-fenoxi)-pirıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıonıco de Fórmula (5 5 101)	
(R)-Ácido 2-[3-fluoro-4-({[5-fluoro-2-(3-metoxı-fenoxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıónıco de Fórmula (5 5 102),	
(R)-Ácido 2-[4-({[2-(3-nıtro-fenoxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıónıco de Fórmula (5 5 103),	
(R)-Ácido 2-[4-({[2-(3-cloro-4-fluoro-fenoxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıónıco de Fórmula (5 5 104),	
(R)-Ácido 2-[4-({[2-(3,4-dıfluoro-fenoxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıonıco de Fórmula (5 5 105),	

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(R)-Ácido 2-[4-({[2-(2,3-dihidro-benzofuran-5-iloxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Formula (5 5 106),	
(R)-Ácido 2-[4-({[2-(2,3-dihidro-benzofuran-6-iloxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 107),	
(S)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(1H-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 108)	
(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(1H-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 109),	
(R)-Ácido 3-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Formula (5 5 110),	

(S)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(2-carbamoil-propoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 111)	
(R)-2-(Benzo[1 3]dioxol-5-iloxi)-5-fluoro-N-{2-fluoro-4-[1-(1H-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 112)	
(±)-2-(3-Metoxi-fenoxi)-N-{4-[1-(1H-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 113)	
Ácido 2-[5-({[2-(benzo[1 3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-tiofen-2-iloxi]-propiónico de Fórmula (5 5 114)	
(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-metil-2-oxo-2-(4H-[1,2 4]triazol-3-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 115)	

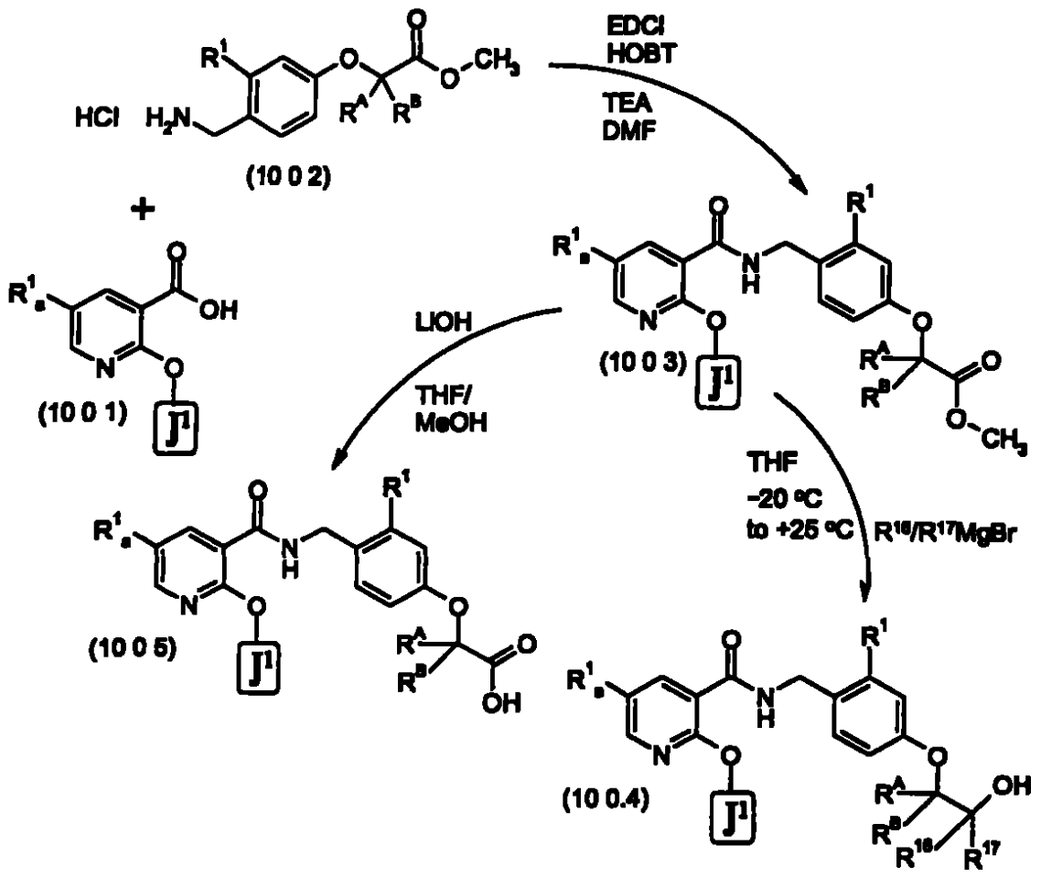
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DESCRIPCIÓN DETALLADA DEL INVENTO

6 0 Procedimientos para preparar los compuestos de Fórmula (1 0 0)

Un metodo apropiado para preparar un compuesto de Fórmula (1 0 0) que pertenece a la clase de éter-ácidos, en los que W^1 y W^2 son ambos -O-, J^2 es fenilo, y D es un resto de Formula parcial (1 1 1), se ilustra en el Esquema de Síntesis (10 0 0) presentado a continuación

ESQUEMA DE SÍNTESIS (10 0 0)

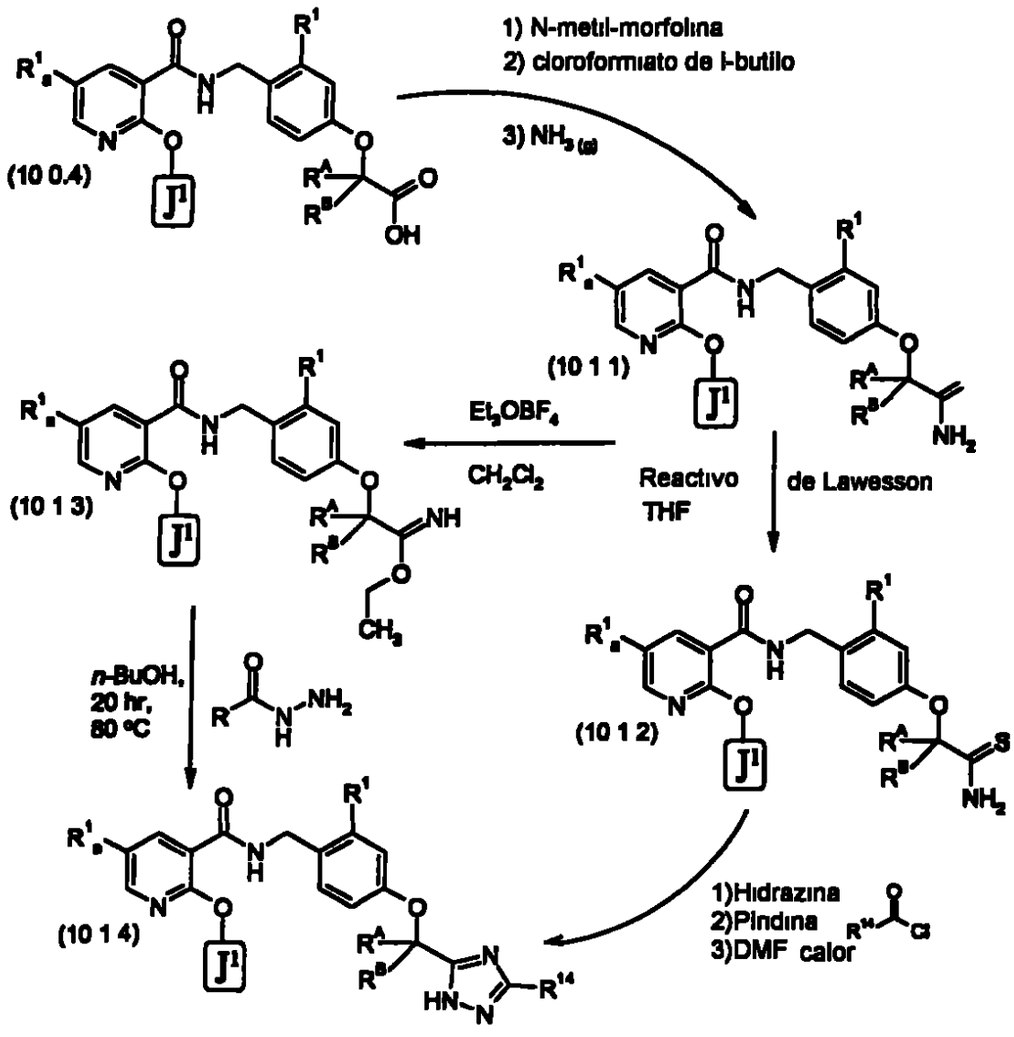


en el que R^1 es -H ó -F, R^A y R^B son -H o alquilo (C_1-C_4), R^1_a y J^1 tienen los mismos significados que antes se definen y R^{16} y R^{17} deben tener el mismo significado

Un método apropiado para preparar un compuesto de Fórmula (1 0 0) que pertenece a la clase de los triazoles, en el que W^1 y W^2 son ambos -O-, J^2 es fenilo y D es un resto de Fórmula parcial (1 1 4) en el que v es 0 y R^8 es triazol, se ilustra en el

Esquema de Síntesis (10 1 0) siguiente La primera operación del Esquema de Síntesis (10 1 0) ilustra la preparación de éter-amidas de Fórmula (1 0 0)

ESQUEMA DE SINTESIS (10 1 0)

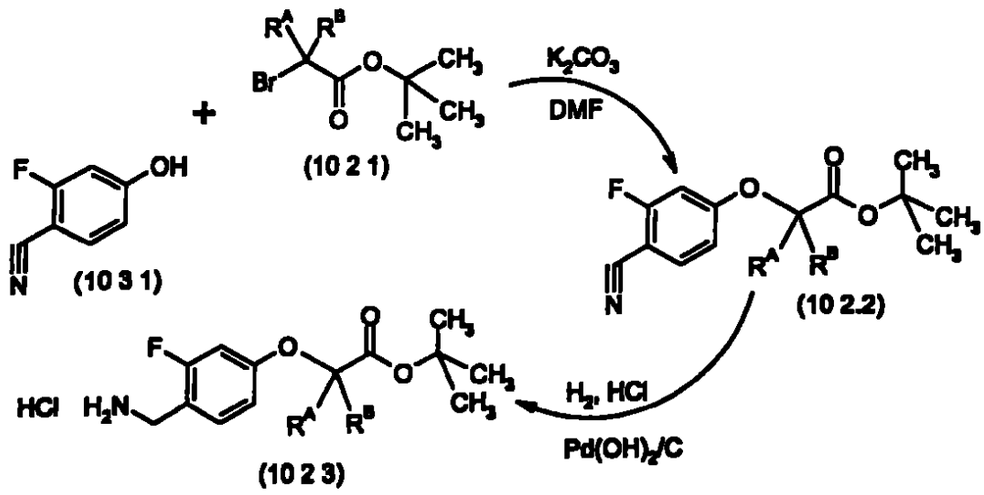


en el que R^1 es -H ó -F, R^A y R^B son -H o alquilo (C_1-C_4), $R^1{}_a$ y J^1 tienen los mismos significados que antes se definen, y R^{14} tiene el mismo significado que anteriormente y es con preferencia metilo, fenilo o *iso*-propilo

Un método apropiado para preparar compuestos de amino-éter-ésteres racémicos de Fórmula (1 0 0) en los que W^1 y W^2 son ambos -O-, J^2 es fenilo y D es un resto de Fórmula parcial (1 1 1), se ilustra en el Esquema de Síntesis (10 2 0) presentado a continuación

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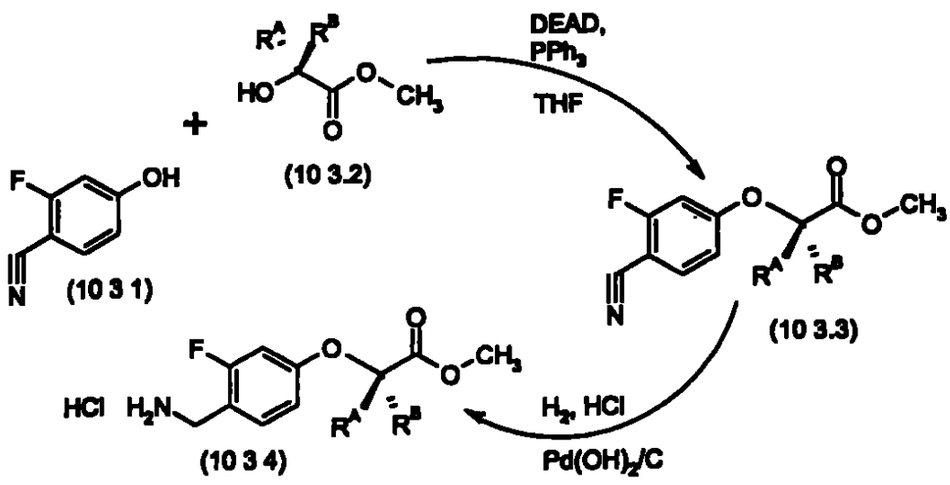
ESQUEMA DE SINTESIS (10 2 0)



en el que R^A y R^B tienen los mismos significados que antes se definen

Un metodo apropiado para preparar compuestos de amino-éter-esteres enantiómeros de Fórmula (1 0 0) en los que W^1 y W^2 son ambos -O-, J^2 es fenilo y D es un resto de Fórmula parcial (1 1 1), se ilustra en el Esquema de Síntesis (10 3 0) que se presenta a continuacion

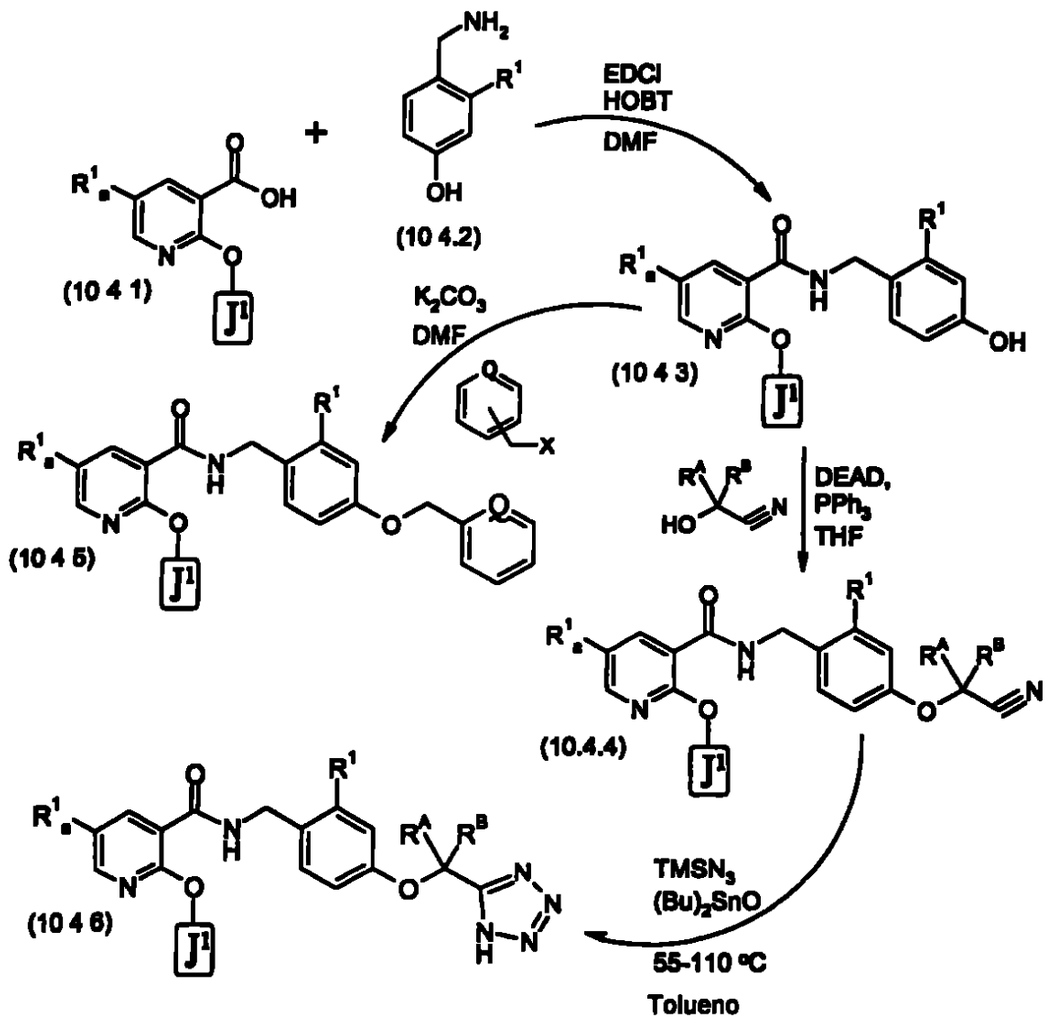
ESQUEMA DE SÍNTESIS (10 3.0)



en el que R^A y R^B tienen los mismos significados que antes se definen

Otros métodos apropiados para preparar compuestos de fenil- pirídil- y tetrazolil-éteres de Fórmula (1 0 0) en los que W^1 y W^2 son ambos -O-, J^2 es fenilo y D es un resto de Fórmula parcial (1 1 4), en el que v es 0 y R^8 es pirídilo o tetrazolilo, se ilustran en el Esquema de Síntesis (10 4 0) siguiente

ESQUEMA DE SÍNTESIS (10 4 0)



en el que R^1 es -H ó -F R^A y R^B son -H o alquilo (C_1-C_4), Q es CH ó N, X es halo, y R^1_a y J^1 tienen los mismos significados que antes se definen

DESCRIPCION DETALLADA DEL INVENTO

7 0 Sales farmacéuticas y otras formas

Los compuestos antes descritos del presente invento se pueden utilizar en la forma de ácidos, ésteres u otras clases químicas de compuestos a los que pertenecen los compuestos que se describen También esta dentro del alcance del presente invento el recurso de utilizar los compuestos en la forma de sus sales farmacéuticamente aceptables que se derivan de diversos/as ácidos y bases orgánicos/as e inorgánicos/as de acuerdo con procedimientos bien conocidos en el sector tecnológico

Las formas de sales farmacéuticamente aceptables de los compuestos de Fórmula (1 0 0) se preparan en su mayor parte por medios convencionales Cuando el compuesto de Fórmula (1 0 0) contiene un grupo de ácido carboxílico, una de sus sales apropiadas se puede formar haciendo reaccionar el compuesto con una base apropiada para proporcionar la correspondiente sal por adicion de base Ejemplos de dichas bases son hidróxidos de metales alcalinos inclusive hidróxido de potasio, hidróxido de sodio e hidróxido de litio, hidróxidos de metales alcalino-térreos tales como hidróxido de bario e hidróxido de calcio, alcóxidos de metales alcalinos, p ej , etanolato de potasio y propanolato de sodio, y diversas bases orgánicas tales como piperidina, dietanol-amina y *N*-metil-glutamina También se incluyen las sales de aluminio de los compuestos de Fórmula (1 0 0)

Para ciertos compuestos de Fórmula (1 0 0) se pueden formar las sales por adición de ácidos tratando dichos compuestos con ácidos orgánicos e inorgánicos farmaceuticamente aceptables, p ej , hidrohaluros tales como hidrocloruro, hidrobromuro o hidroyoduro, otros ácidos inorgánicos y sus correspondientes sales tales como sulfatos, nitratos, fosfatos, etc , y alquil- y mono-aril-sulfonatos tales como etano-sulfonato, tolueno-sulfonato y benceno-sulfonato, y otros ácidos orgánicos y sus correspondientes sales tales como acetato, tartrato maleato succinato citrato, benzoato, salicilato, ascorbato, etc

Correspondientemente las sales por adición de ácidos farmacéuticamente aceptables de los compuestos de Fórmula (1 0 0) incluyen, pero no se limitan a acetato, adipato, alginato, arginato aspartato, benzoato, benceno-sulfonato (besilato), bisulfato (hidrógeno-sulfato), bisulfito (hidrógeno-sulfito), bromuro, butirato, canforato, canfo-sulfonato, caprilato cloruro cloro-benzoato, citrato ciclopentano-propionato digluconato, dihidrógeno-fosfato, dinitro-benzoato dodecil-sulfato, etano-sulfonato, fumarato, galacterato (procedente de ácido mucico), galacturonato, glucoheptanoato, gluconato, gluatamato, glicero-fosfato hemisuccinato, hemisulfato, heptanoato hexanoato, hipurato hidrocloruro, hidrobromuro, hidroyoduro, 2-hidroxi-etano-sulfonato, yoduro, isetionato *iso*-

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butirato, lactato, lactobionato, malato, maleato, malonato, mandelato, metafosfato, metano-sulfonato, metil-benzoato, monohidrogeno-fosfato, 2-naftaleno-sulfonato, nicotinato, nitrato oxalato oleato, pamoato pectinato persulfato, fenil-acetato 3-fenil-propionato, fosfato, fosfonato o ftalato

Además, las sales con base de los compuestos del presente invento incluyen, pero no se limitan a, las de aluminio, amonio, calcio, cobre, férricas, ferrosas, de litio, magnesio mangánicas manganosas, de potasio, sodio y zinc Entre las sales antes citadas se prefieren las de aluminio, entre las sales de metales alcalinos se prefieren las de sodio y potasio, y entre las sales de metales alcalinos se prefieren las de calcio y magnesio Las sales de los compuestos de Fórmula (1 0 0) que se derivan de bases orgánicas no tóxicas farmacéuticamente aceptables incluyen, pero no se limitan a sales de *aminas primarias, secundarias y terciarias, aminas sustituidas* inclusive *aminas* sustituidas que se presentan en la naturaleza, aminas cíclicas, y resinas intercambiadoras de iones de carácter basico p ej las sales de arginina betaina cafeina, cloroprocaína, colina, *N,N'*-dibencil-etilen-diamina (benzatina), diciclohexil-amina, dietanol-amina, dietil-amina, 2-dietil-amino-etanol, 2-dimetil-amino-etanol etanol-amina, etilen-diamina, *N*-etil-morfolina, *N*-etil-piperidina, glucamina glucosamina histidina, hidrabamina, *iso*-propil-amina, lidocaina, lisina, meglumina, *N*-metil-D-glucamina, morfolina, piperazina, piperidina, resinas de poliaminas, procaina purinas, teobromina, trietanol-amina, trietil-amina trimetil-amina tripropil-amina y tris-(hidroximetil)-metil-amina (trometamina)

Los compuestos del presente invento que comprenden grupos de carácter básico que contienen nitrógeno, pueden ser cuaternizados con agentes tales como haluros de alquilo (C_1-C_4), p ej cloruros, bromuros y yoduros de metilo etilo, *iso*-propilo y *terc*-butilo, sulfato de di-alquilo (C_1-C_4), p ej , sulfatos de dimetilo, dietilo y diamilo, haluros de alquilo (C_{10}-C_{18}), p ej , cloruros, bromuros y yoduros de decilo, dodecilo, laurilo, miristilo y estearilo y haluros de aril-alquilo (C_1-C_4), p ej , cloruro de bencilo y bromuro de fenetilo Dichas sales permiten la preparación de compuestos tanto solubles en agua como solubles en aceites del presente invento

Entre las sales farmacéuticas antes citadas las que son preferidas incluyen, pero no se limitan a, acetato, besilato, citrato, fumarato gluconato, hemisuccinato, hipurato, hidrocloruro, hidrobromuro, isetionato, mandelato meglumina, nitrato, oleato, fosfonato, pivalato, sodio-fosfato, estearato, sulfato, sulfo-salicilato, tartrato, tiomalato, tosilato y trometamina

Las sales por adición de ácidos de compuestos de Fórmula (1 0 0) de carácter básico se preparan poniendo en contacto la forma de base libre con una cantidad suficiente del ácido deseado para producir la sal de la manera convencional La base libre puede ser regenerada poniendo en contacto la forma de sal con una base y aislando

la base libre de la manera convencional Las formas de base libre difieren de sus respectivas formas de sales de algun modo en ciertas propiedades físicas tales como solubilidad en disolventes polares, pero por lo demas las sales son equivalentes a sus formas respectivas de bases libres para las finalidades del presente invento

Como se ha indicado, las sales por adición de bases farmacéuticamente aceptables de los compuestos de Fórmula (1 0 0) se forman con metales o aminas, tales como metales alcalinos y metales alcalino-térreos o aminas orgánicas Los metales prefendos son sodio, potasio, magnesio y calcio Las aminas organicas preferidas son *N,N'*-dibencil-etilen-diamina, cloro-procaina, colina dietanol-amina etilen-diamina, *N*-metil-D-glucamina y procaina

Las sales por adición de bases de compuestos de carácter ácido del presente invento se preparan poniendo en contacto la forma de ácido libre con una cantidad suficiente de la base deseada para producir la sal de la manera convencional La forma de ácido libre se puede regenerar poniendo en contacto la forma de sal con un ácido y aislando la forma de ácido libre de la manera convencional Las formas de ácido libre difieren de sus respectivas formas de sal de algun modo en cuanto a propiedades físicas tales como la solubilidad en disolventes polares, pero por lo demás las sales son equivalentes a sus respectivas formas de ácidos libres para las finalidades del presente invento

Las formas de sales multiples se incluyen dentro del alcance del presente invento cuando un compuesto del presente invento contiene más de un grupo capaz de formar dichas sales farmacéuticamente aceptables Ejemplos de formas típicas de sales multiples incluyen, pero no se limitan a, bitartrato, diacetato, difumarato, dimeglumina, difosfato, disodio y trihidrocloruro

A la vista de lo que antecede puede observarse que se pretende que la expresión "sal farmacéuticamente aceptable", como se utiliza en el presente contexto, signifique un ingrediente activo que comprende un compuesto de Fórmula (1 0 0) utilizado en la forma de una sal de éste, especialmente en que dicha forma de sal confiere a dicho ingrediente activo propiedades farmacocinéticas mejoradas en comparación con la forma libre de dicho ingrediente activo o alguna otra forma de sal de dicho ingrediente activo que se haya utilizado con anterioridad La forma de sal farmacéuticamente aceptable de dicho ingrediente activo puede confenr inicialmente también una deseable propiedad farmacocinética a dicho ingrediente activo que éste no poseía con anterioridad, y puede incluso afectar de modo positivo a las condiciones farmacodinámicas de dicho ingrediente activo con respecto a su actividad terapéutica en el cuerpo

Las propiedades farmacocinéticas de dicho ingrediente activo que pueden ser afectadas favorablemente incluyen, p ej , la manera en la que dicho ingrediente activo es transportado a través de las membranas celulares, que a su vez puede afectar directa

y positivamente a la absorcion la distribución, la biotransformación y la excreción de dicho ingrediente activo Mientras que la ruta de administración de la composición farmaceutica es importante, y diversos factores anatómicos, fisiológicos y patológicos pueden afectar de una manera crítica a la biodisponibilidad la solubilidad de dicho ingrediente activo es dependiente usualmente del carácter de la particular forma de sal de éste que ella utiliza Además tal como lo apreciará un profesional, una solución acuosa de dicho ingrediente activo proporcionará la absorción sumamente rápida de dicho ingrediente activo en el cuerpo de un paciente que esté siendo tratado, mientras que las soluciones y suspensiones de lípidos, así como las formas de dosificación sólidas, darán como resultado una absorción menos rápida de dicho ingrediente activo

La ingestión oral de un ingrediente activo de Fórmula (1 0 0) es la ruta de administración más preferida por razones de seguridad, conveniencia y economía, pero la absorción de dicha forma de dosificacion oral puede ser afectada desfavorablemente por caracteristicas fisicas tales como polaridad, emesis causada por irritación de la mucosa gastrointestinal, destrucción por enzimas digestivas y bajo valor del pH, absorción o propulsión irregular en la presencia de un alimento u otros fármacos, y metabolismo, por enzimas de la mucosa la flora intestinal, o el hígado La formulación de dicho ingrediente activo en diferentes formas de sales farmacéuticamente aceptables puede ser eficaz para superar o aliviar uno o más de los problemas antes citados que se encuentran con la absorción de forma de dosificación orales

Un compuesto de Fórmula (1 0 0) preparado de acuerdo con los métodos aquí descritos, puede ser separado de la mezcla de reacción en la que es producido finalmente por cualquier medio ordinario conocido por un profesional químico experto en la preparación de compuestos orgánicos Una vez separado, dicho compuesto se puede purificar por métodos conocidos Diferentes métodos y técnicas se pueden usar como medios para separación y purificación e incluyen, p ej , destilación, recristalización, cromatografía en columna cromatografía con intercambio de iones, cromatografía en gel, cromatografía de afinidad, cromatografía de capa fina preparativa, y extracción con disolventes

7.1. Estereoisómeros

Un compuesto situado dentro del alcance de la Fórmula (1 0 0) puede ser tal que sus átomos constituyentes sean capaces de ser dispuestos en el espacio de dos o más maneras diferentes a pesar de tener conectividades idénticas Como consecuencia, dicho compuesto existe en la forma de estereoisómeros La isomería *syn-trans* es solamente un tipo de estereoisomeria Cuando los estereoisómeros son imágenes especulares no superponibles uno de otros, son enantiomeros que tienen quiralidad o

sentido de giro, a causa de la presencia de uno o mas atomos de carbono asimétricos en su estructura de constituyentes Los enantiómeros son ópticamente activos y por lo tanto distinguibles puesto que hacen girar el plano de la luz polarizada en magnitudes iguales, pero en direcciones opuestas

Cuando dos o más átomos asimétricos están presentes en un compuesto de Fórmula (1 0 0), hay dos configuraciones posibles en cada uno de dichos atomos de carbono Cuando están presentes dos átomos de carbono asimétricos por ejemplo, hay cuatro posibles estereoisómeros Además, estos cuatro posibles estereoisómeros pueden ser dispuestos en seis pares posibles de estereoisómeros que son diferentes unos de otros Con el fin de que un par de moléculas con más de un átomo de carbono asimétrico sean enantiómeras deben tener diferentes configuraciones en cada carbono asimétrico Los pares que no están relacionados como enantiómeros tienen una diferente relación estereoquimica referida como una relación diastereoisoménca Los estereoisómeros que no son enantiómeros son denominados diastereoisómeros, o más comentemente diastereómeros

Todos estos aspectos bien conocidos de la estereoquímica de los compuestos de Fórmula (1 0 0) se considera que son una parte del presente invento Dentro del alcance del presente invento se incluyen por consiguiente compuestos de Fórmula (1 0 0) que son estereoisómeros, y cuando éstos son enantiómeros, los enantiómeros individuales, las mezclas racémicas de dichos enantiómeros, y mezclas artificiales, es decir, mezclas producidas que contienen ciertas proporciones de dichos enantiómeros que son diferentes de las proporciones de dichos enantiómeros encontrados en una mezcla racémica Cuando un compuesto de Fórmula (1 0 0) comprende estereoisómeros que son diastereómeros, se incluyen dentro del alcance de dicho compuesto los diastereómeros individuales así como mezclas de cualquiera dos o más de dichos diastereómeros en cualesquiera proporciones de los mismos

A manera de ilustración, en el caso en el que haya un unico átomo de carbono asimétrico en un compuesto de Fórmula (1 0 0) que dé como resultado los enantiómeros (-)(*R*) y (+)(*S*) de los mismos, se incluyen dentro del alcance de dicho compuesto todas las formas de sales farmaceuticamente aceptables, profármacos y metabolitos del mismo que sean terapéuticamente activas y utiles para tratar o prevenir las enfermedades y condiciones que se describen adicionalmente en el presente texto Cuando un compuesto de Fórmula (1 0 0) existe en la forma de enantiómeros (-)(*R*) y (+)(*S*) se incluye también dentro del alcance de dicho compuesto el enantiómero (+)(*S*) a solas o el enantiómero (-)(*R*) a solas, en el caso en el que la totalidad, sustancialmente la totalidad, o una cuota predominante de la actividad terapéutica se presenta solamente en uno de dichos enantiómeros y/o efectos colaterales indeseados se presentan solamente en uno de

dichos enantiómeros En el caso en el que no haya sustancialmente ninguna diferencia entre las actividades biológicas de ambos enantiómeros, se incluyen además dentro del alcance de dicho compuesto de Fórmula (1 0 0) el enantiómero (+)(*S*) y el enantiómero (-)(*R*) presentes conjuntamente como una mezcla racémica o como una mezcla no racémica en cualquier relación de cantidades proporcionadas de la misma

Por ejemplo, las actividades biológicas y/o las propiedades físicas y químicas particulares de un par o conjunto de enantiómeros de un compuesto de Fórmula (1 0 0), cuando éstos existan, pueden sugerir el uso de dichos enantiómeros en ciertas relaciones para constituir un producto terapéutico final A manera de ilustración, en el caso en el que haya un par de enantiómeros, éstos se pueden emplear en relaciones tales como 90% de (R) - 10% de (S), 80% de (R) - 20% de (S), 70% de (R) - 30% de (S), 60% de (R) - 40% de (S), 50% de (R) - 50% de (S), 40% de (R) - 60% de (S), 30% de (R) - 70% de (S) 20% de (R) - 80% de (S), y 10% de (R) - 90% de (S) Después de haber evaluado las propiedades de los diversos enantiómeros de un compuesto de Fórmula (1 0 0) cuando éstos existan, la cantidad proporcionada de uno o más de dichos enantiómeros con ciertas propiedades deseadas que constituirán el producto terapéutico final, se puede determinar de una manera directa

7.2. Isótopos

Se considera además que están incluidas dentro del alcance de un compuesto de Fórmula (1 0 0) ciertas formas marcadas isotópicamente de éste Una forma marcada isotópicamente de un compuesto de Fórmula (1 0 0) es idéntica a la de dicho compuesto excepto por el hecho de que uno o más átomos de dicho compuesto se ha(n) reemplazado por un átomo o varios átomos que tiene(n) una masa atómica o un numero atómico diferente de la masa atómica o del numero atómico de dicho átomo que se encuentra usualmente en la naturaleza Ejemplos de isótopos que están disponibles comercialmente con facilidad y que se pueden incorporar en un compuesto de Fórmula (1 0 0) de acuerdo con procedimientos bien consagrados, incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno fósforo, azufre, fluor y cloro, p ej , ^{2}H ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F y ^{36}Cl, respectivamente Un compuesto de Fórmula (1 0 0), un profármaco de éste, o una sal farmacéuticamente aceptable de cualquiera de ellos, que contenga uno o mas de los isotopos antes mencionados y/o de otros isótopos de otros átomos, se considera que están dentro del alcance del presente invento

Un compuesto de Fórmula (1 0 0) marcado isotópicamente se puede usar de un cierto número de maneras beneficiosas Por ejemplo un compuesto marcado isotópicamente de Fórmula (1 0 0), p ej , uno en el que se haya incorporado un isótopo radiactivo tal como ^{3}H ó ^{14}P será util en los analisis de distribución en tejidos de fármacos

y/o substratos Estos isótopos radiactivos, es decir, tritio, ^{3}H, y carbono-14 ^{14}C son especialmente preferidos por su facilidad de preparación y eminente detectabilidad La incorporación de isótopos más pesados, p ej , deuterio, ^{2}H, en un compuesto de Fórmula (1 0 0) proporcionara ventajas terapéuticas basadas en la mayor estabilidad metabólica de dicho compuesto marcado isotópicamente Una mayor estabilidad metabólica se traduce directamente en una semivida *in vivo* aumentada o en requisitos de dosificación reducida, que en la mayor parte de las circunstancias constituiría una realización preferida del presente invento Un compuesto de Fórmula (1 0 0) marcado isotópicamente se puede preparar usualmente llevando a cabo los procedimientos descrito en los Esquemas de Síntesis y en la descripción relacionada los Ejemplos y las Preparaciones del mismo en que un reactivo marcado isotópicamente disponible con facilidad reemplaza a su correspondiente reactivo no marcado isotópicamente

El deuterio, ^{2}H se puede incorporar también en un compuesto de Fórmula (1 0 0) con la finalidad de manipular el metabolismo oxidativo de dicho compuesto por la vía del efecto del isótopo cinetico primario El efecto del isótopo cinético primario es un cambio de velocidad para una reacción química que resulta de la sustitución de nucleos isotópicos que a su vez es causada por el cambio en las energías de estado de base, que se requieren para la formación de enlaces covalentes subsiguientemente a su sustitución isotópica La sustitución por un isótopo más pesado dará como resultado usualmente una disminución de la energía del estado de base para un enlace químico, causando de esta manera una reducción en la velocidad para una operación de rotura de enlaces limitadora de la velocidad Si el suceso de rotura de enlaces se realiza en o cerca de la región del punto del mínimo junto con las coordenadas de una reacción de productos multiples, las relaciones de distribucion de productos pueden ser alteradas sustancialmente A manera de ilustracion, cuando el deuterio está unido a un átomo de carbono en un sitio no intercambiable, son típicas unas diferencias de velocidades de $k_H/k_D = 2\text{-}7$ Esta diferencia de velocidades, aplicada satisfactoriamente a un compuesto de Fórmula (1 0 0) inestable frente a la oxidación, puede afectar espectacularmente al perfil *in vivo* de dicho compuesto y dar como resultado mejoradas propiedades farmacocineticas

Para descubrir y desarrollar agentes terapeuticos, un profesional experto busca optimizar parámetros farmacocinéticos al mismo tiempo que retener deseables propiedades *in vitro* Una conjetura razonable es que muchos compuestos con malos perfiles farmacocinéticos sufren de una inestabilidad frente al metabolismo oxidativo Análisis *in vitro* de microsomas del hígado, ahora disponibles, proporcionan una valiosa informacion acerca del curso de este metabolismo oxidativo que a su vez permite el diseño racional de compuestos deuterados de Fórmula (1 0 0) con estabilidad mejorada

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a través de la resistencia frente a dicho metabolismo oxidativo Mejoras significativas en los perfiles farmacocineticos de compuestos de Fórmula (1 0 0) se obtienen de este modo, y se pueden expresar cuantitativamente en términos de aumentos en la semivida *in vivo* (t/2) en la concentración con un efecto terapéutico maximo (C_{max}), en el area bajo la curva de respuesta a la dosis (AUC) y en F, y en términos de disminuciones en el aclaramiento, la dosis y el coste de productos

A manera de ilustración de lo que antecede un compuesto de Fórmula (1 0 0) que tienen multiples sitios potenciales para un metabolismo oxidativo, p ej átomos de hidrógeno bencílicos y átomos de hidrógeno en α con relación a un átomo de nitrógeno se prepara como una sene de compuestos análogos en que diversas combinaciones de átomos de hidrógeno son reemplazadas por átomos de deuterio de manera tal que alguno la mayor parte de, o la totalidad de, dichos átomos de hidrógeno se reemplacen por átomos de deuterio Las determinaciones de la semivida proporcionan una determinación conveniente y segura de la extensión del mejoramiento en cuanto a la resistencia al metabolismo oxidativo De esta manera se determina que la semivida del compuesto progenitor puede ser prolongada en más de hasta 100% como el resultado de dicha sustitución de hidrógeno por deuterio

La sustitución de hidrogeno por deuterio en un compuesto de Fórmula (1 0 0) se puede usar también para conseguir una alteración favorable en el perfil de metabolitos del compuesto progenitor como una manera de disminuir o eliminar metabolitos tóxicos indeseados Por ejemplo cuando un metabolito tóxico surge a través de una escisión por oxidación de enlaces de carbono-hidrogeno C-H se espera razonablemente que el compuesto analogo deuterado disminuya en gran manera, o elimine, la produccion del metabolito indeseado incluso en el caso de que la oxidación particular no sea una operación determinante de la velocidad

Una información adicional concerniente al estado de la técnica con respecto a la sustitución de hidrógeno por deuterio se puede encontrar, p ej , en las citas de Hanzlik y colaboradores *J Org Chem* **55** 3992-3997 1990 Reider y colaboradores, *J Org Chem* **52** 3326-3334, 1987 Foster *Adv Drug Res* **14** 1-40, 1985, Gillete y colaboradores, *Biochemistry* **33**(10) 2927-2937, y Jarman y colaboradores, *Carcinogenesis* **16**(4) 683-688, 1993

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DESCRIPCIÓN DETALLADA DEL INVENTO

8 0 Aplicaciones terapéuticas y puntos finales clínicos

La descripción que sigue concierne a las aplicaciones terapéuticas a las que se pueden dedicar los compuestos de Fórmula (1 0 0), y cuando sea aplicable, una explicacion de los puntos finales vínicos asociados con dichas aplicaciones terapéuticas Se expone tambien una descripción de diversos analisis *in vitro* y de experimentos con modelos en animales que son capaces de proporcionar datos suficientes para definir y demostrar la utilidad terapéutica de los compuestos de Fórmula (1 0 0)

La utilidad terapéutica de los compuestos (1 0 0) es aplicable a un paciente o sujeto que esté afligido con una enfermedad o condición como aquí se expone y por lo tanto se encuentre en necesidad de dicho tratamiento Los beneficiosos resultados son terapéuticos independientemente de que se administren a animales o a seres humanos Como se utiliza en el presente texto, los términos "animal" y "animales" se usan meramente con la finalidad de señalar a los seres humanos distinguiéndolos de otros miembros del reino animal Los compuestos de Fórmula (1 0 0) tienen aplicabilidad terapéutica en el tratamiento de mamíferos y en particular de seres humanos Todas las subdivisiones principales de la clase de mamíferos (*Mammalia*) se incluyen dentro del alcance del presente invento en el sentido de que sean organismos recipientes de un tratamiento terapéutico como aquí se describe Los mamíferos tienen valor como animales domesticados para seres humanos y por lo tanto son susceptibles de ser sujetos del tratamiento Esto se aplica especialmente a los grupos caninos y felinos de mamíferos Otros mamíferos tienen valor como animales domesticados y su tratamiento de acuerdo con el siguiente invento es susceptible de realizarse a la vista del impacto económico desfavorable que tendría no tratar las enfermedades y condiciones que aquí se describen Esto se aplica especialmente a los grupos de animales equinos, bovinos, porcinos y ovinos

Los compuestos de Fórmula (1 0 0) inhiben a la isozima PDE4 y por lo tanto tienen una amplia gama de aplicaciones terapéuticas, como se describen adicionalmente a continuación, a causa del cometido esencial que la familia de isozimas PDE4 desempeña en la fisiología de todos los mamíferos El cometido enzimático realizado por las isozimas PDE4 es la hidrólisis intracelular del adenosina-3',5'-monofosfato (cAMP) dentro de leucocitos pro-inflamatorios El cAMP, a su vez es responsable de mediar en los efectos de numerosas hormonas en el cuerpo, y como consecuencia, la inhibición de las PDE4 desempeña un cometido importante en una diversidad de procesos fisiológicos Existe en el sector tecnológico una extensa bibliografía que describe los efectos de los agentes inhibidores de las PDE sobre diversas respuestas celulares inflamatorias, que

además de la elevacion del cAMP, incluyen una inhibición de la producción de superóxidos desgranulación, quimiotaxis y liberación del factor de necrosis de tumores (TNF) en eosinófilos, neutrófilos y monocitos

Una PDE4 fue identificada por primera vez en 1985, Nemoz y colaboradores, *Biochem Pharmacol* 34 2997-3000, 1985, y los agentes inhibidores de las PDE4, rolipram y denbufilina, se estudiaron tempranamente en pruebas clinicas en cuanto a indicaciones en el SNC (sistema nervioso central) tales como depresión Subsiguientemente, se demostró que una PDE4 es la fosfodiesterasa principal en leucocitos inflamatorios Los cuatro subtipos de las PDE4, es decir, PDE4A, PDE4B, PDE4C y PDE4D, están distribuidos ampliamente en tejidos humanos, tal como se determina por la presencia de sus ARNm (ácidos ribonucleicos mensajeros) La PDE4D es expresada en tejidos de riñón, timo, intestino delgado y colon, y es expresada en gran manera en tejidos de cerebro, pulmón, musculo del esqueleto, próstata y leucocitos de sangre periférica (PBL, de *peripheral blood leukocytes*) Es expresado sólo debilmente en tejidos de corazón, placenta, hígado, páncreas, bazo, testículo y ovario Las PDE4A y PDE4B son también expresadas en gran manera en tejidos de cerebro y musculo del esqueleto y es expresada solo débilmente en tejidos de placenta hígado y ovario La PDE4C es asimismo expresada en gran manera en un tejido de musculo del esqueleto y también es expresada débilmente en un tejido de ovario La PDE4C no es detectable usualmente en la mayoría de los tejidos antes mencionados

La familia de isozimas PDE4 es la forma predominante de fosfodiesterasa encontrada en tipos de células que se implican en enfermedades inflamatorias cronicas, y entre los tipos de células que se derivan de la medula ósea, solamente las plaquetas no expresan las PDE Una PDE4 es la principal enzima metabolizadora de cAMP en células inmunitarias e inflamatorias, y es una de las dos principales enzimas metabolizadoras de cAMP en un musculo liso de vía respiratoria Una PDE4 está presente exclusivamente en neutrófilos, eosinófilos, basófilos y monocitos mientras que en macrófagos se ha demostrado una actividad de las PDE3 y PDE1, y en linfocitos T se ha demostrado también una actividad de las PDE7 Los beneficiosos efectos antiinflamatorios de los agentes inhibidores de las PDE han sido demostrados hasta ahora usando experimentos *in vitro*, que han establecido que dichos compuestos inhiben la generación de superoxidos en monocitos, eosinófilos y neutrófilos humanos, la puesta en libertad de mediadores en basofilos, macrófagos y neutrófilos, y la liberación de TNFα en monocitos y macrófagos Los agentes inhibidores de las PDE inhiben también la puesta en libertad de mediadores en células inflamatorias tales como monocitos y macrófagos derivados de monocitos, células cebadas de pulmones, linfocitos T, linfocitos B, macrófagos alveolares y eosinófilos

Se han observado también *in vivo* hasta ahora efectos antiinflamatorios beneficiosos que incluyen la inhibición del derrame microvascular dentro de los pulmones de cobayas sensibilizados, y la reducción de la hiper-reactividad de los bronquios y de eosinofilia en monos cinomolgos después de una estimulación repetida con antígenos Se ha demostrado también hasta ahora que los agentes inhibidores de las PDE4 suprimen potentemente la liberación de TNFα a partir de fagocitos mononucleares

8,1 Asma

Una de las enfermedades respiratorias más importantes que se pueden tratar con una PDE4 especialmente agentes inhibidores de las PDE4D del tipo situado dentro del alcance de los compuestos de Fórmula (1 0 0), es el asma, que es un trastorno crónico, cada vez más corriente encontrado por todo el mundo y que está caracterizado por una obstrucción intermitente y reversible de las vías respiratorias, una hiper-capacidad de respuesta de las vías respiratorias e inflamación La causa del asma todavía ha de ser determinada pero la expresion patológica más corriente del asma es una inflamación de las vias respiratorias que puede ser importante incluso en las vías respiratorias de pacientes con asma suave Basándose en una biopsia de los bronquios y en estudios de lavado, se ha mostrado con claridad que el asma implica una infiltración por células cebadas, eosinófilos y linfocitos T dentro de las vías respiratorias de un paciente Un lavado bronquioalveolar (BAL de *bronchoalveolar lavage*) en enfermos de asma atópica muestra una activación de interleucina (IL)-3, IL-4, IL-5 y del factor estimulador de colonias de granulocitos/macrófagos (GM-CSF), que sugiere la presencia de una población de células T similares a células T-cooperantes 2 (Th-2, de *T-helper 2*)

Los compuestos de Fórmula (1 0 0) inhiben una PDE4 en eosinofilos humanos y por lo tanto son utiles en el tratamiento del asma atópica y del asma no atópica El término "atopía" se refiere a una predisposición genética hacia el desarrollo de reacciones de hipersensibilidad del tipo I (inmediato) frente a antígenos ambientales corrientes La manifestación clínica más corriente es la rinitis alérgica, mientras que el asma bronquial, la dermatitis atópica y la alergia a los alimentos se presentan con menos frecuencia Correspondientemente, la expresión "asma atópica", como se utiliza en el presente texto, se pretende que sea sinónima con la de "asma alérgica", es decir un asma bronquial que es una manifestación alérgica en una persona sensibilizada Se pretende que el término "asma no atópica", como se usa en el presente contexto, se refiera a todos los otros asmas, especialmente el asma esencial o "verdadera", que es provocada por una diversidad de factores inclusive ejercicios vigorosos, partículas irritantes, estreses o tensiones psicológicas etc

El uso de los compuestos de Formula (1 0 0) para tratar un asma atópica o un asma no atópica se ha consagrado y demostrado por los modelos de inhibición de las PDE, de inhibición de la activación de eosinófilos y de la infiltración de células que seguidamente se describen

Inflamación Pulmonar en Monos Cinomolgos Alérgicos - - La capacidad de las combinaciones de agentes terapéuticos del presente invento para inducir los aumentos en el contenido de células inflamatorias inducidos por antígenos de *Ascans* de un fluido de lavado alveolar de los bronquios procedente de individuos monos cinomolgos, se evalua en este método Usando un diseño cruzado, 8-10 monos cinomolgos sensibles a Ascaris se tratan con un vehículo o fármaco En un momento apropiado del tratamiento previo cada mono es anestesiado (con ketamina 10 mg/kg + xilazina 1 mg/kg, i m (por via intramuscular) y es intubado con un tubo endotraqueal ensanchado en el extremo Se realiza un lavado bronquioalveolar (BAL) usando un lavado con 15 ml de una solucion salina tamponada con fosfato (PBS de *phosphate buffered saline*) suministrada a través de un broncoscópio pediátrico de fibra optica introducido a través del tubo endotraqueal y acuñado dentro de un bronquio de tercera a quinta generación El fluido de lavado es aspirado suavemente y recogido en una jeringa Después de que se haya completado el BAL, cada animal recibe una exposición durante 2 min a una concentración de aerosol de Ascaris suum, que duplica la resistencia del sistema respiratorio que se ha determinado en experimentos anteriores Cada mono es devuelto a su jaula y 24 h más tarde se realiza un segundo lavado, usando 15 ml de PBS, en el lado opuesto del pulmón Una semana despues de la primera prueba, los monos testigos y los monos tratados se invierten y se repite el experimento Para determinar la composición porcentual de cada tipo de leucocitos dos portaobjetos procedentes de cada muestra de BAL de mono se obtienen centrifugando 2 x 150 µl de un fluido de lavado durante 2 min a 500 rpm en una centrifuga Cytospin Los portaobjetos se tiñen en Diff-Quick para el recuento diferencial de celulas y las células se identifican por criterios morfológicos clásicos Los numeros totales de leucocitos por mililitro de fluido de BAL se determinan diluyendo 20 µl de una muestra en 20 ml de una solución isotónica, añadiendo 3 gotas de Zapoglobin para lisar los entrocitos y leer (interpretar) la muestra usando un Contador Coulter Se hacen comparaciones entre la relación de aumento en los niveles de eosinófilos, citocinas o mediadores de lavado alveolar de los bronquios, de una estimulación previa con antígenos frente a una estimulación posterior con antígenos después de 24 horas con y sin tratamiento con un fármaco

En el anterior modelo de ensayo, las combinaciones de agentes terapéuticos del presente invento exhiben una actividad anti-inflamatoria en unas dosificaciones situadas en el intervalo de desde 0,001 a 0,1 mg/kg i v (via intravenosa) o de 0,01 a 10,0 mg/kg

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p o (vía oral) o de 0,001 a 0,1 mg/kg i t (vía intratubular)

Otro análisis util, basado en el uso de primates, es el que se describe en la cita de Turner y colaboradores "Characterization of a primate model of asthma using anti-allergy/anti-asthma agents" (Caracterización de un modelo de asma en primates usando agentes anti-alergicos/anti-asmáticos), *Inflammation Research* 45 239-245 1996

Actividad Antiinflamatoria - La actividad antiinflamatoria de las combinaciones de agentes terapéuticos del presente invento es demostrada por la inhibición de la activación de eosinófilos tal como se mide mediante la producción de LTE4 estimulada por glóbulos de Sephadex en una sangre humana entera Análisis de Sangre Entera en cuanto a LTE4 usando Glóbulos de Sephadex como Estimulantes En el dia anterior al análisis se siliconizan los tubos de vidno con Sigmacote (Sigma, N° de Catálogo SL-2) Antes de extraer la sangre, los compuestos se diluyen a 1 000x (1 000 veces) en DMSO y se añade 1 µl de DMSO o de un compuesto a cada tubo respectivo y se coloca el bastidor de tubos en un baño de agua a 37°C Se hace que la sangre sea impulsada en un tubo Vacutainer N° 6480 (143 unidades USP de heparina de sodio, 10 ml), 10 tubos = 100 ml de sangre Se agrupan los tubos con sangre en dos tubos cónicos de 50 ml Se añade 1 ml de sangre entera a cada tubo siliconizado que contiene DMSO o se trata en vórtice el compuesto y luego se incuba a 37°C durante 15 minutos Para preparar la suspensión de glóbulos de Sephadex G-15 (Pharmacia, N° de Catálogo 17-0020-01) se añaden 3 3 g de Sephadex G-15, se mezcla con 20 ml de PBS en un vaso de boca ancha de 100 ml de capacidad y luego se mezcla con una barra de agitación magnética Despues de 15 minutos, se añaden 100 µl de glóbulos de Sephadex G-15 a cada tubo, excepto los tubos de Sephadex que proporcionarán el valor de linea de base para la liberación de las LTE4 Se somete a vórtice y se incuba durante 90 minutos a 37°C Al final de la incubación durante 90 minutos se añaden 20 µl de EDTA al 15% se trata en vórtice y se centrifuga durante 5 minutos a 1 000 rpm Luego se retira y guarda la muestra de plasma para su análisis Los niveles de las LTE4 se determinan por el estuche Cayman's Cysteinyl-LT ELISA (N° de Catálogo 520501) La inhibición porcentual se calcula como 100 x 1 - (concentración de las LTE4 en la muestra tratada con fármaco, dividida por la concentración de las LTE4 en las muestras testigos no tratadas con fármaco)

Los compuestos de Fórmula (1 0 0) son activos en el anterior método de ensayo en unas concentraciones situadas en el intervalo de desde 0,0001 µM a 20,0 µM, en que realizaciones prefendas son activas en concentraciones situadas en el intervalo entre 0,5 nM y 1 000 nM

A partir de lo que antecede, puede observarse que los compuestos de Formula (1 0 0) son utiles para el tratamiento de enfermedades inflamatorias u obstructivas de las vias respiratorias o de otras condiciones que implican una obstrucción de las vías

respiratorias En particular, éstos son utiles para el tratamiento del asma bronquial

A la vista de su actividad antiinflamatoria, su influencia sobre la hiper-reactividad de las vías respiratorias y su perfil en relación con la inhibición de las isoenzimas de las PDE, en particular como agentes inhibidores selectivos de las PDE4, los compuestos de Fórmula (1 0 0) son utiles para el tratamiento, en particular para el tratamiento profiláctico, de enfermedades obstructivas o inflamatorias de las vias respiratorias Por lo tanto por administración continuada y regular durante períodos de tiempo prolongados los compuestos de Fórmula (1 0 0) son utiles para proporcionar una protección de antemano contra la reaparición de la constricción de los bronquios u otro ataque sintomatico como consecuencia de enfermedades obstructivas o inflamatorias de las vias respiratorias Los compuestos de Fórmula (1 0 0) son también utiles para el control, la mejora o la inversión del estado basal de dichas enfermedades

Tomando en consideración su actividad dilatadora de los bronquios los compuestos de Fórmula (1 0 0) son utiles como agentes dilatadores de los bronquios, p ej , en el tratamiento de una constriccion cronica o aguda de los bronquios, y para el tratamiento sintomático de enfermedades obstructivas o inflamatorias de las vías respiratorias

Las palabras "tratamiento" y "tratar", como se utilizan por toda la presente memoria descriptiva y en las reivindicaciones en relación con las enfermedades obstructivas o inflamatorias de las vías respiratorias, han de ser entendidas, correspondientemente, como que abarcan modos de terapia tanto profilácticos como sintomáticos

A la vista de la descripción anterior, puede observarse que el presente invento se refiere también a un metodo para el tratamiento de una hiper-reactividad de las vías respiratorias en mamíferos a un método para efectuar la dilatación de los bronquios en mamíferos, y en particular, a un método para tratar enfermedades obstructivas o inflamatorias de las vias respiratorias, especialmente asma en un individuo mamífero que necesite de ello cuyo método comprende administrar a dicho individuo mamífero una cantidad eficaz de un compuesto de Fórmula (1 0 0)

Las enfermedades obstructivas o inflamatorias de las vías respiratorias a las que se aplica el presente invento incluyen asma, neumoconiosis, neumonía eosinofílica crónica, enfermedad obstructiva crónica de las vías respiratorias o pulmonar (COAD ó COPD), y síndrome de ahogo respiratorio de adultos (ARDS) así como exacerbación de la hiper-reactividad de las vías respiratorias como consecuencia de otra terapia con fármacos, p ej , de una terapia con aspirina o un agente β-agonista

Los compuestos de Fórmula (1 0 0) son utiles en el tratamiento de un asma de cualquier tipo, etiología o patogénesis, inclusive un asma intrínseca atribuida a perturbaciones patofisiologicas, un asma extrínseca causada por algun factor en el medio

ambiente, y un asma esencial de causa desconocida o no aparente Los compuestos de Fórmula (1 0 0) son utiles en el tratamiento de un asma alérgica (atópica/bronquial/ mediada por IgE), y son utiles también en el tratamiento de un asma no atópica, inclusive, p ej , un asma bronquitica enfisematosa inducida por ejercicio y ocupacional, un asma infecciosa que es una secuela de una infeccion causada por microbios especialmente bacterias hongos protozoos o virus y otras asmas no alergicas p ej , un asma incipiente (síndrome de niño que resuella con dificultad)

Los compuestos de Fórmula (1 0 0) son adicionalmente utiles en el tratamiento de una neumoconiosis de cualquier tipo, etiología o patogénesis, inclusive, p ej , aluminosis (enfermedad de obreros causada por bauxita), antracosis (asma de mineros), asbestosis (asma de instaladores de vapor de agua) calicosis (enfermedad del pedernal) ptilosis causada por inhalación del polvo fino procedente de plumas de avestruz, siderosis causada por la inhalacion de particulas de hierro, silicosis (enfermedad de amoladores), bisinosis (asma causada por polvo fino de algodón) y neumoconiosis con talco

8 2 Enfermedad Pulmonar Obstructiva Crónica (COPD)

Los compuestos de Fórmula (1 0 0) son todavía adicionalmente utiles en el tratamiento de una COPD ó COAD inclusive bronquitis crónica enfisema pulmonar o disnea asociada con éste Una COPD es caracterizada por una obstrucción progresiva e irreversible de las vías respiratorias Una bronquitis crónica es asociada con hiperplasia e hipertrofia de las glandulas secretoras de mucosidad de la submucosa en las vías respiratorias cartilaginosas grandes Una hiperplasia de células de Goblet, una infiltración de células inflamatorias mucosales y submucosales, edema, fibrosis, tapones con mucosidad y musculos lisos aumentados se encuentran todos/as ellos/as en los bronquiolos terminales y respiratorios Las vias respiratorias pequeñas son conocidas por ser un sitio principal de obstrucción de las vias respiratorias El enfisema está caracterizado por una destrucción de la pared alveolar y pérdida de elasticidad de los pulmones Se han identificado también cierto numero de factores de riesgo como vinculados con la presentación de una COPD La vinculación entre la accion de fumar tabaco y una COPD está bien demostrada Otros factores de riesgo incluyen una exposición al polvo fino de carbón y diversos factores genéticos Véase la cita de Sandford y colaboradores, "Genetic risk factors for chronic obstructive pulmonary disease" (Factores de riesgo genéticos para una enfermedad pulmonar obstructiva crónica), *Eur Respir J* 10 1380-1391, 1997 La presentación de una COPD es creciente y representa una importante carga económica sobre las poblaciones de las naciones industrializadas Una COPD se presenta también por sí misma en el sector clínico con

una amplia gama de variación desde una bronquitis crónica simple sin incapacidad de los pacientes hasta un estado gravemente incapacitado con fallo respiratorio crónico

Una COPD es caracterizada por una inflamación de las vías respiratorias, tal como se da el caso con el asma, pero las celulas inflamatorias que se han encontrado en el fluido de lavado bronquioalveolar y en el esputo de pacientes, son neutrófilos en lugar de eosinófilos Niveles elevados de mediadores inflamatorios son encontrados también en pacientes con COPD inclusive IL-8, LTB_4 y TNF-α, y se ha encontrado que el epitelio superficial así como el sub-epitelio de los bronquios de dichos pacientes están infiltrados por linfocitos T y macrófagos Un alivio sintomático para pacientes de COPD se puede proporcionar mediante el uso de un agente β-agonista y dilatadores de los bronquios anticolinérgicos, pero el progreso de la enfermedad permanece inalterado Una COPD ha sido tratada usando teofilina, pero sin demasiado éxito, incluso aunque reduzca los cómputos de neutrófilos en el esputo de pacientes con COPD También los esteroides han sido capaces de mantener muchas de sus promesas como agentes de tratamiento satisfactorios en una COPD

Correspondiente el uso de los compuestos de Fórmula (1 0 0) para tratar una COPD y sus enfermedades de vias respiratorias obstructivas relacionadas e incluidas, representa un avance importante en el sector tecnológico El presente invento no está limitado a ningun modo particular de acción ni a ninguna hipótesis en cuanto a la manera en la que se hayan conseguido los deseados objetivos terapéuticos por utilización de los compuestos de Fórmula (1 0 0) Sin embargo se reconoce en el sector tecnológico que una PDE4 es la PDE predominante en neutrofilos y macrófagos, Cheng y colaboradores, "Synthesis and *in vitro* profile of a novel series of catechol benzimidazoles The discovery of potent, selective phosphodiesterase Type IV inhibitors with greatly attenuated for the [3H]rolipram binding site" [Sintesis y perfil *in vitro* de una nueva sene de catecol-bencimidazoles El descubrimiento de potentes y selectivos agentes inhibidores de las fosfodiesterasas del Tipo IV con una afinidad grandemente atenuada para el sitio de fijación del [3H]rolipram], *Bioorg med Chem Lett* **5** 1969-1972, 1995, Wright y colaboradores, "Differential inhibition of human neutrophil functions role of cyclic AMP-specific, cyclic GMP-insensitive phosphodiesterase" [inhibición diferencial de funciones de neutrófilos humanos cometido de una fosfodiesterasa específico para AMP cíclico e insensible a GMP ciclico], *Biochem Pharmacol* **40** 699-707, 1990, Schudt y colaboradores "Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Cai" [Influencia de agentes inhibidores selectivos de fosfodiesterasas sobre las funciones de neutrófilos humanos y los niveles de cAMP y Cai], *Naunyn Schmiedebergs Arch Pharmacol* **344** 682-690 1991, y Tenor y colaboradores "Cyclic nucleotide phosphodiesterase isoenzyme activities in human alveolar macrophages"

[Actividades de isoenzimas fosfodiesterasas de nucleótidos cíclicos en macrofagos alveolares humanos] *Clin Exp Allergy* **25** 625-633, 1995

Con el fin de proporcionar una mejor comprensión del presente invento, se hace aquí la inferencia de que los compuestos de Fórmula (1 0 0) inhiben a las PDE4's en neutrófilos dando como resultado quimiotaxis, activación, adherencia y desgranulacion reducidas, Schudt y colaboradores, ibid, Nelson y colaboradores, "Effect of selective phosphodiesterase inhibitors on the polymorphonuclear leukocyte respiratory burst" [Efecto de agentes inhibidores selectivos de fosfodiesteresas sobre la bocanada respiratoria de leucocitos polimorfonucleares], *J Allergy Clin Immunol* **86** 801-808, 1990, y Bloeman y colaboradores, "Increased cAMP levels in stimulated neutrophils inhibit their adhesion to human bronchial epithelial cells" [Niveles aumentados de cAMP en neutrófilos estimulados inhiben su adhesión a células epiteliales bronquiales humanas], *Am J Physiol* **272** L580-587, 1997

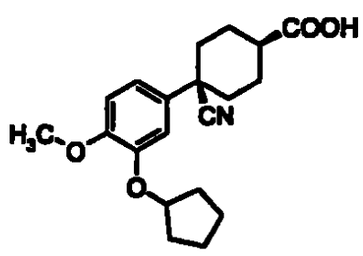
También se infiere que los compuestos de Fórmula (1 0 0) reducen la producción de aniones de superoxidos mediada por las PDE4's en neutrófilos de sangre periférica, y que éstos regulan la síntesis de leucotrienos que es mediada por las PDE4's, Wright y colaboradores, *ibid*· Schudt y colaboradores, *ibid*; Bloeman y colaboradores, *ibid*· Al Essa y colaboradores, "Heterogeneity of circulating and exudated polymorphonuclear leuokytes in superoxide-generating response to cyclic AMP and cyclic AMP-elevating agents, investigation of the underlying mechanism" [Heterogeneidad de leucocitos polimorfonucleares circulantes y exudados en una respuesta generadora de superóxidos al AMP cíclico y a agentes que elevan el AMP cíclico investigación sobre el mecanismo subyacente] *Biochem Pharmacol* **49** 315-322, 1995, Ottonello y colaboradores, "Cyclic AMP-elevating agents down-regulate the oxidative burst induced by granulocyte-macrophage colony stimulating factor (GM-CSF) in adherent neutrophils" [Los agentes elevadores del AMP cíclico regulan en sentido descendente la bocanada oxidativa inducida por el factor estimulante de colonias de granulocitos-macrófagos (GM-CSF) en neutrófilos adherentes], *Clin Exp Immunol* **101** 502-506, 1995 y Otonello y colaboradores, "Tumor necrosis factor alpha-induced oxidative burst in neutrophils adherent to fibronectin effects of cyclic AMP-elevating agents" [La bocanada oxidativa inducida por el factor de necrosis tumoral alfa en neutrófilos adherentes a fibronectina efectos de agentes elevadores del AMP cíclico], *Br J Haematol* **91** 566-570, 1995

Se infiere además que los compuestos de Fórmula (1 0 0) inhiben la expresión de CD11b/CD18, Berends y colaboradores, "Inhibition of PAF-induced expression of CD11b and shedding of L-selectin on human neutrophils and eosinophils by the type-IV selective PDE inhibitor rolipram" [La inhibicion de la expresión inducida por el PAF de la CD11b y desprendimiento de L-selectina en neutrófilos y eosinófilos humanos por el

agente inhibidor de las PDE selectivo del tipo IV rolipram], *Eur Respir J* 10 1000-1007, 1997, y Denan y colaboradores, "Inhibition of chemotactic peptide-induced neutrophil adhesion to vascular endothelium by cAMP modulators" [Inhibición de la adhesión quimiotáctica de neutrofilos, inducida por péptidos, al endotelio vascular por moduladores del cAMP], *J Immunol* **154** 308-317, 1995

Se infiere todavía adicionalmente que los compuestos de Fórmula (1 0 0) inhiben a las PDE4's de macrófagos alveolares, reduciendo con ello la liberación de factores quimiotácticos y del TNF-α, y que los compuestos de Fórmula (1 0 0) aumentan la síntesis y facilitan la liberación a partir de monocitos de la citocina IL-10 anti-inflamatoria, que a su vez es capaz de disminuir la generación de TNF-α y IL-β, y de GM-CSF por células mononucleares de fluido sinovial, aumentando con ello el perfil global antiinflamatorio de los agentes inhibidores de las PDE4 de Fórmula (1 0 0), Schudt y colaboradores "PDE isoenzymes as targets for anti-asthma drugs" [Isoenzimas PDE como dianas para fármacos contra el asma] *Eur Respir J* 8 1179-1183 1995 y Kambayashi y colaboradores, "Cyclic nucleotide phosphodiesterase Type IV participates in the regulation of IL-10 and the subsequent inhibition of TNF-alpha and IL-6 release by endotoxinstimulated macrophages" [Una fosfodiesterasa de nucleótido cíclico del tipo IV participa en la regulación de IL-10 y en la inhibición subsiguiente de la liberación de TNF-alfa y de IL-6 por macrófagos estimulados mediante endotoxinas], *J Immunol* **155** 4909-4916, 1995

La aplicación de agentes inhibidores de las PDE4 en el tratamiento de una COPD en pacientes humanos ha sido demostrada en pruebas clínicas Se ha mostrado que el tratamiento con el SB-207,499, representado por la Fórmula (0 1 9) anterior, en una dosis de 15 mg a razón de dos veces por día durante seis semanas, da como resultado aumentos en el FEV y en la capacidad vital forzada (FVC, de *forced vital capacity*), Brown, W M , "SB-207499", *Anti-inflamm Immunomodulatory Invest Drugs* 1 39-47, 1999 La eficacia clínica del SB-207,499 ha sido también demostrada en una prueba durante cuatro semanas que ha proporcionado evidencia de un FEV_1 mejorado y en un estudio durante seis semanas en pacientes con COPD que recibían 15 mg dos veces al día, que tambien ha proporcionado evidencia de un FEV_1 mejorado, Brown, *Ibid*, El SB-207,499 ya ha sido descrito anteriormente y es representado por la Fórmula (0 1 9)



SB-207,499 (0 1 9)

8.3 Bronquitis y bronquiectasia

De acuerdo con las actividades inhibidoras particulares y diversas antes descritas, que son poseidas por los compuestos de Fórmula (1 0 0) éstos son utiles en el tratamiento de una bronquitis de cualquier tipo, etiologia o patogénesis inclusive, p ej una bronquitis aguda que tiene un curso corto pero grave y es causada por una exposición al frío, una respiracion de sustancias irritantes, o una infección aguda, una bronquitis laringotraqueal aguda que es una forma de garrotillo no diftérico una bronquitis araquídica que es causada por la presencia de una pepita de cacahuete en un bronquio una bronquitis catarral que es una forma de bronquitis aguda con una descarga mucopurulenta profusa, una bronquitis crónica que es una forma de bronquitis continuada durante largo tiempo con una tendencia más o menos señalada a la reaparición después de fases de quietud, debidas a ataques repetidos de bronquitis aguda o enfermedades generales crónicas, caracterizadas por ataques de tos, por expectoración ya sea escasa o profusa, y por cambios secundarios en el tejido pulmonar, bronquitis crupal o de garrotillo, que está caracterizada por una tos violenta y paroxismos de disnea, una bronquitis seca que está caracterizada por una secreción escasa de esputos tenaces, una bronquitis asmática infecciosa que es un sindrome marcado por el desarrollo de síntomas de un broncoespasmo siguiendo a infecciones del tracto respiratorio en personas con asma, bronquitis productiva que es una bronquitis asociada con una tos productiva bronquitis por estafilococos o estreptococos que son causadas por estafilococos o estreptococos y bronquitis vesicular en que la inflamación se extiende dentro de los alveolos que algunas veces son visibles por debajo de la pleura en forma de granulaciones de color amarillo-blancuzco similares a semillas de mijo

La bronquiectasia es una dilatación crónica de los bronquios, marcada por una respiración fétida y una tos paroxismal con la expectoración de materia mucopurulenta Ésta puede afectar uniformemente a los tubos, en cuyo caso es citada como bronquiectasia cilíndrica, o puede presentarse en bolsas irregulares, en cuyo caso es denominada bronquiectasia saculada Cuando los tubos bronquiales dilatados tienen

ensanchamientos bulbosos terminales se usa el término de bronquiectasia fusiforme En aquellos casos en los que la condición de dilatación se extiende a los bronquiolos, ésta es citada como bronquiectasia capilar Si la dilatación de los bronquios es de forma esférica, la condición es citada como bronquiectasia cística La bronquiectasia seca se presenta cuando la infección implicada es episodica y puede estar acompañada por hemoptisis, la expectoracion de sangre o de un esputo teñido con sangre Durante periodos quietos de la bronquiectasia seca la tos que se presenta no es productiva Una bronquiectasia folicular es un tipo de bronquiectasia en la que el tejido linfoide en las regiones afectadas resulta grandemente ensanchado y por proyección dentro del lumen bronquial, puede deformar gravemente y obstruir parcialmente al bronquio Correspondientemente los compuestos de Fórmula (1 0 0) son utiles en el tratamiento beneficioso de los diversos tipos antes descritos de bronquiectasia como un resultado directo de su inhibicion de las isozimas PDE4

La utilidad de los compuestos de Fórmula (1 0 0) como agentes dilatadores de los bronquios o espasmoliticos de los bronquios para tratar un asma bronquial, una bronquitis crónica y enfermedades y trastornos relacionados que aqui se describen, es demostrable mediante el uso de cierto numero de diferentes modelos con animales *in vivo* conocidos en la tecnologia inclusive los que se describen en los párrafos siguientes

Actividad Espasmolitica Bronquial *In Vitro* - La capacidad de los compuestos de Fórmula (1 0 0) para causar una relajación de un musculo liso de la tráquea de un cobaya es demostrada en el siguiente procedimiento de ensayo Se sacrifican cobayas (de 350-500 g) con pentotal sódico (100 mg/kg i p), La tráquea se extirpa y se corta una sección de 2-3 cm de longitud La traquea se corta transversalmente (transeca) en el plano transversal en placas de cartilagos alternados de manera tal que se proporcionan anillos de tejido con una profundidad de 3-5 mm Se desechan los anillos próximo y distante Los anillos individuales se montan verticalmente sobre soportes hechos de acero inoxidable, uno de los cuales es fijado en la base de un baño de órganos, mientras que el otro es fijado a un transductor isométrico Los anillos se bañan en una solución de Krebs (composicion en µM $NaHCO_3$ 25, NaCl 113, KCl 4,7, $MgSO_3$ $7H_2O$ 1,2 KH_2PO_4 1,2, $CaCl_2$ 2,5, glucosa 11 7) a 37°C y se gasean con O_2/CO_2 (95 5, v/v) Los anillos preparados de esta manera, previamente cargados con 1 g, generan un tono espontáneo y, después de un periodo de tiempo de equilibración (45-60 min), se relajan de un modo consistente y coherente al añadir fármacos espasmoliticos Para averiguar la actividad espasmolítica, compuestos de ensayo de la Fórmula (1 0 0) se disuelven en una solución salina fisiológica y se añaden en cantidades crecientes al baño de órganos a intervalos de 5 min para proporcionar una curva acumulativa de concentracion-efecto

En el anterior modelo de ensayo, los compuestos de Fórmula (1 0 0) producen

una relajación de las preparaciones de anillos traqueales de cobaya, relacionada con la concentración en concentraciones en el intervalo de 0 001 a 1 0 µM

La actividad anti-inflamatoria de las combinaciones de agentes terapeuticos del presente invento es demostrada por la inhibicion de la producción de TNFα en sangre entera humana estimulada con un lipopolisacárido (LPS) Los compuestos se analizan en la presencia de un agente beta agonista (10 ng/ml) y de indometacina (1 µM) Se preparan 250 ml de un tampón de análisis con HEPES 200 mM en RPMI 1640 filtrado Lo que sigue se realiza a la temperatura ambiente en el banco de laboratorio Se prepara un coctel "IP" en un tubo de polipropileno de 50 ml de capacidad, añadiendo 0,4 ml de indometacina (carga original 4 mM) y 0 4 ml del agente beta agonista (carga original 0,04 mg/ml) para un f v (volumen final) de 40 ml con el tampón para análisis Se preparan los compuestos a partir de desde cargas originales de polvo en el seno de DMSO hasta soluciones originales de 200 ó 60 mM Se preparan diluciones en serie semi-logaritmicas de ocho puntos en ampollas o microtubos de vidrio Se añaden 0,01 ml de cada dilución de compuesto a los tubos de polipropileno de 5 ml de capacidad cuando se añaden 0,490 ml del tampón para análisis y 0,50 ml del coctel "IP" se añaden para un f v de 1,0 ml (la f c (concentración final) de análisis del compuesto es de 100-0,1 µM) Se prepara una solución de LPS de la siguiente manera se añaden 0,08 ml de LPS (carga original 1 mg/ml) a 40 ml de un tampón para análisis para una f c de 2 µg/ml 6 Se prepara una solución al 2% en DMSO añadiendo 200 µl de DMSO a 9,8 ml del tampón para análisis Se añaden 10 ml de un coctel IP a la solución al 2% en DMSO Este coctel se usa para pocillos con testigos tales que la f c del análisis de indometacina sea de 1 µM y la f c del beta agonista sea de 10 mg/ml Lo que sigue se realiza bajo la campana de cultivo de tejido Se añaden 0,0125 ml del compuesto diluido al pocillo apropiado en una placa estéril de 96 pocillos con fondo en U Costar Nº 3790 Se añaden 0,0125 ml de LPS a todos los pocillos (f c de 0,1 µg/ml) excepto los pocillos con testigos negativos Se extrae sangre entera humana recientemente recogida (~ 22 ml por placa de 96 pocillos), usualmente 4 "cabezas verdes" (*green tops*) dentro de tubos estériles con heparina mantenidos a 37ºC Se añaden 0,225 ml de sangre entera a las placas Se tapa, se incuba a 37ºC y se voltea durante cuatro horas Se centrifugan las placas a 2 000 rpm durante 10 minutos Se preparan patrones con ELISA Se retiran 100 µl de suero dentro de una placa de fondo plano Se diluye a 1 20 retirando 15 µl y añadiendo 285 µl del diluyente RD6 Se congela a -20ºC Para el análisis, se descongela y se añaden 200 µl a un ELISA para TNFα de R & D Systems Se tratan las placas de acuerdo con el protocolo de R & D Systems Se lee e interpreta la placa a 450 nm usando SoftMax Pro Se analiza e interpreta con un adaptador Java Fitter a fin de determinar los valores de la IC50 Se representa gráficamente una curva de respuesta a dosis de los datos

expresados como porcentaje del testigo Se generan para cada compuesto seis puntos en triplicado como mínimo Los valores de IC50 se calculan usando el programa de adaptación de curvas Java Fitter bajo el parámetro "IC50 fija de ambos = *IC50 fix both*"

En el modelo de ensayo anterior, las combinaciones de agentes terapéuticos del presente invento producen una inhibición de la producción de TNFα relacionada con la concentración en concentraciones en el intervalo de 0,001 a 1,0 µM

8 4 Rinitis Alérgica y de Otros Tipos, Sinusitis

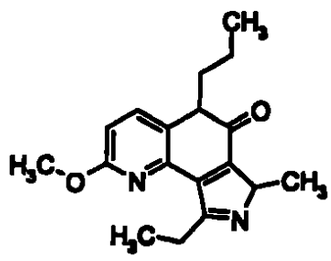
La rinitis alérgica está caracterizada por obstrucción nasal, picazón, rinorrea aguada, estornudo y anosmia ocasional La rinitis alérgica es dividida en dos categorías de enfermedad la estacional y la perenne, en que la primera es atribuida a polen y esporas de mohos de una zona exteriores, mientras que la última es atribuida a alergenos comunes tales como ácaros de polvo doméstico, caspas de animales y esporas de mohos La rinitis alérgica exhibe en términos generales una respuesta en fase temprana y una respuesta en fase tardía La respuesta en fase temprana está asociada con una desgranulación de células cebadas, mientras que la respuesta en fase tardía está caracterizada por una infiltración de eosinófilos basófilos, monocitos y linfocitos T Se liberan por estas células también una diversidad de mediadores inflamatorios, todos los cuales pueden contribuir a la inflamación exhibida en la respuesta en fase tardía

Una forma particularmente prevalente de rinitis alérgica estacional es la fiebre del heno, que está marcada por una conjuntivitis aguda con lacrimación y comezón, hinchamiento de la mucosa nasal, catarro nasal, ataques repentinos de estornudos, y frecuentemente con síntomas asmáticos Los compuestos de Fórmula (1 0 0) son especialmente útiles en el tratamiento beneficioso de la fiebre del heno

Otros tipos de rinitis para los que se pueden usar los compuestos de Fórmula (1 0 0) como agentes terapéuticos incluyen la rinitis catarral que es un enfriamiento en la cabeza que implica congestión aguda de la membrana mucosa de la nariz, marcada por sequedad y seguida por secreción mucosa incrementada a partir de la membrana, una respiración obstaculizada a través de la nariz y algo de dolor, la rinitis atrófica que es una forma crónica marcada por agotamiento de la membrana mucosa y de las glándulas, la rinitis purulenta que es una rinitis crónica con la formación de pus, y la rinitis vasomotora que es una rinitis no alérgica en la que se efectuan cambios transitorios en el tono y en la permeabilidad vascular con los mismos síntomas que la rinitis alérgica por estímulos tales como enfriamiento suave, fatiga, cólera y ansiedad

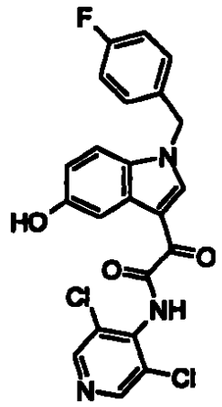
Existe una vinculación reconocida entre la rinitis alérgica y el asma La rinitis alérgica es un acompañamiento frecuente del asma y se ha demostrado que el

tratamiento de la rinitis alérgica mejorará el asma Se han usado también datos epidemiológicos para mostrar una vinculación entre una rinitis grave y un asma más grave Por ejemplo, se ha demostrado que el compuesto D-22888 en fase de desarrollo preclínico para el tratamiento de la rinitis alérgica, exhibe un fuerte efecto anti-alérgico y que inhibe la rinorrea en un cerdo estimulado por antígenos Véase la cita de Marx y 30 colaboradores "D-22888 - a new PDE4 inhibitor for the treatment of allergic rhinitis and other allergic disorders", [D-22888 - un nuevo agente inhibidor de las PDE4 para el tratamiento de la rinitis alérgica y otros trastornos alérgicos], *J Allergy Clin Immunol* 99 S444 1997 Se ha demostrado que otro compuesto experimental, AWD-12 281, es activo en un modelo de rinitis alérgica en ratas Véase la cita de Poppe y colaboradores "Effect of AWD 12-281 a new selective PDE-4 inhibitor, loteprednol and beclomethasone in models of allergic rhinitis and airway inflammation in brown norway-rats" [Efecto del AWD 12-281, que es un nuevo agente inhibidor selectivo de las PDE4, loteprednol y beclometasona en modelos de rinitis alérgica e inflamación de las vías respiratorias en ratas noruegas pardas], *Am J Respir Crit Care Med* A95, 1999 Los compuestos D-22888 y AWD-12,281 ya han sido descritos más arriba y representados por las Fórmulas (0 0 28) y (0 0 34), respectivamente



D-22888

(0 0.28)



Loteprednol (AWD - 12,281)

(0 0 34)

La sinusitis está relacionada con la rinitis en términos de proximidad anatómica así como una etiología y una patogenesis compartidas en algunos casos La sinusitis es la inflamación de un seno y esta condición puede ser purulenta o no purulenta así como aguda o crónica Dependiendo del seno en donde esté situada la inflamacion la condición es conocida como sinusitis del hueso etmoides frontal, maxilar o esfenoides El seno etmoidal es un tipo de seno paranasal, situado en el hueso etmoides El seno

frontal es uno de los senos paranasales emparejados situados en el hueso frontal El seno maxilar es uno de los senos paranasales emparejados situados en el cuerpo de la maxila Correspondientemente, los compuestos de Fórmula (1 0 0) son utiles en el tratamiento beneficioso de una sinusitis aguda o crónica, pero especialmente de una sinusitis crónica

8 5 Artritis Reumatoide, Osteoartritis, Dolor, Fiebre y Gota

La artritis es definida como una inflamación de las articulaciones, y la artritis reumatoide es una enfermedad sistémica crónica principalmente de las articulaciones, usualmente poliarticular, marcada por cambios inflamatorios en las membranas sinoviales y estructuras articulares, y por atrofia muscular y rarefacción de los huesos Las etapas tardías de la artritis reumatoide están marcadas por anquilosamiento y deformidad La artritis reumatoide es una enfermedad autoinmunitaria tullidora de etiología desconocida, que afecta a mas de 1% de la población

Como se utiliza en el presente texto se pretende que el término "artritis reumatoide" incluya dentro de su alcance, cuando sea aplicable, formas relacionadas y asociadas de artritis bien conocidas en el sector tecnológico puesto que éstas se pueden tratar también con los compuestos de Fórmula (1 0 0) Correspondientemente, el término "artritis reumatoide" incluye la artritis aguda, que es una artritis marcada por dolor, calor, enrojecimiento e hinchamiento debidos a inflamación, infección o trauma, la artritis gotosa aguda, que es una artritis aguda asociada con la gota, la artritis inflamatoria crónica, que es una inflamacion de las articulaciones en trastornos crónicos tales como artritis reumatoide, la artritis degenerativa, que es una osteoartritis, la artritis infecciosa, que es una artritis causada por bacterias rickettsias, micoplasmas virus hongos o parásitos artritis de Lyme que es una artritis de las articulaciones grandes asociadas con la enfermedad de Lyme 20, la artritis proliferativa, que es una inflamación de las articulaciones con proliferación del sinovio, observada en una artritis reumatoide, la artritis psoriásica, que es un síndrome en el que se presenta psoriasis en asociación con la artritis inflamatoria y la artritis vertebral que es una inflamación que implica a los discos intervertebrales

Las tres características patológicas principales de la artritis reumatoide, que son responsables de la progresiva destrucción de las articulaciones, son inflamación, respuestas celulares y humorales anormales, e hiperplasia sinovial La patología celular particular de la artritis reumatoide incluye la presencia de células T y monocitos Las células T que predominantemente son células T con memoria constituyen hasta el 50% de las células recuperadas del tejido sinovial de pacientes con artritis reumatoide, y de los monocitos encontrados en el mismo tejido, 30-50% son células que presentan

antígenos, lo que es indicativo del caracter autoinmunitario de la enfermedad Las citocinas pro-inflamatorias, p ej , IL-1 IL-4 IL-5, IL-6 IL-9, IL-13 y TNF-α, son los contribuyentes principales a la lesión de tejido de articulación, inflamación, hiperplasia, formacion de paño (pannus) y resorcion de huesos Véase la cita de Firestein, G S y Zvaifler W J , "How important are T-cells in chronic rheumatoid synovitis?" [¿Cuan importantes son las células T en la sinovitis reumatoide crónica?] *Arth Rheum* 33 768-773, 1990 Esto ha sido demostrado p ej , por el hecho de que los anticuerpos monoclonales (Mab's de *Monoclonal antibodies*) contra el TNF-α han mostrado ser prometedores en pruebas clinicas de artritis reumatoide, Maini y colaboradores, "Beneficial effects of tumor necrosis factor-alpha (TNF-α) blockade in rheumatoid arthritis (RA)" (Efectos beneficiosos del bloqueo del factor de necrosis tumoral alfa (TNF-α) en artritis reumatoide (RA de *reumathoid artrhitis*)], *Clin Exp Immunol* 101 207-212, 1995

Los agentes inhibidores de las PDE4 con la Fórmula (1 0 0) son utiles en el tratamiento de la artritis reumatoide como un resultado de su capacidad para suprimir la actividad de una diversidad de células inflamatorias, inclusive basófilos, eosinófilos y células cebadas Estas actividades inhibidoras de los compuestos de Fórmula (1 0 0) ya se han descrito más arriba como lo ha sido también su amplia gama de acción antiinflamatoria *in vitro* por medio de la liberación de especies oxigenadas reactivas prostaglandinas y citocinas inflamatorias p ej IL-5, IFN-γ y TNF-α Véase además la cita de Cohan y colaboradores "*In vitro* pharmacology of the novel phosphodiesterase Type IV inhibitor, CP-80 633" [Farmacología *in vitro* del nuevo agente inhibidor de fosfodiesterasa del Tipo IV CP-80 633] *J Pharm Exp Ther* 278 1356-1361, 1996, y Barnette y colaboradores "SB207499 (Ariflo), a potent and selective second generation phosphodiesterase 4 inhibitor *in vitro* anti-inflammatory actions" (SB207499 (Ariflo), un potente y selectivo agente inhibidor de las fosfodiesterasas 4 de segunda generación acciones antiinflamatorias *in vitro*), *J Pharm Exp Ther* 284 420-426, 1998 Los agentes inhibidores de las PDE4 de Fórmula (1 0 0) son también utiles en el tratamiento de la artritis reumatoide como un resultado de su eficiencia para inhibir la proliferación de células T mediada a través de cierto numero de diferentes agentes, inclusive antígenos tales como ácaros de polvo doméstico, como se ha demostrado en la tecnología, Barnette y colaboradores *Ibid* La capacidad de los compuestos de Fórmula (1 0 0) para facilitar la liberación de la citocina IL-10 a partir de monocitos, que a su vez es capaz de disminuir la generación de TNF-α, IL-1 IL-4, IL-5, IL-6, IL-9, IL-13 y GM-CSF por células mononucleares de fluidos sinoviales, aumenta aun más el perfil antiinflamatorio global de los agentes inhibidores de las PDE4 de Formula (1 0 0), Kambayashi y colaboradores, *Ibid* Además, la capacidad de los compuestos de Fórmula (1 0 0) para inhibir la liberación de TNF-α a partir de monocitos estimulados se puede correlacionar con

modelos de inflamacion en animales, en los que se puede mostrar que los efectos antiinflamatorios corresponden a la supresión de la acumulación de TNF-α Uno de dichos modelos en animales implica una inhibicion de la liberación de TNF-α en ratones inducida por un LPS, mediante administración por vía oral de un agente inhibidor de las PDE4, Cheng y colaboradores, "The phosphodiesterase Type 4 (PDE4) inhibitor CP-80,633 elevates cyclic AMP levels and decreases TNF-α production in mice effect of adrenalectomy" [El agente inhibidor de las fosfodiesterasas del Tipo 4 (PDE4) CP-80,633 eleva los niveles de AMP cíclico y disminuye la producción de TNF-α en ratones efecto de la adrenalectomía], *J Pharm Exp Ther* 280 621-626, 1997 Otro de dichos modelos con animales implica la inhibición del edema de la pata de una rata, inducida por carragenano mediante administración por via oral de rolipram, Singh y colaboradores, "Synovial fluid levels of tumor necrosis factor a in the inflamed rat knee Modulation by dexamethasone and inhibitor of matrix metalloproteinases and phosphodiesterases" [Los niveles del factor de necrosis tumoral alfa en fluidos sinoviales en la rodilla inflamada de una rata Modulación por dexametasona y agentes inhibidores de metaloproteinasas de matriz y fosfodiesterasas], *Inflamm Res* 46 (suplemento 2) S153-S154, 1997

La gota se refiere a un grupo de trastornos del metabolismo de purina, y una gota plenamente desarrollada se manifiesta por diversas combinaciones de hiperuricemia, artritis inflamatoria aguda, característica, reaparecida inducida por cristales de monohidrato de urato monosódico, depósitos arenosos y ásperos de dichos cristales en y alrededor de las articulaciones de las extremidades, que pueden conducir a una destrucción de las articulaciones y a un grave tullimiento, y urolitiasis causada por ácido urico La gota reumatoide es otro nombre de la artritis reumatoide La gota arenosa es una gota en la que hay granos arenosos o depósitos gredosos de urato sódico Algunos agentes terapéuticos son utiles para tratar ambos tipos de gota y su inflamación consiguiente, p ej , fenilbutazona y colquicina, mientras que otros agentes terapéuticos poseen solamente propiedades uricosuricas, p ej , sulfinpirazona y benzobromarona

La fiebre, o pirexia, puede ser el resultado de uno cualquiera entre un gran numero de diferentes factores pero con respecto al presente invento dicha fiebre es o bien la manifestada en una fiebre faringo-conjuntiva o fiebre reumática o la manifestada durante una inflamación Un fenómeno concomitante de la inflamación es el dolor, especialmente el experimentado en las articulaciones y el tejido conjuntivo de los que padecen de artritis reumatoide y gota

Correspondientemente, los compuestos inhibidores de las PDE4 de Fórmula (1 0 0) proporcionan resultados beneficiosos en el tratamiento de la gota así como de la fiebre y del dolor que se asocian con dicha inflamación

Modelos de artritis reumatoide en animales se han usado también en la tecnología

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con el fin de demostrar la correlación existente entre la modulación *in vivo* del TNF-α por los agentes inhibidores de las PDE4 y su utilidad en el tratamiento de la artritis reumatoide La actividad del rolipram en modelos de inflamación aguda en animales, tales como el modelo de artritis por adyuvante en ratones, se ha demostrado en la tecnología, Sekut y colaborados, "Anti-inflammatory activity of phosphodiesterase (PDE) IV inhibitors in acute and chronic models of inflammation" [Actividad antiinflamatoria de los agentes inhibidores de fosfodiesterasas (PDE) IV en modelos agudos y crónicos de inflamación], *Clin Exp Immunol* 100(1) 126-132, 1995 La capacidad del rolipram para reducir la gravedad de una enfermedad en el modelo de la artritis inducida por el colágeno II (CIA de *collagen II induced arthritis*) después de inyección por vía subcutánea (s c) o intraperitoneal (i p) se ha demostrado en la tecnología Nyman y colaboradores, "Amelioration of collagen II induced arthritis in rats by Type IV phosphodiesterase inhibitor rolipram" [Mejoramiento de la artritis inducida por el colágeno II en ratas por el agente inhibidor de las fosfodiesterasas del Tipo IV rolipram], *Clin Exp Immunol* 108 415-419 1997 En este estudio, el régimen de dosificación para el rolipram era de 2 mg/kg a razón de dos veces por día durante cinco días antes del comienzo de una artritis, y esto retrasó importantemente la aparición de síntomas de artritis Después del cese del tratamiento, los animales de ensayo desarrollaron artritis y alcanzaron la misma calificación superior de artritis que el grupo testigo En el mismo estudio se administró también el rolipram a razón de 3 mg/kg dos veces por vía en el momento en que era evidente la artritis Este tratamiento cambió drásticamente el desarrollo de la enfermedad con lo que se detuvo la progresión de la gravedad, e incluso después del cese del tratamiento, la calificación de artritis no alcanza los niveles observados en animales sin tratar Los investigadores fueron capaces también de demostrar una intensa regulación en sentido descendente de la expresión de ARNm de TNF-α e IFN-γ en nodos linfáticos regionales, lo que sugiere que el efecto principal del rolipram es ejercido en la fase de efectores del proceso inflamatorio Nyman y colaboradores, *Ibid*

Inhibición de la Producción de TNF-α por Monocitos Humanos *In Vitro* - El efecto inhibidor de los compuestos de Fórmula (1 0 0) sobre la producción *in vitro* de TNF-α por monocitos humanos se puede determinar de acuerdo con el protocolo descrito en el documento de patente europea EP 411 754 (de Badger y colaboradores) y en el documento de solicitud de patente internacional WO 90/15534 (de Hanna) Las publicaciones citadas describen también dos modelos de choque endotóxico que se pueden usar para determinar la actividad inhibidora *in vivo* de los compuestos de Fórmula (1 0 0) Se detallan los protocolos usados en estos modelos y los compuestos de ensayo demuestran un resultado positivo por reducción de los niveles en suero de TNF-α inducidos por la inyección de una endotoxina

Se ha mostrado que agentes inhibidores selectivos de las PDE4, tales como el RP73401, exhiben un importante mejoramiento de la enfermedad, especialmente mejoras en la destrucción de las articulaciones, sinovitis y fibrosis, en modelos con animales tales como los que implican una artritis inducida por la pared celular de estreptococos (SCW de *Streptococcal cell wall*), Souness y colaboradores, "Potential of phosphodiesterase Type IV inhibitors in the treatment of rheumatoid arthritis" [Potencial de los agentes inhibidores de las fosfodiesterasas del Tipo IV en el tratamiento de la artritis reumatoide], *Drugs* 1 541-553, 1998

Presenta interés particular para el tratamiento de la artritis reumatoide la observación de que los agentes inhibidores de las PDE4 tienen efectos positivos en el sitio de acción de la enfermedad Por ejemplo, se ha demostrado que el compuesto RP73401 disminuye la expresión del ARNm de TNF-α en la interfase entre el paño y el cartílago de las articulaciones de patas de ratones tratados con colágeno II Souness y colaboradores *Ibid* El RP73401 ha sido tambien estudiado a escala clínica en pacientes con artritis reumatoide en un estudio de Fase II doble ciego, controlado por un placebo, de 35 pacientes con artritis reumatoide a los que se administraron 400 pg del compuesto t i d (tres veces por día) El compuesto fue capaz de inducir una tendencia positiva hacia el mejoramiento clínico asociado con una reducción de los niveles en suero de la proteina C reactiva y de IL-6 Chikanza y colaboradores, "The clinical effects of RP73401 phosphodiesterase Type 4 inhibitor in patients with rheumatoid arthritis" [los efectos clínicos del agente inhibidor de las fosfodiesterasas del Tipo 4 RP73401 en pacientes con artritis reumatoide], *Br J Rheumatol* 36 Resumen suplemento I, 186, 1997

<u>Analizar la Acumulación Aumentada de cAMP en Tejidos Intactos Usando Células U-937</u> -

Otro análisis apropiado para demostrar la actividad inhibidora de las PDE4 que poseen los compuestos de Fórmula (1 0 0) es uno que utiliza células U-937 procedentes de una línea celular de monocitos humanos de la que se ha demostrado que contiene una gran cantidad de las PDE4 Con el fin de determinar la inhibición de la actividad de las PDE4 en células intactas, se incuban células U-937 no diferenciadas a una densidad de aproximadamente 10^6 células por tubo de reacción con unas concentraciones que fluctuan entre 0,01 y 1 000 pM del compuesto en ensayo durante un minuto y con 1 µM de prostaglandina E2 durante cuatro minutos adicionales A los cinco minutos después de haberse iniciado la reacción, las células son lisadas por la adición de ácido perclórico al 17,5%, después de lo cual el pH es llevado al valor neutro por la adición de carbonato de potasio 1 M El contenido en cAMP del tubo de reacción es medido usando técnicas de RIA (inmunoanalisis radiológico) Un protocolo detallado para llevar a cabo este análisis es descrito en la cita de Brooker y colaboradores, "Radioimmunoassay of cyclic

AMP and cyclic GMP" [inmunoanálisis radiológico de AMP cíclico y GMP cíclico], *Adv Cyclic Nucleotide Res* 10 1-33, 1979

8 6 Trastornos Relacionados con Eosinófilos

La capacidad de los compuestos inhibidores de las PDE4 de Fórmula (1 0 0) para inhibir la activación de eosinófilos como una parte de su actividad antiinflamatoria global ha sido descrita más arriba Correspondientemente, los compuestos de Fórmula (1 0 0) son utiles en el tratamiento terapeutico de trastornos relacionados con eosinófilos Tales trastornos incluyen eosinofilia, que es la formación y la acumulación de un numero anormalmente grande de eosinófilos en la sangre El nombre del trastorno se deriva de "eosina" que es un tinte o colorante de color rosa que comprende un derivado bromado de fluoresceína y que tiñe con facilidad a "leucocitos eosinofílicos" en la sangre de pacientes los cuales por lo tanto son identificados con facilidad Un trastorno eosinofílico particular que puede ser tratado de acuerdo con el presente invento es la eosinofilia por infiltración pulmonar, que esta caracterizada por la infiltración del parenquima pulmonar por eosinófilos Este trastorno incluye especialmente el síndrome de Loffler, que es una condición caracterizada por infiltraciones transitorias de los pulmones, acompañadas por tos, fiebre, disnea y eosinofilia

Otros trastornos eosinofílicos incluyen la neumonía eosinofílica crónica que es una enfermedad pulmonar intersticial cronica caracterizada por tos, disnea, malestar fiebre sudores nocturnos, pérdida de peso eosinofilia y una película torácica que revela infiltrados no segmentarios y no migratorios en la periferia pulmonar, la eosinofilia pulmonar tropical, que es una forma sub-aguda o crónica de filariasis oculta, que implica usualmente a *Brugia malayi Wucherena bancrofti*, o filarias que infectan a animales, que se presenta en los trópicos y está caracterizada por ronquera y tos nocturnas episódicas, una eosinofilia sorprendentemente elevada e infiltraciones reticulo-nodulares difusas de los pulmones, la aspergilosis bronconeumónica, que es una infección de los bronquios y pulmones por hongos de *Aspergillus* que dan como resultado una condición enfermiza marcada por lesiones granulomatosas inflamatorias en los senos nasales y en los pulmones, pero también en la piel en las orejas, en las órbitas y algunas veces en los huesos y las meninges, y que conduce a un aspergilloma, que es el tipo más comun de apelotonamiento de hongos formados por colonizacion de *Aspergillus* en una cavidad bronquial o pulmonar

El término "granulomatoso" significa "que contiene granulomas" y el término "granuloma" se refiere a cualquier pequeña aglomeración delimitada nodular de células inflamatorias mononucleares o una colección de macrófagos modificados que se asemejan a células epiteliales, rodeada usualmente por un reborde o cerco de linfocitos,

observandose comentemente una fibrosis alrededor de la lesión Algunos granulomas contienen eosinófilos La formación de granulomas representa una respuesta inflamatoria cronica iniciada por diversos agentes infecciones y no infecciosos Cierto numero de dichas condiciones granulomatosas se pueden tratar usando un compuesto de Fórmula (1 0 0), p ej , la angitis granulomatosa alérgica, también denominada síndrome de Churg-Strauss que es una forma de vasculitis necrotizante sistémica en la que hay una prominente implicación de los pulmones, manifestada generalmente por eosinofilia, reacciones granulomatosas, y usualmente asma grave Un trastorno relacionado es la poliarteritis nodosa (PAN), que está marcada por multiples lesiones arteriales inflamatorias y destructivas y es una forma de vasculitis necrotizante sistémica que implica a las arterias de tamaños pequeños e intermedios con signos y síntomas que resultan de una infarción y una cicatrización del sistema del órgano afectado, en particular los pulmones Otros trastornos relacionados con eosinófilos, que se pueden tratar de acuerdo con el presente invento, son los que afectan a las vías respiratorias y que son inducidos u ocasionados por una reaccion frente a un agente terapéutico no relacionado con cualquiera de los compuestos de Fórmula (1 0 0)

8 7 Dermatitis Atópica, Urticaria, Conjuntivitis y Uveitis

La dermatitis atopica es un trastorno cutáneo inflamatorio crónico que se observa en individuos que presentan una predisposición hereditaria a un umbral cutáneo disminuido para el prurito, que está acompañado frecuentemente por rinitis alergica, fiebre del heno y asma y que está caracterizado principalmente por un comezón extremado La dermatitis atópica es denominada tambien dermatitis alérgica, y eczema alérgico o atópico

La dermatitis atópica (AD de *atopic dermatitis*) es la enfermedad cutánea inflamatoria crónica más corriente en niños pequeños, y afecta a desde un 10% hasta un 15% de la población durante la niñez La dermatitis atópica está asociada frecuentemente con asma y alergias y por lo tanto ha resultado conocido como un componente de la denominada "triada atópica", puesto que se presenta frecuentemente en individuos con asma y/o rinitis alérgica Véase Leung Dym, *Atopic Dermatitis From Pathogenesis To Treatment* (Dermatitis atópica desde la patogénesis al tratamiento), R G Landes Co , Austin, Texas, 1-226, 1996 Correspondientemente, la disfunción inmunitaria asociada con la dermatitis atópica se puede tratar con agentes terapéuticos que son inhibidores de las PDE4 Por ejemplo, se ha informado que el rolipram Ro-201724, y la denbufilina producen una inhibición relacionada con la concentración, de la proliferación de células mononucleares de sangre periférica humana (HPBM de *human peripheral blood mononuclear cells*) procedente de pacientes normales, así como también de individuos

con dermatitis atopica Véanse respectivamente, las citas de Torphy y colaboradores *Drugs and the Lung*, coordinadores de edicion Page y Metzger, Raven Press, Nueva Yorkm 1994, y O'Brien *Mol medicine Today*, 369, 1997 Estos estudios determinaron también que la respuesta proliferativa de las HPBM procedentes de pacientes con dermatitis atopica era mas sensible a la inhibición de las PDE4 que lo que era la proliferación observada en las HPBM procedente de individuos normales

Las celulas T que segregan citocinas del tipo Th2 que expresan el antígeno asociado con linfocitos cutáneos, desempeñan un cometido primordial en la inducción de respuestas locales a la IgE y al reclutamiento de eosinófilos en esta enfermedad La inflamación crónica observada en dermatitis atópica es considerada como el resultado de varios factores dependientes entre ellos, tales como una exposición repetida o persistente a alergenos, que puede conducir a la expansión de células Th2 Se ha demostrado que hay una frecuencia aumentada de células T especificas para alergenos, que producen niveles aumentados de IL-4, IL-5 e IL-3 en la sangre de pacientes con dermatitis atópica Véase Leung Dym y colaboradores, "Allergic and immunological skin disorders" (Trastornos alergicos e inmunológicos de la piel), *JAMA* 278(22) 1914-1923 1997 Esto es importante puesto que las IL-4 e IL-3 inducen la expresion de la molécula de adhesión vascular-1 (VCAM-1 de *vascular adhesión molecule-1*), que es una molécula de adhesión implicada en la migración de células mononucleares y de eosinófilos hacia sitios con inflamación tisular Además, la IL-5 es una mediadora clave de la activación de eosinófilos la cual constituye una caracteristica comente de una enfermedad atópica

Desde hace mucho tiempo se ha sabido que una concentración aumentada de cAMP en linfocitos y basófilos está asociada con una liberación disminuida de mediadores procedentes de estas células, y más recientemente se ha informado de que la histamina, al actuar sobre receptores H2, aumenta los niveles de cAMP e inhibe la producción de IL-4 en células Th2 murinas Correspondientemente, se supone que está presente en enfermedades atópicas tales como dermatitis atópica respuestas β-adrenérgicas perjudicadas o actividad de PDE4 aumentada de las respuestas inflamatorias de leucocitos Una respuesta disminuida al cAMP puede dar como resultado una actividad de PDE4 aumentada, que tiene una base genética, o que es una condición adquirida

Se han llevado a cabo estudios que comparan diferentes tipos de células procedentes de pacientes atópicos con las procedentes de voluntarios sanos, y los resultados han mostrado que una actividad aumentada de las PDE de cAMP en células atópicas se correlaciona con una función celular inflamatoria e inmunitaria anormal en dermatitis atópica Además, la enzima PDE4 procedente de leucocitos atópicos es más sensible a los agentes inhibidores de las PDE4 que la enzima PDE4 procedente de

leucocitos normales, y se ha demostrado una diferencia en un multiplo hasta de 14 veces Véase Chan y Hanifin, "Differential inhibitory effects of cAMP phosphodiesterase isoforms in atopic and normal leukocytes" (Efectos inhibidores diferenciales de las isoformas de las fosfodiesterasas de cAMP en leucocitos atópicos y normales), *J Lab Clin Med* 121(1) 44-51 1993 Se puede observar también una sensibilidad aumentada en la inhibición de la proliferación de células mononucleares de sangre periférica procedentes de donantes atópicos al realizar el tratamiento con agentes inhibidores de las PDE4 Por ejemplo, se ha encontrado que el rolipram es más eficaz para inhibir una proliferación de las PBMC de una dermatitis atópica, estimuladas por PHA, que para inhibir la proliferación de las PBMC normales estimuladas por PHA, con una IC_{50} = 280 nM comparada con una IC_{50} = 2 600 nM, respectivamente

Además, se ha mostrado que una gama estructuralmente diversa de agentes inhibidores selectivos de las PDE4 son eficaces para reducir una eosinofilia de la piel en un cobaya que ha sido mediada a través de una gama de agentes tales como el PAF ácido araquidónico, plasma activado por zimosán y una proteína de anafilaxis cutánea Véase Beasley y colaboradores, "Synthesis and evaluation of a novel series of phosphodiesterase 4 inhibitors A potential treatment for asthma" (Síntesis y evaluación de una serie de agentes inhibidores de las fosfodiesterasas 4 Un tratamiento potencial para el asma), *Bioorg Med Chem Letts* 8 2629-2634, 1998 Tales datos muestran la utilidad de los agentes inhibidores de las PDE4 para tratar enfermedades de la piel, impulsadas por eosinofilos Dicho tratamiento se realiza mediante administración tópica, p ej , de atizoram tópico aplicado bilateralmente a lo largo de ocho días a veinte pacientes en una prueba clínica, de la que se ha encontrado que inhibe efectivamente todos los parámetros inflamatorios ensayados mostrando mejoras tanto cualitativas como cuantitativas sin efectos desfavorables Véase Hanifin y colaboradores, "Type 4 phosphodiesterase inhibitors have clinical and *in vitro* anti-inflammatory effects in atopic dermatitis" (Los agentes inhibidores de fosfodiesterasas del Tipo 4 tienen efectos antiinflamatorios clínicos e *in vitro* en dermatitis atópica), *J Invest Dermatol* 107 51-56, 1996

Correspondientemente, los agentes inhibidores de las PDE4 de Fórmula (1 0 0) son utiles para el tratamiento beneficioso de una dermatitis atópica como antes se ha descrito Un sector relacionado de aplicación terapeutica para el que los compuestos de Fórmula (1 0 0) también producen resultados beneficiosos, se encuentra en el tratamiento de la urticaria La urticaria es una reacción vascular, usualmente transitoria, que implica a la dermis superior, y que representa un edema localizado causado por una dilatacion y una permeabilidad aumentada de los capilares y marcada por el desarrollo de ronchas o habones Muchos estimulos diferentes son capaces de inducir una reacción

de urticaria, y ésta se puede clasificar de acuerdo con las causas que la precipitan, tales como mediada por inmunidad mediada por el complemento que puede implicar mecanismos inmunologicos y no inmunológicos, inducida por material urticariogénico, inducida por agentes físicos inducida por estrés o idiopática La condición puede ser designada también como aguda o crónica dependiendo de la duración de un ataque Un angio-edema es la misma respuesta en la dermis profunda o en tejidos subcutáneos o submucosales

Los tipos mas corrientes de urticarias que se pueden tratar con los compuestos de Fórmula (1 0 0) son la urticaria colinérgica que está caracterizada por la presencia de ronchas punteadas distinguibles rodeadas por zonas de entema, de las que se cree que constituyen una reacción de hipersensibilidad no inmunológica en la que la acetilcolina liberada a partir de terminales nerviosos parasimpáticos o motores induce la liberación de mediadores a partir de celulas cebadas, y evocada por condiciones de ejercicio, estrés o calor ambiental aumentado urticaria al frio que es una urticaria precipitada por aire, agua u objetos frios, que se presenta en dos formas En la forma dominante autosómica que está asociada con fiebres artralgias y leucocitosis las lesiones presentes son pápulas y máculas eritematosas ardientes, y en la forma adquirida, más corriente que es usualmente idiopática y auto-limitada, la urticaria por contacto que es una respuesta con ronchas y ensanchamientos transitoria localizada o generalizada, que es provocada por una exposicion a agentes urticariogenicos absorbibles rápidamente, la urticaria gigante que es un angio-edema y la urticaria papulosa que es una erupción cutánea persistente que representa una reaccion de hipersensibilidad a las mordeduras de insectos

Correspondientemente los agentes inhibidores de las PDE4 de Fórmula (1 0 0) son utiles para el tratamiento beneficioso de los diversos tipos de urticaria que antes se han descrito Un sector relacionado de aplicación terapéutica, para el que los compuestos de Fórmula (1 0 0) tambien producen resultados beneficiosos, se encuentra en diversos usos oftálmicos, en particular en el tratamiento de conjuntivitis y uveitis

La conjuntiva es una delicada membrana que bordea los párpados y cubre la superficie expuesta de la esclerótica La conjuntivitis es una inflamación de la conjuntiva, que consiste en términos generales en una hiperemia conjuntival asociada con una descarga Los tipos más corrientes de conjuntivitis, que se pueden tratar con los compuestos de Fórmula (1 0 0), son la conjuntivitis actínica producida por luz ultravioleta, la conjuntivitis catarral aguda que es una conjuntivitis infecciosa aguda, asociada con el frío o catarro, y caracterizada por hiperemia vivida, edema pérdida de translucidez, y descarga mucosa o mucopurulenta la conjuntivitis contagiosa aguda que es una conjuntivitis epidemica mucopurulenta, causada por *Haemophilus aegyptius*, que tiene

los mismos síntomas que la conjuntivitis catarral aguda y es denominada también "influenza", la conjuntivitis alérgica que es una componente de la fiebre del heno la conjuntivitis atópica que es una conjuntivitis alérgica del tipo inmediato, causada por alérgenos llevados por el aire, p ej pólenes polvos finos, esporas, y caspa de animales, la conjuntivitis catarral crónica que es una conjuntivitis crónica suave, acompañada con una hiperemia y una descarga mucosa solamente ligeras, la conjuntivitis purulenta que es una conjuntivitis aguda causada por bacterias o virus, particularmente gonococos, meningococos, neumococos y estreptococos, y caracterizada por una grave inflamación de la conjuntiva y una copiosa descarga de pus, y la conjuntivitis vernal que es una conjuntivitis bilateral de aparición estacional, de causa desconocida, que afecta a niños, especialmente muchachos, y está caracterizada por pápulas aplanadas y un exudado espeso y gelatinoso Correspondientemente, los agentes inhibidores de las PDE4 de Fórmula (1 0 0) son útiles para el tratamiento beneficioso de los diversos tipos de conjuntivitis que se han descrito más arriba Un sector relacionado de aplicación terapéutica para el que los compuestos de Fórmula (1 0 0) también producen resultados beneficiosos, se encuentra en el tratamiento de la uveítis

La úvea es el revestimiento o la túnica central vascular del ojo, que comprende el iris, el cuerpo ciliar y la coroides La uveítis es una inflamación de la totalidad o una parte de la úvea e implica corrientemente a las otras túnicas del ojo, es decir, a la esclerótica y la córnea, y asimismo a la retina Los tipos más comentes de uveítis, que se pueden tratar con los compuestos de Fórmula (1 0 0), son la uveítis anterior que es una uveítis que implica a las estructuras del iris y/o del cuerpo ciliar que incluye iritis, ciclitis e indociclitis la uveítis granulomatosa que es una uveítis de cualquier parte del tracto uveal, pero particularmente de la porción posterior, caracterizada por colecciones nodulares de células epitelioides y células gigantes rodeadas por linfocitos, la uveítis no granulomatosa que es una inflamación de la porción anterior del tracto uveal es decir el iris y el cuerpo ciliar; la uveítis facoantigénica que es una de las uveítis inducidas por el cristalino, es una uveítis anterior grave similar a la oftalmia simpática, que se observa semanas o incluso meses después de una cirugía extracapsular del cristalino u otro trauma para la cápsula, y la uveítis posterior que es una uveítis que implica al segmento posterior del ojo, inclusive coroiditis y coriorretinitis Correspondientemente, los agentes inhibidores de las PDE4 de Fórmula (1 0 0) son útiles para el tratamiento beneficioso de los diversos tipos de uveítis que antes se han descrito

8 8 Psoriasis

La psoriasis es una dermatosis escamosa crónica corriente, con herencia poligenética y un curso fluctuante, que está caracterizada por microabscesos y pústulas

espongiformes, así como por parches exfoliantes secos y eritematosos, de diversos tamaños La psoriasis es una enfermedad cutánea corriente que afecta aproximadamente a un 2% de la población y más de un millon y medio de pacientes en los EE UU consultan anualmente a los médicos para solicitar un tratamiento La psoriasis es usualmente recurrente y en algunos casos puede ser muy debilitadora La etiología de la psoriasis es desconocida, pero parece que es una enfermedad auto-inmunitaria con predisposición genética

La psoriasis implica una gran infiltración de células T en las regiones afectadas de la piel, con linfocitos CD4+ en la dermis y linfocitos CD8+ en la epidermis Estos linfocitos segregan IL-2, IFN-γ y TNF-α, que alteran a la proliferación y a la diferenciación de queratinocitos Además, de un 5% a un 10% de los pacientes con psoriasis desarrollan artritis psoriásica, cuyos síntomas son muy similares a los de artritis reumatoide El amplio espectro de actividades anti-inflamatorias que son presentadas por los agentes inhibidores de las PDE4, que ya se ha discutido anteriormente, hace posible que tales agentes inhibidores se usen de modo beneficioso en el tratamiento de la psoriasis

Se ha demostrado que el tratamiento de células basales epidérmicas, en un cultivo primario, con el agente inhibidor de las PDE4 Ro 20-1724 conduce a un aumento en un multiplo de tres veces en las concentraciones de cAMP Se ha mostrado también que el tratamiento con Ro 20-1724 de rebanadas epidérmicas psoriásicas y rebanadas epidérmicas psoriásicas queratomadas da como resultado una elevación muy marcada de concentraciones de cAMP con respecto a los testigos Específicamente, se ha observado un aumento de 1 395% en la concentración de cAMP en una epidermis psoriásica queratomada Se ha mostrado también que los agentes inhibidores de las PDE4 inhiben la respuesta inflamatoria de cierto numero de mediadores a través de una administración ya sea atópica o sistémica Por ejemplo, se ha mostrado que el rolipram inhibe la inflamación de los oídos inducida por aceite de crotón en un ratón en unas dosis tópicas tan bajas como de 0,03 mg por oído El agente inhibidor selectivo de las PDE4, Ro 20-1724, ha sido investigado también en estudios doble ciegos, que comparan su efectividad con la de un vehículo, en los se ha mostrado que aquél mejora a las lesiones psoriásicas sin efectos sistémicos o cutáneos desfavorables

8 9 Esclerosis Multiple y Otras Enfermedades Autoinmunitarias Inflamatorias

La esclerosis es una induración, o endurecimiento y se refiere especialmente al endurecimiento de una parte procedente de una inflamación y de una formación aumentada de tejido conjuntivo, y en enfermedades de la sustancia intersticial El término "esclerosis" se usa principalmente para un tipo de endurecimiento del sistema nervioso

debido a la deposicion de tejido conjuntivo, o para designar al endurecimiento de los vasos sanguíneos La esclerosis multiple (MS, de *multiple sclerosis*) es una enfermedad en la que hay focos de desmielinación de diversos tamaños por toda la sustancia blanca del sistema nervioso central, extendiéndose algunas veces a la sustancia gris, dando como resultado debilidad, descoordinación parestesias perturbaciones del habla y quejas visuales La esclerosis multiple es una enfermedad de etiologia desconocida con un curso prolongado, que implica muchas remisiones y muchos relapsos

La esclerosis multiple es una enfermedad autoinmunitaria que además de una inflamación crónica y una desmielinación, da como resultado también una gliosis dentro del sistema nervioso central Hay varios subtipos de esta enfermedad inclusive la esclerosis multiple progresiva primaria, y la esclerosis multiple en remisión y en relapso Estos subtipos de la enfermedad pueden ser distinguidos unos de otros sobre la base del curso de la enfermedad del tipo de inflamación que está implicada y por medio del uso de una reproduccion de imágenes por resonancia magnética (MRI de *magnetic resonance imaging*) También es posible que el mecanismo fundamental de la enfermedad cambie durante el curso de una esclerosis multiple, siendo reemplazado un proceso basado en una inflamación más tarde por uno que implica desmielinación y deterioro de las axonas Véase Weilbach y Gold, "Disease modifying treatment for multiple sclerosis What is on the horizon?" (Tratamientos de la esclerosis multiple que modifica la enfermedad ¿Qué hay en el horizonte?), *CNS Drugs* 11 133-157, 1999

En la esclerosis multiple las lesiones inflamatorias están localizadas en pero son prevalecientes a lo largo de la sustancia blanca del sistema nervioso central aunque las placas escleróticas caracterizadas por una desmielinación son una marca de contraste de la enfermedad El desarrollo de una desmielinación, a su vez, es causado por la necrosis de oligodendrocitos, y la desmielinación está asociada con un material infiltrado que se compone principalmente de células T y macrófagos, que juntamente con células locales, tales como astrocitos, microglía y células endoteliales cerebrales microvasculares, expresan el complejo de histocompatibilidad principal (MHC de *major histocompatibility*) de la clase II Por lo tanto, estas células están implicadas en la presentación de antigenos y en una respuesta inflamatoria, y se han identificado cierto numero de citocinas pro-inflamatorias, inclusive TNF-α, TNF-β, IL-1, IL-6 e IFN-γ, en el tejido cerebral de pacientes con esclerosis multiple y su presencia está asociada en términos generales con lesiones activas En particular el TNF-α ha sido el foco de atención puesto que media en el deterioro de la mielina y de los oligodendrocitos *in vitro* induce que los astrocitos expresen moléculas de adhesión superficial, y está asociado con la rotura de la barrera hematoencefalica

Se han usado modelos en animales para demostrar el cometido del TNF-α en la

esclerosis multiple, p ej en una encefalomielitis alergica experimental (EAE) se ha mostrado que la administracion de anticuerpos anti-TNF o receptores solubles de TNF proporciona un efecto protector Vease la cita de Selmaj y colaboradores "Prevention of chronic relapsing experimental autoimmune encephalomyelitis by soluble tumor necrosis factor" (La prevencion de la encefalomielitis autoinmunitaria experimental en relapso crónica por el factor de necrosis de tumores soluble), *J Neuroimmunol* **56** 135-141, 1995 Se ha informado también acerca de la existencia de una correlación directa entre el nivel de ARNm del TNF-α y la progresión de una EAE Véase la cita de Reeno y colaboradores, "TNF-alpha expression by resident microglia and infiltrating leukocytes in the central nervous of mice with experimental allergic encephalomyelitis regulation by the Th1 cytokines" (La expresión de TNF-α por microglia residente y leucocitos infiltrados en el sistema nervioso central de ratones con encefalomielitis alérgica experimental regulación por las citocinas de Th1" *J Immunol* **154** 944-953, 1995 Una evidencia adicional que demuestra que el TNF-α es un mediador de la esclerosis multiple, la constituye la concentración aumentada de TNF-α en el fluido cerebroespinal de pacientes con esclerosis multiple durante el curso de la enfermedad Además, un ratón transgénico que expresa en exceso el TNF-α en el sistema nervioso central ha puesto de manifiesto signos de desmielinación espontánea mientras que un ratón transgénico puesto fuera de combate con TNF-α ha mostrado un efecto protector Véase Probert y colaboradores "Spontaneous inflammatory desmyelinating disease in transgenic mice showing central nervous system-specific expression of tumor necrosis factor alpha" (La enfermedad desmielizante inflamatoria espontánea en ratones transgénicos que muestran expresión del factor de necrosis de tumores alfa especifica para el sistema nervioso central), *Proc. Natl Acad Sci USA* **92** 11294-11298, 1995, y Liu y colaboradores "TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination" (El TNF es una citocina antiinflamatoria potente en una desmielinación mediada por causas auto-inmunitarias), *Nature Med* **4** 78-83, 1998

Puesto que los agentes inhibidores de las PDE4 reducen también al TNF-α, son beneficiosos en el tratamiento de la esclerosis multiple, puesto que el TNF-α desempeña un cometido principal en la mediación de una esclerosis multiple, como antes se ha discutido Por ejemplo en un modelo en ttl de encefalomielitis alérgica experimental, se ha encontrado que el rolipram suprime la aparición de signos clínicos y anula las anormalidades en una representación en imágenes por MRI En otro estudio de los efectos del rolipram sobre la encefalomielitis alérgica experimental crónica en relapso en ratones SJL, se ha mostrado que el rolipram mejora los signos clínicos y los cambios patológicos en este modelo Véase Genain y colaboradores, "Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phosphodiesterase"

(Prevención de la desmielinación autoinmunitaria en primates no humanos por una fosfodiesterasa específica para cAMP), *Proc Natl Acad Sci USA* 92 3601-3605, 1995, y Sommer y colaboradores "Therapeutic potential of phosphodiesterase Type 4 inhibition in cronic autoimmune demyelinating disease" (Potencial terapéutico de inhibicion de las fosfodiesterasas del Tipo 4 en una enfermedad desmielinante autoinmunitaria crónica) *J Neuroimmunol* 79 54-61, 1997

Además de inhibir la actividad de las PDE4 y la producción del TNF-α, los compuestos de Fórmula (1 0 0) poseen tambien actividad como agentes supresores de inmunidad y son especialmente utiles para tratar enfermedades autoinmunitarias en las que una inflamación es una parte componente de la enfermedad autoinmunitaria, o en las que una inflamación es parte de la etiología de la enfermedad autoinmunitaria, o en las que una inflamación está implicada de otro modo con la enfermedad autoinmunitaria Alternativamente, los compuestos de Fórmula (1 0 0) son agentes antiinflamatorios utiles en el tratamiento de enfermedades inflamatorias en las que las reacciones autoinmunitarias son una parte componente de la enfermedad inflamatoria, o en las que las reacciones autoinmunitarias son una parte de la etiología de la enfermedad inflamatoria, o en las que reacciones autoinmunitarias están implicadas de otro modo con la enfermedad inflamatoria Correspondientemente, los compuestos de Fórmula (1 0 0) son utiles en el tratamiento de la esclerosis multiple, tal como se discute arriba con más detalle

Otras enfermedades autoinmunitarias/inflamatorias que se pueden someter a tratamiento por agentes terapéuticos que comprenden los compuestos de Fórmula (1 0 0), incluyen, pero no se limitan a, trastornos hematológicos autoinmunitarios tales como anemia hemolitica anemia aplásica anemia de glóbulos rojos puros, y purpura trombocitopénica idiopatica, lupus eritematoso sistémico, policondritis, esclerodema, granulomatosis de Wegner dermatomiositis, hepatitis activa crónica, miastenia grave, el síndrome de Stevens-Johnson psilosis idiopática enfermedades inflamatorias autoinmunitarias de los intestinos tales como colitis ulcerativa y la enfermedad de Crohn oftalmopatía endocrina enfermedad de Grave sarcoidosis, alveolitis neumonitis con hipersensibilidad crónica cirrosis biliar primaria, diabetes juvenil (diabetes mellitus del tipo I), uveitis anterior y uveítis granulomatosa (posterior) queratoconjuntivitis seca y queratoconjuntivitis epidémica, fibrosis pulmonar intersticial difusa (fibrosis intersticial de los pulmones), fibrosis pulmonar idiopática, fibrosis cística, artritis psoriásica, glomerulonifritis con o sin síndrome nefrótico, inclusive glomerulonifritis aguda, síndrome nefrótico idiopático, y nefropatía con cambios mínimos, enfermedades inflamatorias / hiperproliferativas de la piel, inclusive psoriasis y dermatitis atópica que se han discutido arriba con detalle, dermatitis por contacto dermatitis alergica por contacto, penfigo

familiar benigno, pénfigo entematoso, pénfigo foliáceo y pénfigo vulgar

Además, los compuestos de Fórmula (1 0 0) se pueden usar como agentes supresores de inmunidad para la prevención de un rechazo de injerto alogeneico después de un transplante de órganos en que dichos organos incluyen típicamente a un tejido procedente de médula ósea, intestinos, corazón, riñones, hígado, pulmones, páncreas, piel y córnea

8 10 Enfermedad inflamatoria de los intestinos

La colitis ulcerativa (UC de *ulcerative colitis*) es una ulceración recurrente y crónica en el colon principalmente de la mucosa y la submucosa, que es de causa desconocida, y que se manifiesta clinicamente por dolor abdominal acalambrante, hemorragia rectal y descargas sueltas de sangre, pus y mucosidad con particulas fecales escasas Enfermedades relacionadas de los intestinos incluyen la colitis colagenosa, que es un tipo de colitis de etiología desconocida que se caracteriza por depósitos de material colagenoso por debajo del epitelio del colon, y está marcada por un dolor abdominal acalambrante con una reducción conspicua en la absorción de fluidos y electrólitos, que conduce a una diarrea aguada la colitis poliposa que es una colitis ulcerativa asociada con la formación de pseudopólipos, es decir islotes edematosos e inflamados de mucosa entre zonas de ulceración y la colitis transmural, que es una inflamación del espesor total de los intestinos en vez de ser una enfermedad mucosal y submucosal, usualmente con la formación de granulomas no caseificantes, que se asemeja clinicamente a la colitis ulcerativa, pero en que la ulceración es con frecuencia longitudinal o profunda, la enfermedad es con frecuencia segmentada, la formación de constricción y estrechez es comente y las fístulas, particularmente en el perineo, son una complicación frecuente

La enfermedad de Crohn (CD) es una enfermedad inflamatoria granulomatosa crónica de etiología desconocida, que implica a cualquier parte del tracto gastrointestinal pero corrientemente implica al ileon terminal con cicatrización y espesamiento de la pared de los intestinos, que conduce frecuentemente a una obstrucción intestinal, y a formacion de fístulas y abscesos, y que tiene una alta tasa de reaparición después del tratamiento La colitis ulcerativa, la enfermedad de Crohn y las enfermedades relacionadas que antes se han discutido se citan colectivamente como una enfermedad inflamatoria de los intestinos (IBD) Estas enfermedades son trastornos crónicos, con relapso espontáneo de causa desconocida, que son mediados por causas inmunológicas y cuya patogénesis ha sido demostrada por medio del uso de modelos en animales y técnicas inmunológicas avanzadas Véase Bickston y Caminelli, "Recent developments in the medical therapy of IBD" (Recientes desarrollos en la terapia medica de la IBD), *Curr Opin Gastroenterol* 14 6-10, 1998, y Murthy y colaboradores, "Inflammatory bowel disease A new wave of

therapy" (Enfermedad inflamatoria de los intestinos Una nueva ola de terapia) *Exp Opin Ther Patents* 8(7) 785-818 1998 Mientras que ha permanecido relativamente estable la incidencia de colitis ulcerativa, la incidencia de la enfermedad de Crohn ha aumentado significativamente

La terapia actual para la enfermedad inflamatoria de los intestinos incluye al ácido 5-amino-salicílico, a corticoesteroides, y a agentes moduladores de inmunidad tales como azatioprina, 6-mercapto-purina y metotrexato Estos agentes tienen una amplia gama de efectos colaterales desfavorables y no modifican a la enfermedad propiamente dicha, y por consiguiente hay una necesidad apremiante de agentes de tratamiento que sean más eficaces Los compuestos de Fórmula (1 0 0) son capaces de tratar beneficiosamente a enfermedades inflamatorias de los intestinos como resultado de su capacidad para inhibir la producción del TNF-α, puesto que el TNF-α causa una activación y una proliferación de celulas inmunitarias y una liberacion de mediadores en una enfermedad inflamatoria de los intestinos Véase Radford-Smith y Jewell, "Cytokines and inflammatory bowel disease" (Citocinas y enfermedad inflamatoria de los intestinos), *Baillieres Clin Gasteroenterol* 10 151-164, 1996 El TNF-α ha sido detectado también en los excrementos y en la mucosa intestinal de pacientes con una enfermedad inflamatoria de los intestinos Además estudios clínicos tempranos de la enfermedad de Crohn usando anticuerpos monoclonales de TNF han mostrado una importante promesa

Como ya se ha detallado más arriba, los agentes inhibidores selectivos de las PDE4 tienen un marcado efecto sobre la inhibición de la liberación de TNF-α a partir de células mononucleares de sangre periférica después de que esas células hayan sido estimuladas con una amplia gama de mediadores tanto *in vitro* como *in vivo* Se ha mostrado que el agente inhibidor selectivo de las PDE4, arofilina, proporciona efectos beneficiosos cuando se ensaya en modelos de colitis en una rata Además en un modelo de colitis inducida por sulfato de dextrano en una rata, el rolipram y el agente inhibidor selectivo de las PDE4 LAS31025 han demostrado efectos beneficiosos comparables con los de la prednisolona Se ha mostrado que ambos compuestos mejoran una hemorragia y los marcadores inflamatorios Véase Puig y colaboradores, "Curative effects of phosphodiesterase 4 inhibitors in dextran sulfate sodium induced colitis in the rat" (Efectos curativos de los agentes inhibidores de fosfodiesterasa 4 en una colitis inducida por dextrano-sulfato sódico en una rata), *Gastroenterology* 114(4) A1064, 1998 Otros autores han usado modelos adicionales para demostrar la capacidad de los agentes inhibidores selectivos de las PDE4 para proporcionar una protección gastrointestinal Por ejemplo, se ha mostrado que la extravasación de entrocitos inducida por lipopolisacáridos en ratas y la hipoperfusion intestinal en perros se pueden atenuar con los agentes inhibidores selectivos de las PDE4, rolipram y denbufilina Véase Cardelus y

colaboradores "Inhibiting LPS induced bowel erythrocyte extravasation in rats, and of mesenteric hypoperfusion in dogs by phosphodiesterase inhibitors" (La inhibición de una extravasación de eritrocitos intestinales inducida por LPS en ratas y de la hipoperfusion mesentérica en perros, por agentes inhibidores de las fosfodiesterasas), *Eur J Pharmacol* **299** 153-159 1996, y Cardelus y colaboradores, "Protective effects of denbufylline against endotoxin induced bowel hyperplasia" (Efectos protectores de la denbufilina contra la hiperplasia intestinal inducida por endotoxinas", *Met Find Exp Clin Pharmacol* 17 (Suplemento A) 142, 1995

8 11 Choque Séptico, Fallo Renal, Caquexia e Infección

El choque séptico es un choque asociado con una infección agobiante, lo más corrientemente una infección con bacterias gram negativas, aunque puede ser producido por otras bacterias y por otros virus hongos y protozoos Se estima que el choque séptico es el resultado de la acción de endotoxinas u otros productos del agente infeccioso sobre el sistema vascular, causando que se secuestren grandes volumenes de sangre en los capilares y las venas La activación de los sistemas del complemento y de las cininas, y la liberación de histaminas, citocinas, prostaglandinas y otros mediadores, también estan implicadas

Se ha mostrado en un modelo de fallo renal agudo inducido por endotoxinas en ratas, que el agente inhibidor selectivo de las PDE4, Ro-201724, administrado como un tratamiento posterior a razón de 10 µg/kg/min, aumenta de manera importante la excreción urinaria de cAMP atenua marcadamente los aumentos, inducidos por endotoxinas, en la resistencia vascular renal y las disminuciones en el flujo sanguíneo renal y en la velocidad de filtración glomerular Se ha mostrado también que el Ro-201724 mejora las tasas de supervivencia para ratas tratadas con endotoxinas Véase la cita de Carcillo y colaboradores *Pharmacol Exp Ther* **279**, 1197, 1996 También se ha estudiado la pentoxifilina en pacientes que sufren de choque séptico En este estudio se han seleccionado veinticuatro individuos que cumplen los criterios de un choque séptico, doce de los cuales han recibido pentoxifilina a razón de 1 mg/kg/h durante un período de 24 horas, mientras que los otros doce han servido como un grupo testigo Después de 24 horas se ha encontrado que los niveles de TNF-α en el grupo sometido a terapia han sido disminuidos de manera importante mientras que los niveles de IL-6 han sido aumentados de manera importante

En otro estudio, se ha mostrado que un tratamiento previo con pentoxifilina a razón de 5 a 50 mg/kg i p 3X (3 veces al día), o con los agentes inhibidores selectivos de las PDE4, rolipram a razón de 10 a 30 mg/kg i p 3x y denbufilina a razón de 3 mg/kg i p 3X reduce la extravasación de eritrocitos intestinales inducida por lipopolisacáridos,

en ratas, y que la denbufilina es 100 veces mas potente que la pentoxifilina para inhibir la disminución del flujo sanguíneo mesentérico, inducido por lipopolisacáridos, pero sin afectar al flujo sanguíneo renal ni al índice cardíaco Vease Cardelus y colaboradores *Ibid*, *Eur J Pharmacol*

El fallo renal es la incapacidad del riñón para excretar metabolitos a niveles normales en plasma en condiciones de carga normal, o la incapacidad de retener eritrocitos en condiciones de ingestión normal En la forma aguda, está marcado por uremia y usualmente por oliguria o anuria junto con hipercaliemia y edema pulmonar Sobre la base de las actividades antes descritos de los agentes inhibidores selectivos de las PDE4, se ha demostrado que los agentes inhibidores selectivos de las PDE4 son utiles en el tratamiento de un fallo renal, especialmente de un fallo renal agudo Véase Begany y colaboradores, "Inhibition of Type IV phosphodiesterase by Ro-20-1724 attenuates endotoxin-induced acute renal failure" (La inhibición de las fosfodiesterasas del Tipo IV por Ro-20-1724 atenua el fallo renal agudo inducido por endotoxinas), *J Pharmacol Exp Thera* 278 37-41, 1996 Véase también el documento WO 98/00135 cedido a la Universidad de Pittsburgh Correspondientemente, los compuestos de Fórmula (1 0 0) son utiles en el tratamiento de un fallo renal, particularmente de un fallo renal agudo

Una caquexia es un estado profundo y señalado de trastorno constitucional caracterizado por mala salud y malnutrición generales La caquexia puede ser el resultado final de un cierto numeros de factores causantes, p ej , puede resultar de una infección causada por uno cualquiera de cierto numero de organismos o microorganismos unicelulares inclusive bacterias, virus, hongos y protozoos La caquexia maláric a es representativa y comprende un grupo de signos de una naturaleza crónica, que resultan de ataques antecedentes de malaria grave, siendo los signos principales anemia piel cetrina, esclerótica amarilla, esplenomegalia y hepatomegalia Otra causa de caquexia es la privación o el deterioro de funciones humorales u orgánicas de otro tipo, p ej , la caquexia de hipófisis comprende una sucesión de síntomas que resultan de la privación total de la función de la glándula pituitaria, inclusive tisis, pérdida de la función sexual, atrofia de las glándulas dianas pituitarias, bradicardia, hipotermia, apatía y coma La caquexia urémica es una caquexia asociada con otros síntomas sistémicos de fallo renal avanzado La caquexia cardíaca comprende una extenuación debida a una enfermedad cardiaca La caquexia suprarrenal o enfermedad de Addison, es un trastorno caracterizada por hipotensión, pérdida de peso, anorexia y debilidad, que es causada por una deficiencia en la hormona adrenocortical Es debida a una destrucción inducida por tuberculosis o autoinmunidad, de la corteza adrenal que da como resultado una deficiencia de aldosterona y cortisol

Una caquexia puede también ser el resultado de estados patológicos de diversos tipos La caquexia cancerosa comprende la condición extenuada y débil que se observa en casos de un tumor maligno Una caquexia puede ser también una consecuencia de una infección por un virus de la inmunodeficiencia humana (HIV) y comprende los síntomas que corrientemente se citan como el síndrome de inmunodeficiencia adquirida (SIDA) Los compuestos de Fórmula (1 0 0) son también utiles para tratar una caquexia de los diferentes tipos antes descritos, como resultado de su capacidad de proporcionar una regulación en sentido descendente o una inhibición de la liberación de TNF-α Los agentes inhibidores selectivos de las PDE4 del presente invento tienen un efecto marcado sobre la inhibición de la liberación de TNF-α a partir de células mononucleares de sangre periférica, después de que esas células hayan sido estimuladas con una amplia gama de mediadores La liberación del TNF-α está implicada o desempeña un cometido mediador en enfermedades o condiciones cuya etiología implica o comprende una liberación mórbida, es decir, insana, excesiva o sin regular, de TNF-α

Los compuestos inhibidores de las PDE4 de Fórmula (1 0 0) son utiles adicionalmente en el tratamiento de una infección, especialmente una infección causada por virus, en que dichos virus aumentan la producción de TNF-α en su hospedante, o en que dichos virus son sensibles a la regulación en sentido ascendente de TNF-α en su hospedante de manera tal que se ejerce un impacto desfavorable sobre su replicación u otras actividades vitales Dichos virus incluyen, p ej , los HIV-1, HIV-2 y HIV-3 citomegalovirus, CMV, los de influenza, los adenovirus, y los virus del Herpes, especialmente los de *Herpes zoster* y *Herpes simplex*

Los compuestos inhibidores de las PDE4 de Fórmula (1 0 0) son utiles adicionalmente en el tratamiento de infecciones causadas por levaduras y hongos, en que dichas levaduras y dichos hongos son sensibles a una regulación en sentido ascendente por el TNF-α o provocan una producción de TNF-α en su hospedante Una enfermedad particular que se puede tratar de esta manera es la meningitis fungica Los compuestos de Fórmula (1 0 0) proporcionan también efectos beneficiosos cuando se combinan con, es decir, se administran en conjunción con, otros fármacos selectos para el tratamiento de infecciones sistémicas causadas por levaduras y hongos Dichos fármacos selectos incluyen, pero no se limitan a polimixinas, p ej , Polimicina B, imidazoles, p ej , clotrimazol, econazol, miconazol y ketoconazol, triazoles, p ej , fluconazol e itranazol y anfotericinas, p ej , Anfotericina B y Anfotericina B liposomal Se pretende que el término "administración conjunta" como se usa en el presente contexto con referencia a los compuestos de Fórmula (1 0 0) y fármacos selectos para el tratamiento de infecciones sistémicas causadas por levaduras y hongos signifique e incluya (*a*) la administración simultánea de dicho(s) compuesto(s) y dicho(s) farmaco(s)

a un individuo cuando se formulan conjuntamente en una unica forma de dosificación (*b*) la administración sustancialmente simultánea de dicho(s) compuesto(s) y dichos fármaco(s) a un individuo cuando se formulan por separado unos de otros en formas de dosificación separadas y (*c*) la administración secuencial de dichos compuestos y fármacos a un individuo cuando se formulan por separado unos de otros y se administran consecutivamente con algun intervalo de tiempo importante entre ellos

8.12 Lesión del Hígado

Ademas de los efectos desfavorables antes descritos del TNF-α, éste también causa un fallo hepático en seres humanos, que es un fenomeno que se ha manifestado en cierto numero de modelos con animales Por ejemplo en un modelo agudo de fallo hepático mediado por celulas T, se ha mostrado que el rolipram administrado a razón de 0,1 a 10 mg/kg i p 30 minutos antes de la estimulación o bien con la concanavalina A o con la enterotoxina B de estafilococos reduce de manera importante las concentraciones en plasma de TNF-α y INF-γ mientras que también eleva de manera importante los niveles de IL-10 Véase Gantner y colaboradores, *J Pharmacol Exp Ther* **280** 53 1997 En este mismo estudio, se ha mostrado tambien que el rolipram suprime la liberación de IL-4 inducida por la concanavalina A Las actividades en plasma de las enzimas ALT, AST y SDH, especificas para el higado han sido también determinadas en este estudio, puesto que cualquier aumento en sus niveles podria indicar una destrucción masiva de células del hígado Se ha encontrado, que en el tratamiento previo de ratones inexpertos que reciben la concanavalina A, o ratones sensibilizados por una galactosamina, que reciben una mezcla de la galactosamina y la enterotoxina B de estafilococos, con rolipram a razón de 0,1 hasta 10 mg/kg i p el rolipram ha inhibido de un modo dependiente de la dosis las actividades de las enzimas de plasma antes mencionadas Correspondientemente, los compuestos de Fórmula (1 0 0) son utiles en el tratamiento de trastornos de células T tales como fallo del hígado

8 13 Hipertensión Pulmonar

Es conocido que la actividad de las fosfodiesterasas, que hidrolizan a los segundos mensajeros vasodilatadores, cAMP y cGMP, puede ser aumentada por una hipertensión pulmonar inducida por hipoxia (HPH) Una hipoxia es una reducción del suministro de oxigeno a un tejido hasta por debajo de niveles fisiológicos a pesar de una adecuada perfusión del tejido por la sangre La resultante hipertensión pulmonar está caracterizada por una presión aumentada a saber la sistólica por encima de 30 mm de Hg y la diastólica por encima de 12 mm de Hg, dentro de la circulación arterial pulmonar Usando un modelo que utiliza anillos de arterias pulmonares aisladas procedentes de

ratas normales y procedentes de ratas con hipertensión pulmonar inducida por hipoxia, se ha puesto de manifiesto que el agente inhibidor selectivo de las PDE4, rolipram, potencia las actividades relajantes del isoproterenol y de la forskolina El mismo efecto ha sido observado con la milrinona, que es un agente inhibidor selectivo de las PDE3, apoyando de este modo la inhibición tanto de las PDE3 como de las PDE4 con el fin de mejorar de manera significativa la relajacion de arterias pulmonares en una hipertensión pulmonar inducida por hipoxia Véase Wagner y colaboradores, *J Pharmacol Exp Ther* **282** 1850, 1997 Correspondientemente, los compuestos de Fórmula (1 0 0) son utiles en el tratamiento de una hipertensión pulmonar, especialmente de una hipertensión pulmonar inducida por hipoxia

8 14 Enfermedad de pérdida de hueso

La enfermedad con perdida de hueso, más comentemente citada como osteoporosis es una condición de baja masa ósea y rotura microarquitectural que da como resultado fracturas con traumas mínimos La osteoporosis secundaria es debida a una enfermedad o debilidad sistémica o a medicaciones tales con glucocorticoides La osteoporosis, tal como se ha afirmado deberá ser considerada como que comprende dos condiciones la osteoporosis del Tipo I que es una pérdida de hueso trabecular debida a una deficiencia en estrogenos durante la menopausia, y la osteoporosis del Tipo II que es una pérdida de hueso cortical y trabecular, debida a una ineficacia de la remodelación a largo plazo una inadecuación dietetica y una activación del eje del paratiroides con la edad Los reguladores primarios de la masa ósea de adultos incluyen la actividad física, un estado endocrino reproductivo, y la ingestión de calcio, y el mantenimiento óptimo del hueso requiere suficiencia en la totalidad de los tres sectores

Se ha demostrado que los agentes inhibidores selectivos de las PDE4 son utiles en el tratamiento beneficioso de una enfermedad de pérdida de hueso, particularmente de osteoporosis El efecto de la denbufilina sobre la pérdida de hueso en ratas preñadas Walker 256/S y sobre la formación de nódulos mineralizados y la formación de células similares a osteoclastos ha sido estudiado en sistemas de cultivo de médula ósea Se ha descubierto que las administraciones orales en serie de denbufilina inhiben la disminución en la densidad de minerales óseos de fémures procedentes de ratas preñadas Walker 256/S, y restauran la masa ósea y el numero de osteoclastos y osteoblastos por superficie trabecular en la metáfisis del fémur Se ha encontrado también que la administración de denbufilina da como resultado un aumento en el numero de nódulos mineralizados y una disminución en el numero de células similares a osteoclastos en el sistema de cultivo de médula ósea *in vitro* Estos efectos beneficiosos son específicos para la inhibición de las PDE4 y son imitados por el dibutiril-

cAMP, demostrando que la isozima PDE4 desempeña un cometido importante en la reorganización del hueso a través del cAMP Véanse las citas de Miyamoto y colaboradores *Biochem Pharmacol* 54 613, 1997, Waki y colaboradores, "Effects of XT-44, a phosphodiesterase 4 inhibitors in osteoblastgenesis and osteoclastgenesis in culture and its therapeutic effects in rat osteopenia models" (Efectos del XT-44 que es un agente inhibidor de las fosfodiesterasas 4 en la génesis de osteoblastos y en la génesis de osteoclastos en cultivo y sus efectos terapéuticos en modelos de osteopenia de rata), *Jpn J Pharmacol* 79 477-483, 1999, y el documento JP 9169665 cedido a Miyamoto (1997) Consiguientemente, los agentes inhibidores selectivos de las PDE4 de Fórmula (1 0 0) son utiles en el tratamiento de enfermedades que implican una pérdida de hueso especialmente la osteoporosis

8 15 Trastornos del Sistema Nervioso Central

El agente inhibidor selectivo de las PDE4, rolipram, fue desarrollado inicialmente como un agente antidepresivo y continua siendo estudiado en pruebas clínicas para esa indicación Además se ha demostrado que los agentes inhibidores selectivos de las PDE4 proporcionan efectos beneficiosos en otros trastornos del sistema nervioso central, inclusive la enfermedad de Parkinson, Hulley y colaboradores en "Inhibitors of Type IV phosphodiesterase reduce the toxicity of MPTP in substantia nigra neurons *in vivo*" (Los agentes inhibidores de fosfodiesterasas del Tipo IV reducen la toxicidad del MPTP en neuronas de sustancia negra *in vivo*), *Eur J Neurosol* 7 2431-2440, 1995, así como el perjuicio del aprendizaje y de la memoria, Egawa y colaboradores, "Rolipram and its optical isomers, phosphodiesterase 4 inhibitors, attenuate the scopolamine-induced impairments of learning and memory in rats" (El rolipram y sus isómeros ópticos, agentes inhibidores de las fosfodiesterasas IV, atenuan los perjuicios del aprendizaje y de la memoria en ratas, inducidos por escopolamina), *Jpn J Pharmacol* 75 275-281, 1997, Imanishi y colaboradores "Ameliorating effects of rolipram on experimentally induced impairments of learning and memory in rodents" (Efectos mejoradores del rolipram sobre los perjuicios del aprendizaje y de la memoria en roedores, inducidos experimentalmente), *Eur J Pharmacol* 321 273-278, 1997, y Barad y colaboradores, "Rolipram, a Type IV-specific phosphodiesterase inhibitors, facilitates the establishment of long-lasting long-term potentiation and improves memory" (El rolipram, que es un agente inhibidor de las fosfodiesterasas específico para el Tipo IV, facilita el establecimiento de una potenciación a largo plazo y de larga duración y mejora la memoria), *Proc Natl Acad Sci USA* 95 15020-15025, 1998

El uso de los agentes inhibidores de las PDE4 para tratar la discinesia tardía y la dependencia respecto de fármacos también se ha descrito en el sector de la tecnología,

en los documentos WO 95/28177 y JP 92221423 (1997) ambos cedidos a Meiji Seika Kaisha Ltd Se ha encontrado que la isozima PDE4 desempeña un cometido principal para controlar la biosíntesis de dopamina en neuronas mesencefálicas correspondientemente, los agentes inhibidores de las PDE4 son utiles en el tratamiento de trastornos y de enfermedades que se asocian con, o se median por dopamina dentro y alrededor de las neuronas mesencefálicas Yamashita y colaboradores, "Rolipram a selective inhibitor of phosphodiesterase Type 4, pronouncedly enhances the forskolin-induced promotion of dopamine biosynthesis in primary cultured rat mesencephalic neurons" (El rolipram, que es un agente inhibidor selectivo de las fosfodiesterasas del Tipo 4, intensifica pronunciadamente la promoción inducida por forskolina de la biosintesis de dopamina en neuronas mesencefálicas de ratas cultivadas primarias) *Jpn J Pharmacol* 75 91-95 1997

Los compuestos inhibidores de las PDE4 con la Fórmula (1 0 0) son adicionalmente utiles en el tratamiento de la demencia arterioesclerótica y de la demencia subcortical La demencia arterioesclerótica, también denominada demencia vascular y demencia por multiples infartos es una demencia con un transcurso deteriorante escalonado en la forma de una serie de pequeños ictus, y con una distribución irregular de deficiencias neurológicas causadas por una enfermedad cerebrovascular Las demencias subcorticales son causadas por lesiones que afectan a las estructuras cerebrales subcorticales y se caracterizan por una pérdida de memoria con lentitud en el tratamiento de la información o en la producción de respuestas intelectuales Se incluyen las demencias que acompañan a la corea de Huntington, a la enfermedad de Wilson, a la parálisis agitante y a las atrofias talámicas

8 16 Otras aplicaciones terapéuticas

Se ha demostrado que los agentes inhibidores de las PDE4 son utiles en el tratamiento de una lesion por isquemia y reperfusión Block y colaboradores, "Delayed treatment with rolipran protects against neuronal damage following global ischemia in rats" (Un tratamiento retrasado con rolipram protege contra el deterioro neuronal después de una isquemia global en ratas), *NeuroReport* 8 3829-3832, 1997, y Belayev y colaboradores, "Protection against blood-brain barrier disruption in focal cerebral ischemia by the Type 4 phsophodiesterase inhibitor BBB022 a quantitative study" (La protección contra la rotura de la barrera hematoencefálica en una isquemia cerebral focal por el agente inhibidor de las fosfodiesterasas del Tipo IV BBB022 un estudio cuantitativo), *Brain Res* 787 277-285, 1998, en el tratamiento de una diabetes autoinmunitaria Liang y colaboradores, "The phosphodiesterase inhibitors pentoxifylline and rolipram prevent diabetes in NOD mice" (Los agentes inhibidores de fosfodiesterasas

pentoxifilina y rolipram previenen la diabetes en ratones NOD), *Diabetes* 47 570-575, 1998 en el tratamiento de la autoinmunidad retinal, Xu y colaboradores, "Protective effect of the Type IV phosphodiesterase inhibitor rolipram in EAU protection is independent of the IL-10-inducing activity" (Efecto protector del agente inhibidor de fosfodiesterasas del Tipo IV rolipram en EAU la protección es dependiente de la actividad inductora de IL-10) *Invest Ophthalmol Visual Sci* 40 942-950, 1999 en el tratamiento de una leucemia linfocítica crónica, Kim y Lener, "Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic agent in chronic lymphocytic leukemia" (la fosfodiesterasa de monofosfato cíclico de adenosina del Tipo 4 como un agente terapeutico en una leucemia linfocítica crónica), *Blood* 92 2484-2494, 1998, en el tratamiento de infecciones causadas por un HIV, Angel y colaboradores, "Rolipram, a specific Type IV phosphodiesterase inhibitor, is a potent inhibitor of HIV-1 replication" (El rolipram, que es un agente inhibidor especifico de las fosfodiesterasas del Tipo IV, es un potente agente inhibidor de la replicación de HIV-1), *AIDS* 9 1137-1144, 1995 y Navarro y colaboradores "Inhibition of phosphodiesterase Type IV suppresses human immunodeficiency virus Type 1 replication and cytokine production in primary T cells involvement of NF-kappaB and NFAT" (La inhibicion de las fosfodiesterasas del Tipo IV supnme la replicación del virus de inmunodeficiencia humana del Tipo 1 y la producción de citocinas en células T primarias, implicación de NF-kappaB y NFAT), *J Virol* 72 4712-4720, 1998, en el tratamiento de lupus entematoso, documento JP 10067682 (1998) cedido a Fujisawa Pharm Co Ltd , en el tratamiento de la enfermedad del rifion y los uréteres, documento DE 4239755 (1994) cedido a Schering AG, en el tratamiento de trastornos urogenitales y gastrointestinales, documento WO 94/06423 cedido a Schering AG, y en el tratamiento de enfermedades de la próstata, WO 99/02161, cedido a Porssmann y documento WO 99/02161 cedido a Stief

De acuerdo con las descripciones anteriores se entenderá que los compuestos de Fórmula (1 0 0) son utiles en el tratamiento beneficioso de uno o más cualesquiera miembros seleccionados entre el grupo que consta de las siguientes enfermedades, trastornos y condiciones

- un asma de cualquier tipo, etiología o patogénesis, o un asma que es un miembro seleccionado entre el grupo que consta de asma atópico, asma no atópico, asma alérgico, asma atópico, bronquial, mediado por IgE, asma bronquial, asma esencial, asma verdadero, asma intrinseco causado por perturbaciones patofisiológicas, asma extrinseco causado por factores ambientales asma esencial de causa desconocida o no evidente, asma no atópico, asma bronquítico asma enfisematoso, asma inducido por ejercicio, asma ocupacional asma infeccioso causado por una infección bacteriana, fungica, protozoaria o vinca, asma no alérgico, asma incipiente, síndrome de niño que

resuella con dificultad

- constricción crónica o aguda de los bronquios, bronquitis crónica, obstrucción de las vias respiratorias pequeñas y enfisema,

- enfermedades obstructivas o inflamatorias de las vías respiratorias de cualquier tipo, etiología o patogénesis o una enfermedad obstructiva o inflamatoria de las vias respiratorias que es un miembro seleccionado entre el grupo que consta de asma, neuomoconiosis, neumonia eosinofilica crónica, enfermedad pulmonar obstructiva crónica (COPD), una COPD que incluye bronquitis crónica, enfisema pulmonar o disnea asociada con ella, una COPD que está caracterizada por una obstrucción irreversible y progresiva de las vías respiratorias sindrome de ahogo respiratorio de adultos (ARDS), y exacerbacion de la hiper-reactividad de las vías respiratorias consiguiente a otra terapia con fármacos,

- una neumoconiosis de cualquier tipo, etiología o patogénesis, o una neumoconiosis que es un miembro seleccionado entre el grupo que consta de aluminosis o enfermedad de obreros causada por bauxita, antracosis o asma de mineros asbestosis o asma de instaladores de vapor de agua, calicosis o enfermedad del pedernal, ptilosis causada por una inhalación del polvo fino procedente de las plumas de avestruz, siderosis causada por la inhalacion de particulas de hierro, silicosis o enfermedad de los amoladores, bisinosis o asma causada por el polvo de algodón y neumoconiosis causada por talco,

- una bronquitis de cualquier tipo etiología o patogénesis, o una bronquitis que es un miembro seleccionado entre el grupo que consta de bronquitis aguda bronquitis laringotraqueal aguda, bronquitis araquidica (del cacahuete), bronquitis catarral, bronquitis crupal o garrotillo bronquitis seca, bronquitis asmática infecciosa, bronquitis productiva bronquitis causada por estafilococos o estreptococos, y bronquitis vesicular,

- una bronquiectasia de cualquier tipo, etiología o patogénesis, o una bronquitiectasia que es un miembro seleccionado entre el grupo que consta de bronquiectasia cilíndrica, bronquiectasia saculada, bronquiectasia fusiforme, bronquiectasia capilar bronquiectasia cistica, bronquiectasia seca, y bronquiectasia folicular

- rinitis alérgica estacional o rinitis alérgica perenne, o una sinusitis de cualquier tipo, etiología o patogénesis o una sinusitis que es un miembro seleccionado entre el grupo que consta de sinusitis purulenta o no purulenta, sinusitis aguda o crónica, y sinusitis del hueso etmoides frontal maxilar o esfenoides,

- una artritis reumatoide de cualquier tipo etiología o patogénesis, o una artritis reumatoide que es un miembro seleccionado entre el grupo que consta de artritis aguda, artritis gotosa aguda artritis inflamatoria crónica, artritis degenerativa, artritis infecciosa,

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artritis de Lyme artritis proliferante, artritis psonásica y artritis vertebral,

- gota, así como fiebre y dolor asociados con una inflamación,

- una enfermedad relacionada con eosinófilos de cualquier tipo, etiología o patogénesis, o una enfermedad relacionada con eosinófilos que es un miembro seleccionado entre el grupo que consta de eosinofilia, eosinofilia por infiltración pulmonar, síndrome de Loffler, neumonía eosinofílica crónica, eosinofilia pulmonar tropical, aspergilosis bronconeumónica, aspergiloma, granulomas que contienen eosinófilos, angiitis granulomatosa alergica o síndrome de Churg-Strauss, poliarteritis nodosa (PAN) y vasculitis necrotizante sistémica,

- dermatitis atópica, o dermatitis alérgica, o eczema alérgico o atópico,

- una urticaria de cualquier tipo, etiología o patogénesis o una urticaria que es un miembro seleccionado entre el grupo que consta de urticaria mediada por inmunidad urticaria mediada por el complemento, urticaria inducida por material urticariogénico, urticaria inducida por agentes físicos urticaria inducida por estrés urticaria idiopática, urticaria aguda urticaria crónica, angioedema, urticaria colinérgica, urticaria al frío en la forma dominante autosómica o en la forma adquirida, urticaria por contacto, urticaria gigante, y urticaria papulosa,

- una conjuntivitis de cualquier tipo, etiología o patogénesis, o una conjuntivitis que es un miembro seleccionado entre el grupo que consta de conjuntivitis actínica, conjuntivitis catarral aguda, conjuntivitis contagiosa aguda conjuntivitis alérgica conjuntivitis atópica conjuntivitis catarral crónica, conjuntivitis purulenta, y conjuntivitis vernal,

- una uveítis de cualquier tipo, etiología o patogénesis, o una uveítis que es un miembro seleccionado entre el grupo que consta de una inflamación de la totalidad o una parte de la uvea, uveítis anterior, iritis, ciclitis, iridociclitis uveitis granulomatosa, uveitis no granulomatosa, uveítis facoantigenica, uveitis posterior, coroiditis, y coriorretinitis,

- psoriasis,

- una esclerosis multiple de cualquier tipo, etiología o patogénesis, o una esclerosis multiple que es un miembro seleccionado entre el grupo que consta de esclerosis multiple progresiva primaria, y esclerosis multiple en remisión y en relapso

- enfermedades autoinmunitarias/inflamatorias de cualquier tipo, etiología o patogénesis, o una enfermedad autoinmunitaria/inflamatoria que es un miembro seleccionado entre el grupo que consta de trastornos hematológicos autoinmunitarios anemia hemolítica, anemia aplásica anemia de glóbulos rojos puros purpura trombocitopénica idiopática, lupus eritematoso sistémico policondritis, esclerodermia, granulomatosis de Wegner, dermatomiositis, hepatitis activa crónica, miastenia grave, síndrome de Stevens-Johnson, psilosis idiopática enfermedades inflamatorias

autoinmunitarias de los intestinos, colitis ulcerativa, enfermedad de Crohn, oftalmopatía endocrina enfermedad de Grave, sarcoidosis, alveolitis neumonitis por hipersensibilidad crónica cirrosis biliar primaria, diabetes juvenil o diabetes mellitus del tipo I, uveítis anterior uveítis granulomatosa o posterior, queratoconjuntivitis seca, queratoconjuntivitis epidemica, fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial fibrosis pulmonar idiopática, fibrosis cística, artritis psoriásica, glomerulonefritis con y sin síndrome nefrótico, glomerulonefritis aguda, síndrome nefrótico idiopatico, nefropatía por cambios mínimos, enfermedades inflamatorias/hiperproliferativas de la piel, psoriasis, dermatitis atópica, dermatitis por contacto, dermatitis alérgica por contacto, pénfigo familiar benigno pénfigo eritematoso, pénfigo foliáceo, y pénfigo vulgar,

- prevención del rechazo alogeneico de un injerto como continuación del transplante de un órgano

- una enfermedad inflamatoria de los intestinos (IBD) de cualquier tipo, etiología o patogénesis o una enfermedad inflamatoria de los intestinos que es un miembro seleccionado entre el grupo de consta de colitis ulcerativa (UC), colitis colagenosa, colitis poliposa, colitis transmural, y enfermedad de Crohn (CD),

- un choque séptico de cualquier tipo, etiología o patogénesis, o un choque séptico que es un miembro seleccionado entre el grupo que consta de fallo renal, fallo renal agudo, caquexia, caquexia malárica, caquexia de la hipofisis, caquexia urémica, caquexia cardíaca caquexia suprarrenal o enfermedad de Addison, caquexia cancerosa, y caquexia como consecuencia de una infección causada por un virus de la inmuno-deficiencia humana (HIV),

- lesión del hígado,

- hipertensión pulmonar, e hipertensión pulmonar inducida por hipoxia

- enfermedades con pérdida de hueso, osteoporosis primaria, y osteoporosis secundaria,

- trastornos del sistema nervioso central de cualquier tipo, etiología o patogénesis, o un trastorno del sistema nervioso central que es un miembro seleccionado entre el grupo que consta de una depresión, la enfermedad de Parkinson, perjuicio del aprendizaje y de la memoria, discinesia tardía, dependencia de drogas o fármacos, demencia arterioesclerótica, y demencias que acompañan a la corea de Huntington, la enfermedad de Wilson, parálisis agitante, y atrofias del tálamo,

- una infección, especialmente una infección causada por virus, en que dichos virus aumentan la producción de TNF-α en su hospedante, o en que dichos virus son sensibles a la regulación creciente del TNF-α en su hospedante de manera tal que se impacta desfavorablemente sobre su replicación u otras actividades vitales, inclusive un virus que es un miembro seleccionado entre el grupo que consta de HIV-1, HIV-2 y

HIV-3 citomegalovirus CMV, influenza los adenovirus y los virus de Herpes inclusive los de *Herpes zoster* y *Herpes simplex*

- infecciones causadas por levaduras y hongos, en que dichas levaduras y dichos hongos son sensibles a la regulación creciente por TNF-α o provocan la producción de TNF-α en su hospedante, p ej meningitis fungica, particularmente cuando se administra en conjunción con otros fármacos selectos para el tratamiento de infecciones sistémicas causadas por levaduras y hongos, inclusive, pero sin limitarse a polimixinas p ej , Polimicina B, imidazoles, p ej , clotrimazol, econazol, miconazol y ketoconazol, triazoles, p ej , fluconazol e itranazol y anfotericinas, p ej , Anfotericina B y Anfotericina B liposomal,

- lesión por isquemia y reperfusión diabetes autoinmunitaria, autoinmunidad de la retina leucemia crónica de linfocitos, infecciones causadas por un HIV lupus entematoso, enfermedad de riñones y uréteres, trastornos urogenitales y gastrointestinales y enfermedades de la próstata

DESCRIPCIÓN DETALLADA DEL INVENTO

9 0 Combinación con otros farmacos y terapias

El presente invento considera realizaciones en las que un compuesto de Fórmula (1 0 0) es el unico agente terapéutico que se emplea en un método de tratamiento aqui descnto ya sea usado a solas o más corrientemente de modo conjunto con un vehiculo farmacéuticamente aceptable para producir una forma apropiada de dosificación para su administración a un paciente Otras realizaciones del presente invento consideran un a combinación de un compuesto de Fórmula (1 0 0) juntamente con uno o más agentes terapéuticos adicionales que se ha(n) de administrar conjuntamente a un paciente para obtener algun resultado terapeutico final particularmente deseado El segundo, etc , agente terapéutico puede ser también uno o mas compuestos de Fórmula (1 0 0) o bien uno o más agentes inhibidores de las PDE4 conocidos en el sector tecnológico y descntos con detalle en el presente texto Más típicamente, el segundo etc agente terapéutico se seleccionara entre una clase diferente de agentes terapéuticos Estas selecciones se describen seguidamente con detalle

Como se usan en el presente contexto, se pretende que los términos "administración conjunta", "conjuntamente administrados" y "en combinación con", al referirse a los compuestos de Fórmula (1 0 0) y uno o más agentes terapéuticos distintos signifiquen, y se refieran e incluyan lo siguiente (*a*) la administración simultánea de dicha combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente que necesita del tratamiento, cuando dichos componentes se formulan de modo conjunto en una unica forma de dosificación que libera dichos componentes sustancialmente al mismo tiempo a dicho paciente (*b*) la administración sustancialmente simultánea de dicha combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente que necesita del tratamiento cuando dichos componentes se formulan por separado unos de otros en formas de dosificación separadas que se ingieren sustancialmente al mismo tiempo por dicho paciente, después de lo cual dichos componentes son liberados sustancialmente al mismo tiempo a dicho paciente (*c*) la administración secuencial de dicha combinación de compuestos y agentes terapéuticos a un paciente que necesita del tratamiento, cuando dichos componentes son formulados por separado unos de otros en formas de dosificación separadas que se ingieren en momentos consecutivos por dicho paciente con un intervalo de tiempo importante entre cada ingestión, después de lo cual dichos componentes son liberados en momentos sustancialmente diferentes a dicho paciente, y (*d*) la administración secuencial de dicha combinación de compuestos y agentes terapéuticos a un paciente que necesita del tratamiento, cuando dichos componentes son formulados conjuntamente en una unica forma de dosificacion que libera dichos

componentes de una manera controlada despues de lo cual éstos son ingeridos concurrente, consecutiva y/o solapadamente al mismo tiempo y/o en diferentes momentos por dicho paciente

9 1 Con agentes inhibidores de la biosíntesis de leucotrienos Agentes inhibidores de 5-lipoxigenasa (5-LO) y agentes antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP)

Uno o más compuestos de Fórmula (1 0 0) se usa(n) en combinación con agentes inhibidores de la biosíntesis de leucotrienos, es decir agentes inhibidores de 5-lipoxigenasa y/o agentes antagonistas de una proteina activadora de 5-lipoxigenasa, para formar realizaciones del presente invento Como ya se ha advertido anteriormente, la 5-lipoxigenasa (5-LO) es una entre dos grupos de enzimas que metabolizan al ácido araquidónico, siendo el otro grupo las ciclooxigenasas, COX-1 y COX-2 La proteína activadora de 5-lipoxigenasa es una proteína que fija a un araquidonato, fijada a una membrana, con un tamaño de 18 kDa que estimula la conversión del ácido araquidónico celular por la 5-lipoxigenasa El ácido araquidónico es convertido en ácido 5-hidroperoxi-eicosatetraenoico (5-HPETE) y esta ruta conduce finalmente a la producción de leucotrienos inflamatorios, consiguientemente, el bloqueo de la proteína activadora de 5-lipoxigenasas o de la propia enzima 5-lipoxigenasa proporciona una diana deseable para inferir beneficiosamente en tal ruta Uno de tales agentes inhibidores de 5-lipoxigenasa es el zileuton representado por la Fórmula (0 1 14), que se puede encontrar tanto en el texto anterior como en el que sigue Entre las clases de agentes inhibidores de la síntesis de leucotrienos que son utiles para formar combinaciones terapéuticas con los compuestos de Fórmula (1 0 0), están los siguientes

(*a*) agentes activos en redox inclusive N-hidroxi-ureas, ácidos N-alquil-hidroxámicos, selenita hidroxi-benzofuranos, hidroxil-aminas, y catecoles, véase Ford-Hutchinson y colaboradores, "5-Lipoxygenase" (5-lipoxigenasa), *Ann Rev Biochem* **63** 383-417, 1994, Weitzel y Wendel, "Selenoenzymes regulate the activity of leukocyte 5-lipoxygenase via the peroxide tone" (Las selenoenzimas regulan la actividad de 5-lipoxigenasa de leucocitos a través del tono de peróxidos), *J Biol Chem* **268** 6288-92 1993, Björnstedt y colaboradores, "Selenite incubated with NADPH and mammalian thioredoxin reductase yields selenide, which inhibits lipoxygenase and changes the electron spin resonance spectrum of the active site iron" (La selenita incubada con NADPH y la reductasa de tiorredoxina de mamíferos produce seleniuros que inhiben la lipoxigenasa y cambian el espectro de resonancia por espin de electrones en el hierro de sitios activos), *Biochemistry* **35** 8511-6, 1996, y Stewart y colaboradores, "Structure-activity relationships of N-hydroxyurea 5-lipoxygenase inhibitors" (Relaciones de

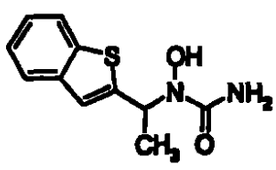
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estructura y actividad de los agentes inhibidores 5-lipoxigenasa N-hidroxi-ureas) *J Med Chem* 40 1955-68, 1997,

(*b*) se ha encontrado que los agentes alquilantes y los compuestos que reaccionan con grupos SH inhiben la síntesis de leucotrienos *in vitro* véase Larsson y colaboradores, "Effects of 1-chloro-2,4,6-trinitrobenzene on 5-lipoxygenase activity and cellular leukotriene synthesis" (Efectos del 1-cloro-2,4,6-trinitro-benceno sobre la actividad de 5-lipoxigenasa y síntesis de leucotrienos celulares), *Biochem Pharmacol* 55 863-71, 1998, y

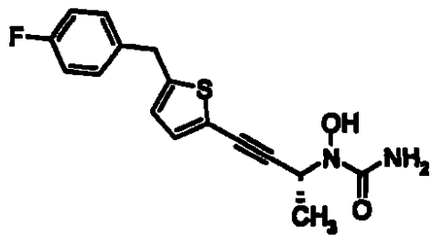
(*c*) los agentes inhibidores competitivos de 5-lipoxigenasa, basados en estructuras de tiopirano-indoles y metoxialquil-tiazoles, que pueden actuar como agentes inhibidores no redox de 5-lipoxigenasa, véase Ford-Hutchinson y colaboradores, *Ibid*, y Hamel y colaboradores, "Substituted (pyridylmethoxy)naphthalenes as potent and orally active 5-lipoxygenase inhibitors - synthesis, biological profile, and pharmacokinetics of L-739,010" (Los (piridilmetoxi)naftalenos sustituidos como agentes inhibidores de 5-lipoxigenasa potentes y activos por vía oral - síntesis, perfil biológico y condiciones farmacocinéticas del L-739 010), *J Med Chem* 40 2866-75, 1997

La observación de que el hidroxamato de araquidonoílo inhibe a la 5-lipoxigenasa ha conducido al descubrimiento de agentes inhibidores de 5-lipoxigenasa selectivos que son clínicamente utiles, tales como los derivados de N-hidroxi-urea zileuton y ABT-761, representados por las Formulas (0 1 14) y (5 2 1)



Zileuton

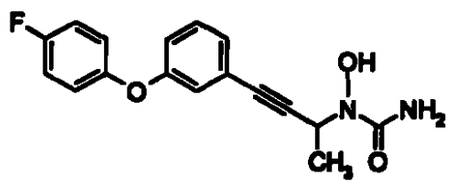
(0 1 14)



ABT-761

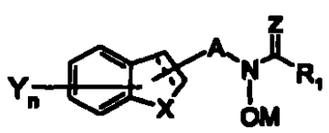
(5.2 1)

Otro compuesto del tipo de N-hidroxi-urea es el fenleuton (Abbott-76745) que está representado por la Fórmula (5 2 2)



Fenleuton (5.2.2)

El zileuton esta cubierto por la patente de los EE UU 4 873 259 (de Summers y colaboradores) cedida a Abbott Laboratories que describe compuestos inhibidores de lipoxigenasa que contienen indol, benzofurano y benzotiofeno, que se pueden representar por la Fórmula (5 2 3)



(5.2.3)

en la que R_1 es H alquilo (C_1-C_4), alquenilo (C_2-C_4), o NR_2R_3 en que R_2 y R_3 son H, alquilo (C_1-C_4) ó OH, X es O, S, SO_2, ó NR_4 en que R_4 es H, alquilo (C_1-C_8), alcanoilo (C_1-C_8), aroilo, o alquil-sulfonilo A es alquileno (C_1-C_8), o alquenileno (C_2-C_8), n es 1-5, e Y es H, halo, OH, CN, alquilo sustituido con halo, alquilo (C_1-C_{12}), alquenilo (C_2-C_{12}), alcoxi (C_1-C_{12}), cicloalquilo (C_3-C_8), tioalquilo (C_1-C_8), arilo, ariloxi aroilo, aril-alquilo (C_1–C_{12}), aril-alquenilo (C_2-C_{12}) aril-alcoxi (C_1-C_{12}), aril-tio-alcoxi (C_1-C_{12}) o derivados sustituidos de arilo, ariloxi ariloilo, aril-alquilo (C_1-C_{12}), aril-alquenilo (C_2-C_{12}) aril-alcoxi (C_1-C_{12}), aril-tio-alcoxi (C_1-C_{12}), en que dicho sustituyente es halo, NO_2, CN, o alquilo sustituido con alquilo o alcoxi (C_1-C_{12}) y halo, Z es 0 ó S, y M es H, un catión farmacéuticamente aceptable, aroilo, o alcanoilo (C_1-C_{12})

Compuestos afines se describen en los documentos US 4 769 387 (de Summers y colaboradores) US 4 822 811 (de Summers), US 4 822 809 (de Summers y Stewart), US 4 897 422 (de Summers), US 4 992 464 (de Summers y colaboradores) y US 5 250 565 (de Brooks y Summers), cada uno de los cuales se incorpora a la presente por su referencia en su totalidad, como si hubieran sido expuestos totalmente en el presente texto

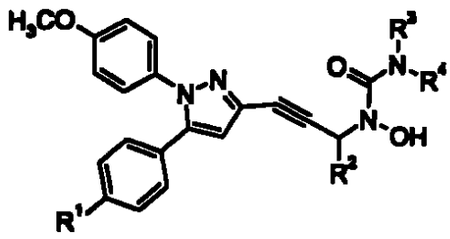
El zileuton o cualquiera de sus derivados antes descritos se combinan con los compuestos de Fórmula (1 0 0) para formar realizaciones del presente invento

El fenleuton se describe en los documentos US 5 432 194 US 5 446 062, US 5 484 786 US 5 559 144 US 5 616 596, US 5 668 146, US 5 668 150, US 5 843 968,

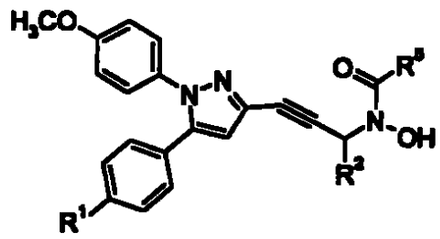
US 5 407 959, US 5 426 111 US 5 446 055 US 5 475 009 US 5 512 581, US 5 516 795 US 5 476 873, US 5 714 588 US 5 783 586 US 5 399 699 US 5 420 282 US 5 459 150 y US 5 506 261 cada uno de los cuales se incorpora a la presente por su referencia en su totalidad como si hubieran sido expuestos totalmente en el presente texto

Descripciones adicionales de dichos agentes inhibidores de 5-lipoxigenasa del tipo de N-hidroxi-urea y compuestos relacionados en la síntesis de leucotrienos inflamatorios se pueden encontrar en los documentos WO 95/30671, WO 96/02507, WO 97/12865, WO 97/12866, WO 97/12867, WO 98/04555 y WO 98/14429

La tepoxalina es un doble agente inhibidor de COX/5-LO con una actividad *in vivo* de corta vida, que ha conducido al desarrollo de dos series de compuestos híbridos, que son N-hidroxi-ureas y ácidos hidroxámicos de Fórmulas (5 2 4) y (5 2 5), respectivamente



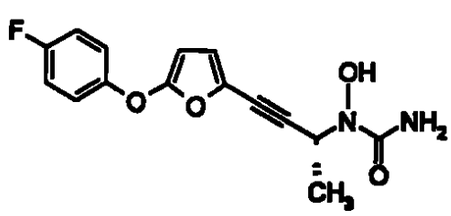
(5 2.4)



(5.2 5)

en las que R^1 hasta R^4 son H Cl CH_3 etilo, *iso*-propilo o *n*-propilo, o R^3 y R^4 conjuntamente son $(CH_2)_3$ ó $(CH_2)_2O(CH_2)_2$, y R^5 es metilo, etilo, *iso*-propilo, metoxi, trifluorometilo, clorometilo etil-propionato fenilo, 2-furilo 3-piridilo o 4-piridilo Véase Connolly y colaboradores "N-Hydroxyurea and hydroxamic acid inhibitors of cyclooxygenase and 5-lipoxygenase' (Agentes inhibidores de ciclooxigenasa y 5-lipoxigenasa del tipo de N-hidroxi-ureas y acidos hidroxámicos), *Bioorganic & Medicinal Chemistry Letters* 9 979-984 1999

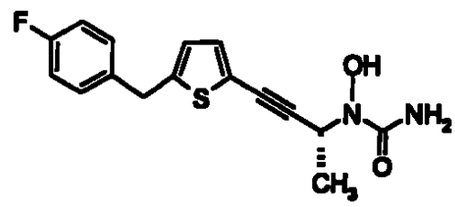
Otro compuesto del tipo de N-hidroxi-urea es el Abbott-79175 que está representado por la Fórmula (5 2 6)



Abbott-79175 (5.2 6)

El Abbott-79175 tiene una duracion de la accion mas larga que la del zileuton Brooks y colaboradores, *J Pharm Exp Therapeut* **272** 724 1995

Todavia otro compuesto de N-hidroxi-urea es el Abbott-85761 que está representado por la Fórmula (5 2 7)

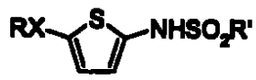


Abbott-85761 **(5 2 7)**

El Abbott-85761 es suministrado a los pulmones mediante administración por aerosoles de una formulación homogénea físicamente estable y casi monodispersa Gupta y colaboradores, "Pulmonary delivery of the 5-lipoxygenase inhibitor, Abbott-85761, in beagle dogs" (Suministro pulmonar del agente inhibidor de 5-lipoxigenasa, Abbott-85761, a perros beagle), *International Journal of Pharmaceutics* **147** 207-218, 1997

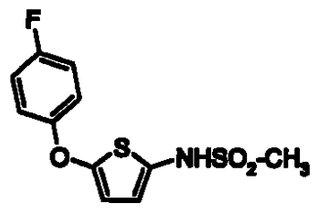
El fenleuton, el Abbott-79175, el Abbott-85761 o cualquiera de sus derivados antes descritos o el tepoxalin se combinan con los compuestos de Fórmula (1 0 0) para formar realizaciones del presente invento

A partir de la dilucidación de la ruta de biosíntesis de 5-LO ha habido un debate creciente en cuanto a si es más ventajoso inhibir a la enzima 5-lipoxigenasa o antagonizar a los receptores de leucotrienos (LT) peptídicos o no peptídicos Se estima que los agentes inhibidores de 5-lipoxigenasa son superiores a los agentes antagonistas de receptores de LT, puesto que los agentes inhibidores de 5-lipoxigenasa bloquean a la acción del pleno espectro de productos de 5-LO, mientras que los agentes antagonistas de LT producen efectos más estrechos No obstante, las realizaciones del presente invento incluyen combinaciones de los compuestos de Fórmula (1 0 0) con agentes antagonistas de LT así como con agentes inhibidores de 5-LO, como se describe seguidamente Los agentes inhibidores de 5-lipoxigenasa que tienen estructuras químicas que difieren de las clases de N-hidroxi-ureas y ácidos hidroxámicos, antes descritas, se usan también en combinación con los compuestos de Fórmula (1 0 0) para formar realizaciones adicionales del presente invento Un ejemplo de dicha clase diferente son las N-tiofeno(sustituido en posición 5)-2-alquil-sulfonamidas de Fórmula (5 2 8)



(5.2 8)

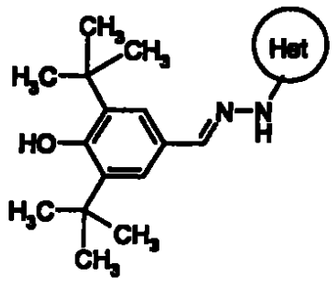
n la que X es O ó S R' es metilo, *iso*-propilo, *n*-butilo, *n*-octilo o fenilo, y R es *n*-pentilo, ciclohexilo, fenilo tetrahidro-1-naftilo, 1- ó 2-naftilo, o fenilo mono- o di-sustituido con Cl, F Br CH_3, OCH_3 SCH_3, SO_2CH_3, CF_3 o *iso*-propilo Un compuesto prefendo es el de la Fórmula (5 2 9)



(5.2 9)

Una descripción adicional de estos compuestos puede encontrarse en la cita de Beers y colaboradores, "N-(5-substituted)thiophene-2-alkylsulfonamides as potent inhibitors of 5-lipoxygenase" (N-tiofeno(sustituido en posición 5)-2-alquil-sulfonamidas como potentes agentes inhibidores de 5-lipoxigenasa) *Bioorganic & Medicinal Chemistry* 5(4) 779-786, 1997

Otra clase distinta de agentes inhibidores de 5-lipoxigenasa es la de las 2,6-di-*terc* -butil-fenol-hidrazonas descritas en la cita de Cuadro y colaboradores, "Synthesis and biological evaluation of 2,6-di-*tert*-butylphenol hydrazones as 5-lipoxygenase inhibitors" (Síntesis y evaluación biológica de 2,6-di-*terc* -butil-fenol-hidrazonas como agentes inhibidores de 5-lipoxigenasa) *Bioorganic & Medicinal Chemistry* 6 173-180, 1998 Los compuestos de este tipo son representados por la Fórmula (5 2 10)



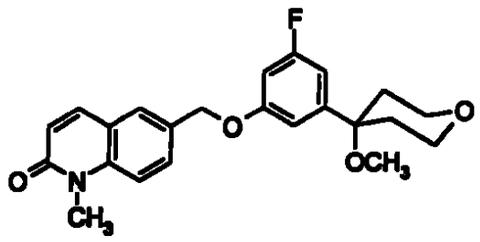
(5.2 10)

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en la que "Het" es benzoxazol-2-ilo, benzotiazol-2-ilo, pindin-2-ilo, pirazin-2-ilo, pirimidin-2-ilo, 4-fenil-pirimidin-2-ilo, 4,6-difenil-pirimidin-2-ilo 4-metil-pirimidin-2-ilo, 4,6-dimetil-pirimidin-2-ilo 4-butil-pirimidin-2-ilo, 4 6-dibutil-pirimidin-2-ilo y 4-metil-6-fenil-pirimidin-2-ilo

Las N-tiofeno(sustituido en posición 5)-2-alquil-sulfonamidas de Fórmula (5 2 8), o las 2,6-di-*terc* -butil-fenol-hidrazonas de Fórmula (5 2 10), o cualquiera de sus derivados antes descritos, se combinan con los compuestos de Fórmula (1 0 0) para formar realizaciones del presente invento

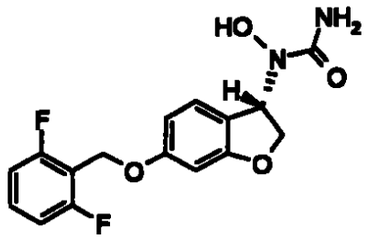
Otra clase distinta de agentes inhibidores de 5-lipoxigenasa es la de los metoxi-tetrahidropiranos a los que pertenece el Zeneca ZD-2138 El ZD-2138 está representado por la Fórmula (5 2 11)



(5.2 11)

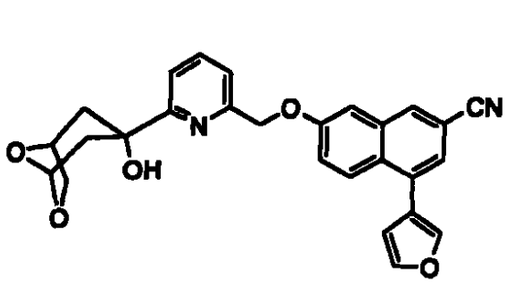
El ZD-2138 es altamente selectivo y altamente activo por via oral en cierto numero de especies y ha sido evaluado en el tratamiento del asma y de la artritis reumatoide por administracion oral Detalles adicionales concernientes al ZD-2138 y sus derivados se describen en la cita de Crawley y colaboradores, *J Med Chem*, **35** 2600, 1992, y Crawley y colaboradores *J Med Chem*, **36** 295, 1993

Otra clase distinta de agentes inhibidores de 5-lipoxigenasa es aquélla a la que pertenece el compuesto de SmithKline Beecham SB-210661 El SB-210661 está representado por la Fórmula (5 2 12)



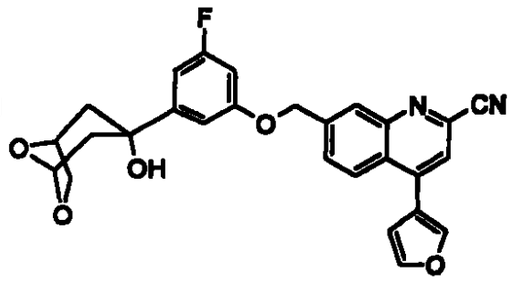
(5.2 12)

Otras dos clases distintas y relacionadas de agentes inhibidores de 5-lipoxigenasa comprenden una serie de compuestos de 2-ciano-naftaleno sustituidos con pirdinilo y una serie de compuestos de 2-ciano-quinolina descubiertos por Merck Frosst Estas dos clases de agentes inhibidores de 5-lipoxigenasa son ejemplificados por L-739,010 y L-746,530, representados por las Fórmulas (5 2 13) y (5 2 14), respectivamente



L-739,010

(5 2 13)



L-746,530

(5 2 14)

Detalles concernientes a los L-739 010 y L-746,530 se describen en la cita de Dubé y colaboradores "Quinolines as potent 5-lipoxygenase inhibitors synthesis and biological profile of L-746 530 (Quinolinas como potentes agentes inhibidores de 5-lipoxigenasa sintesis y perfil biológico del L-746,530), *Bioorganic & Medicinal Chemistry*, 8 1255-1260, 1998 y en el documento WO 95/03309 (de Friesen y colaboradores)

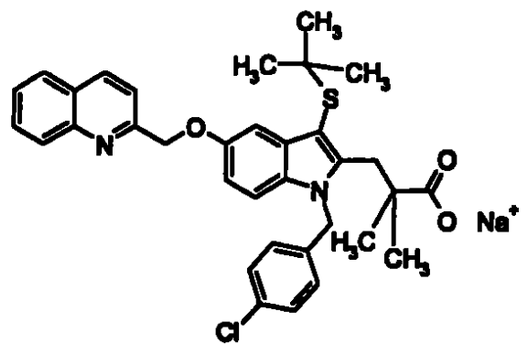
La clase de metoxi-tetrahidropiranos inclusive el Zeneca ZD-2138 de Fórmula (5 2 11) o el compuesto de plomo SB-210661 de Fórmula (5 2 12) y la clase a la que éste pertenece o la serie de compuestos de 2-ciano-naftaleno sustituidos con pirdinilo, a los que pertenece el L-739,010 o la serie de compuestos de 2-ciano-quinolina a los que pertenece el L-746,530, o cualquiera de los derivados antes descritos de cualquiera de las clases antes mencionadas, se combinan con los compuestos de Fórmula (1 0 0) para formar realizaciones del presente invento

Ademas de la enzima 5-lipoxigenasa, el otro agente endógeno que desempeña un cometido importante en la biosintesis de los leucotrienos es la proteína activadora de 5-lipoxigenasa (FLAP) Este cometido es uno indirecto, en contraste con el cometido directo de la enzima-5-lipoxigenasa No obstante, los agentes antagonistas de la proteina activadora de 5-lipoxigenasa se emplean para inhibir la síntesis celular de leucotrienos, y como tales se usan también en combinación con los compuestos de Formula (1 0 0) para formar realizaciones del presente invento

Los compuestos que se fijan a la proteína activadora de 5-lipoxigenasa y con ello bloquean la utilización de la reunión endógena de ácido araquidónico que está presente,

han sido sintetizados a partir de estructuras de indoles y quinolinas véase la cita de Ford-Hutchinson y colaboradores, *Ibid* , Rouzer y colaboradores, "MK-886, a potent and specific leukotriene biosynthesis inhibitor blocks and reverses the membrane association of 5-lipoxygenase in ionophore-challenged leukocytes" (El MK-886, que es un potente y específico agente inhibidor de la biosintesis de leucotrienos, bloquea e invierte la asociación a una membrana de 5-lipoxigenasa en leucocitos estimulados por ionóforos), *J Biol Chem* **265** 1436-42, 1990, y Gorenne y colaboradores, "{(R)-2-quinolin-2-yl-methoxy)phenyl)-2-cyclopentyl acetic acid} (BAY x 1005), a potent leukocyte synthesis inhibitor effects on anti-IgE challenge in human airways" ({El ácido (R)-2-quinolin-2-il-metoxi)fenil)-2-ciclopentil-acético} (BAY x 1005) un potente agente inhibidor de la síntesis de leucotrienos efectos sobre la estimulación anti-IgE en vías respiratorias de seres humanos), *J Pharmacol Exp Ther* **268** 868-72, 1994

El MK-591, que ha sido designado como quiflipon sódico, está representado por la Fórmula (5 2 15)



(5.2 15)

Las clases de compuestos de indoles y quinolinas que antes se mencionan y los compuestos específicos MK-591, MK-886 y BAY x 1005, a los que éstos pertenecen, o cualquiera de los derivados antes descritos de cualquiera de las clases antes mencionadas, se combinan como compuestos de Fórmula (1 0 0) para formar realizaciones del presente invento

9.2 Con agentes antagonistas de receptores para los leucotrienos LTB_4, LTC_4, LTD_4 y LTE_4

Uno o más compuestos de Fórmula (1 0 0) se usa(n) en combinación con agentes antagonistas de receptores para los leucotrienos LTB_4, LTC_4, LTD_4 y LTE_4 Los más importantes de estos leucotrienos en términos de mediar en una respuesta inflamatoria, son LTB_4 y LTD_4 Clases de agentes antagonistas para los receptores de estos

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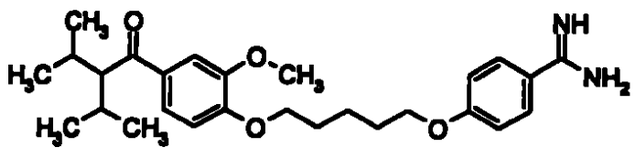
leucotrienos se describen en los párrafos que siguen

Las 4-bromo-2,7-dimetoxi-3*H*-fenotiazin-3-onas inclusive al L-651,392, son potentes agentes antagonistas de receptores para LTB_4 que se describen en los documentos US 4 939 145 (de Guindon y colaboradores) y US 4 845 083 (de Lau y colaboradores). El L-651,392 está representado por la Fórmula (5.2.16)



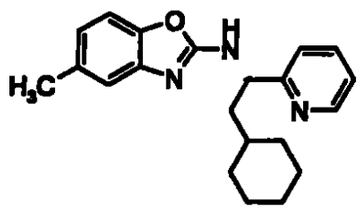
L-651,392 (5.2.16)

Una clase de compuestos de amidina, que incluye al CGS-25019c se describe en los documentos US 5 451 700 (de Morrissey y Suh), US 5 488 160 (de Morrissey), y US 5 639 768 (de Morrissey y Suh). Estos agentes antagonistas de receptores para LTB_4 son tipificados por el CGS-25019c, que está representado por la Fórmula (5.2.17)



CGS-25019c (5.2.17)

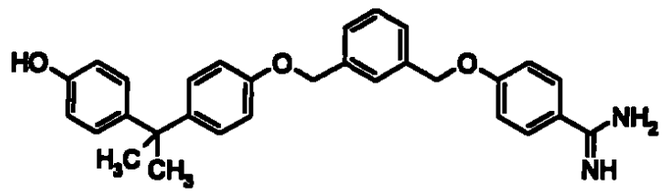
El ontazolast, que es un miembro de una clase de benzoxazol-aminas que son agentes antagonistas de receptores para LTB_4, se describe en el documento EP 535 521 (de Anderskewitz y colaboradores), y está representado por la Fórmula (5.2.18)



Ontazolast (5.2.18)

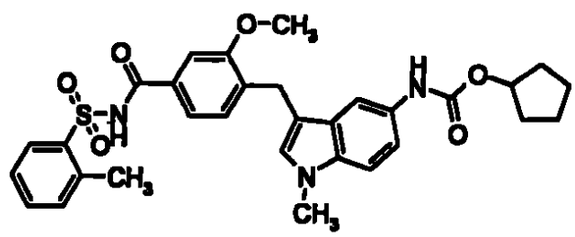
El mismo grupo de autores ha descubierto también una clase de benceno-carboximido-amidas que son agentes antagonistas de receptores para LTB_4, descritos

en los documentos WO 97/21670 (de Anderskewitz y colaboradores), y WO 98/11119 (de Anderskewitz y colaboradores) y que son tipificados por el BIIL 284/260, representado por la Formula (5 2 19)



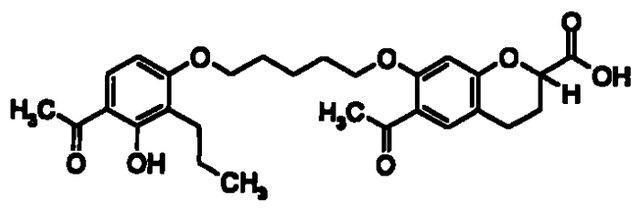
BIIL 284/260 (5 2 19)

El zafirlukast es un agente antagonista de receptores para LTC_4, LTD_4 y LTE_4 que es vendido comercialmente bajo el nombre de Accolate® Éste pertenece a una clase de derivados de amidas heterocíclicas que se describen en los documentos US 4 859 692 (de Bernstein y colaboradores), US 5 319 097 (de Holohan y Edwards), US 5 294 636 (de Edwards y Sherwood), US 5 482 963, US 5 583 152 (de Bernstein y colaboradores), y US 5 612 367 (de Timko y colaboradores) El zafirlukast está representado por la Fórmula (5 2 20)



Zafirlukast (5.2.20)

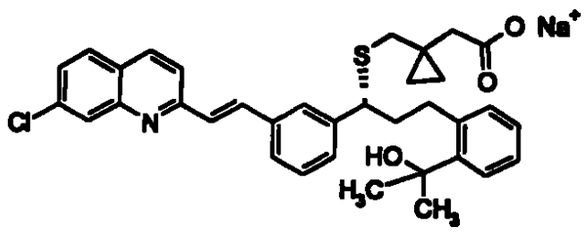
El ablukast es un agente antagonista de receptores para LTD_4 que es designado como Ro 23-3544/001 y está representado por la Fórmula (5 2 21)



Ablukast (5.2.21)

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El montelukast es un agente antagonista de receptores para LTD_4 que es vendido comercialmente bajo el nombre de Singulair® y está descrito en el documento US 5 565 473 El montelukast es representado por la Formula (5 2 22)



Montelukast **(5.2.22)**

Otros agentes antagonistas de receptores para LTD_4 incluyen pranlukast verlukast (MK-679), RG-12525 Ro-245913, iralukast (CGP 45715A) y BAY x 7195

La clase de compuestos de fenotiazin-3-ona antes mencionados, que incluye el L-651,392, la clase de compuestos de amidina que incluye al CGS-25019c, la clase de benzoxazol-aminas que incluye ontazolast la clase de benceno-carboximido-amidas que está tipificada por el BIIL 284/260 los derivados de amidas heterociclicas inclusive zarfirlukast, ablukast y montelukast, y las clases de compuestos a las que estos pertenecen, o cualquiera de los derivados antes descritos de cualquiera de las clases antes mencionadas, se combinan con los compuestos de Fórmula (1 0 0) para formar realizaciones del presente invento

9 3 Con otros agentes terapeuticos para formar combinaciones adicionales

Uno o más compuestos de Fórmula (1 0 0) se usa(n) juntamente con otros agentes terapéuticos así como con agentes no terapéuticos para formar combinaciones que son realizaciones adicionales del presente invento y que son utiles en el tratamiento de un importante numero de diferentes enfermedades, trastornos y condiciones que aquí se describen Dichas realizaciones comprenden uno o más compuestos de Fórmula (1 0 0) juntamente con uno o más de los siguientes,

(a) Agentes inhibidores de las PDE4 inclusive agentes inhibidores de la isoforma PDE4D

(b) Agentes inhibidores de 5-lipoxigenasa (5-LO), o agentes antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP),

(c) Dobles agentes inhibidores de 5-lipoxigenasa (5-LO) y antagonistas del factor activador de plaquetas (PAF)

(d) Agentes antagonistas de leucotrienos (LTRA's) inclusive agentes antagonistas de

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LTB_4 LTC_4, LTD_4 y LTE_4

(e) Agentes antagonistas de receptores H_1 antihistamínicos, inclusive cetirizina, loratadina, desloratadina fexofenadina, astemizol, azelastina y clorofeniramina,

(f) Agentes antagonistas de receptores de H_2 protectores del estómago,

(g) Agentes simpatomiméticos vasoconstrictores agonistas de α_1- y α_2-adrenoceptores, administrados por vía oral o tópica para uso descongestionante, inclusive propilhexedrina, fenilefrina, fenilpropanolamina, pseudoefedrina, hidrocloruro de nafazolina, hidrocloruro de oximetazolina, hidrocloruro de tetrahidrozolina, hidrocloruro de xilometazolina e hidrocloruro de etilnorepinefrina,

(h) Agentes agonistas de α_1- y α_2-adrenoceptores en combinación con agentes inhibidores de 5-lipoxigenasa (5-LO),

(i) Agentes anticolinérgicos inclusive bromuro de ipratropio,

(j) Agentes agonistas de β_1- hasta β_4-adrenoceptores inclusive isoprenalina, albuterol, salbutamol, formoterol, salmeterol, terbutalina, orciprenalina mesilato de bitolterol y pirbuterol,

(k) Teofilina y aminofilina

(l) Cromoglicato de sodio

(m) Agentes antagonistas de receptores muscarínicos (M1, M2 y M3),

(n) Agentes inhibidores de COX-1 (NSAID's), agentes inhibidores selectivos de COX-2 inclusive rofecoxib, y NSAID's de óxido nítrico,

(o) Agentes miméticos del factor de crecimiento del tipo I similar a insulina (IGF-1),

(p) Ciclesonida,

(q) Glucocorticoides inhalados con efectos colaterales sistemicos reducidos, inclusive flunisolida, acetonuro de triamcinolona dipropionato de beclometasona, budesonida, propionato de fluticasona, y furoato de mometasona,

(r) Agentes inhibidores de triptasas,

(s) Agentes antagonistas del factor activador de plaquetas (PAF),

(t) Anticuerpos monoclonales contra entidades inflamatorias endógenas,

(u) IPL 576,

(v) Agentes contra el factor de necrosis de tumores (TNFα) inclusive Etanercept, Infliximab y D2E7

(w) DMARD's inclusive Leflunomida

(x) Péptidos de TCR,

(y) Agentes inhibidores de la enzima convertidora de interleucina (ICE),

(z) Agentes inhibidores de IMPDH

(aa) Agentes inhibidores de moléculas de adhesión inclusive agentes antagonistas de VLA-4

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(bb) Catepsinas

(cc) Agentes inhibidores de cinasas de MAP

(dd) Agentes inhibidores de la deshidrogenasa de glucosa-6 fosfato,

(ee) Agentes antagonistas de receptores de cininas-B_1 y -B_2

(ff) Oro en la forma de un grupo aurotio juntamente con diversos grupos hidrófilos,

(gg) Agentes supresores de inmunidad, p ej , ciclosporina, azatioprina y metotrexato

(hh) Agentes contra la gota, p ej , colquicina,

(ii) Agentes inhibidores de la oxidasa de xantina, p ej , alopurinol,

(jj) Agentes uricosuricos, p ej , probenecida, sulfinpirazona y benzobromarona,

(kk) Agentes antineoplásicos, especialmente fármacos antimitóticos inclusive los alcaloides de vinca, tales como vinblastina y vincristina,

(ll) Secretagogos de las hormonas del crecimiento,

(mm) Agentes inhibidores de metaloproteasas de matriz (MMP's), es decir, las estromelisinas las colagenasas y las gelatinasas asi como agrecanasa, especialmente colagenasa-1 (MMP-1), colagenasa-2 (MMP-8), colagenasa-3 (MMP-13) estromelisina-1 (MMP-3), estromelisina-2 (MMP-10) y estromelisina-3 (MMP-11),

(nn) El factor del crecimiento transformante (TGFβ),

(oo) El factor del crecimiento derivado de plaquetas (PDGF),

(pp) El factor de crecimiento de fibroblastos p ej , el factor del crecimiento de fibroblastos de carácter básico (bFGF),

(qq) El factor estimulador de colonias de granulocitos-macrófagos (GM-CSF),

(rr) Crema de capsaicina,

(ss) Agentes antieméticos inclusive agentes antagonistas de receptores NK-1 y D-4418 y

(tt) Agentes anti-depresivos

DESCRIPCIÓN DETALLADA DEL INVENTO

10 0 Composiciones y Formulaciones Farmacéuticas

La descripción que se da seguidamente concierne a la manera en la que los compuestos de Formula (1 0 0), juntamente con otros agentes terapéuticos o agentes no terapéuticos cuando éstos se desean, se combinan con lo que son en su mayor parte vehículos farmacéuticamente aceptables convencionales para establecer unas formas de dosificación que son apropiadas para las diferentes rutas de administración que se utilizan para cualquier paciente dado, asi como apropiadas para la enfermedad, el trastorno o la condición por la que esté siendo tratado cualquier paciente dado

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Las rutas preferidas de administración para los compuestos de Formula (1 0 0) son por la vía de formulaciones orales y aerosoles que se preparan y suministran de una manera convencional Se discuten adicionalmente a continuación una información detallada en lo que se refiere a la preparación de dichas formulaciones y a la manera en la que éstas se han de administrar a un paciente que necesite de tratamiento

Las composiciones farmacéuticas del presente invento comprenden uno cualquiera o más de los compuestos inhibidores antes descritos del presente invento, o una sal farmacéuticamente aceptable del o de los mismos que también se ha descrito anteriormente, juntamente con un vehículo farmacéuticamente aceptable de acuerdo con las propiedades y el rendimiento esperado de dichos vehículos, que son bien conocidos en el sector tecnológico pertinente

La cantidad de ingrediente activo que se puede combinar con los materiales de vehículo para producir una unica forma de dosificación variara dependiendo del hospedante tratado y del modo particular de administración Deberá entenderse, sin embargo, que una dosificación y un régimen de tratamiento específicos para cualquier paciente particular dependeran de una diversidad de factores, inclusive la actividad del compuesto especifico empleado, la edad, el peso corporal, la salud general, el sexo, la dieta, el momento de la administración, el régimen de excreción, la combinación con fármacos y el criterio del médico que efectue el tratamiento, así como de la gravedad de la enfermedad particular que se esté tratando La cantidad del ingrediente activo puede depender también del agente terapéutico o profiláctico, si es que lo hay, con el que sea administrado conjuntamente el ingrediente

Los compuestos antes descritos del presente invento se pueden utilizar en la forma de ácidos ésteres u otras clases químicas de compuestos a los que pertenecen los compuestos descritos Tambien se encuentra dentro del alcance del presente invento utilizar esos compuestos en la forma de sales farmaceuticamente aceptables derivadas de diversos acidos y bases orgánicos/as e inorgánicos/as de acuerdo con procedimientos descritos con detalle en lo que antecede y bien conocidos en el sector tecnológico Un ingrediente activo que comprende un compuesto de Fórmula (1 0 0) se utiliza con frecuencia en la forma de una de sus sales, especialmente cuando dicha forma de sal confiere a dicho ingrediente activo propiedades farmacocineticas mejoradas en comparacion con la forma libre de dicho ingrediente activo o alguna otra forma de sal de dicho ingrediente activo que se haya utilizado con anterioridad La forma de sal farmacéuticamente aceptable de dicho ingrediente activo puede conferir inicialmente a dicho ingrediente activo también una propiedad farmacocinética deseable que éste no posea previamente, y puede incluso afectar positivamente a las condiciones farmacodinámicas de dicho ingrediente activo con respecto a su actividad terapéutica en el cuerpo

Las propiedades farmacocinéticas de dicho ingrediente activo, que pueden ser afectadas favorablemente, incluyen, p ej la manera en la que dicho ingrediente activo es transportado a través de las membranas celulares que a su vez puede afectar directa y positivamente a la absorcion, la distribución, la biotransformación y la excreción de dicho ingrediente activo Mientras que es importante la ruta de administración de la composición farmacéutica y diversos factores anatómicos, fisiológicos y patológicos pueden afectar críticamente a la biodisponibilidad la solubilidad de dicho ingrediente activo es dependiente usualmente del carácter de la forma particular de sal del mismo, que éste utilizó Además, tal como lo comprende un profesional, una solución acuosa de dicho ingrediente activo proporcionará la absorción más rápida de dicho ingrediente activo en el cuerpo de un paciente que esté siendo sometido a tratamiento, mientras que las soluciones y suspensiones de lípidos, así como las formas de dosificación sólidas, darán como resultado una absorcion menos rápida de dicho ingrediente activo La ingestión por vía oral de dicho ingrediente activo es la ruta más prefenda de administración por razones de seguridad, conveniencia y economía, pero la absorción de dicha forma de dosificación oral puede ser afectada desfavorablemente por características físicas, tales como polaridad, emesis causada por irritación de la mucosa gastrointestinal, destrucción por enzimas digestivas y bajo valor del pH, absorción o propulsión irregular en la presencia de alimentos u otros fármacos y metabolismo por enzimas de la mucosa, la flora intestinal o el hígado La formulación de dicho ingrediente activo en diferentes formas de sales farmacéuticamente aceptables puede ser eficaz para superar o aliviar uno o mas de los problemas antes citados que se encuentran con una absorción de formas de dosificación orales

Entre las sales farmacéuticas que se citan más arriba, las que son prefendas incluyen, pero no se limitan a, acetato, besilato, citrato, fumarato, gluconato, hemisuccinato, hipurato, hidrocloruro, hidrobromuro, isetionato, mandelato, meglumina, nitrato, oleato, fosfonato, pivalato sodio fosfato, estearato, sulfato, sulfo-salicilato, tartrato, tiomalato, tosilato y trometamina

Se incluyen dentro del alcance del presente invento formas de sales multiples cuando un compuesto del presente invento contiene más de un grupo capaz de formar dichas sales farmacéuticamente aceptables Ejemplos de típicas formas de sales multiples incluyen, pero no se limitan a, bitartrato, diacetato, difumarato, dimeglumina, difosfato, disodio y trihidrocloruro

Las composiciones farmacéuticas del presente invento comprenden uno cualquiera o más de los compuestos inhibidores antes descritos del presente invento o una de sus sales farmaceuticamente aceptables como también se describen con anterioridad, juntamente con un vehiculo farmacéuticamente aceptable de acuerdo con

las propiedades y el rendimiento esperado de dichos vehículos que son bien conocidos en el sector tecnológico pertinente

El término "vehículo" como se usa en el presente contexto incluye diluyentes, excipientes, adyuvantes, vehículos, agentes auxiliares de solubilización modificadores de la viscosidad, conservantes y otros agentes aceptables bien conocidos por un profesional para proporcionar propiedades favorables en la composición farmacéutica final Con el fin de ilustrar a dichos vehículos, sigue una breve recopilación de vehículos farmacéuticamente aceptables que se pueden usar en las composiciones farmacéuticas del presente invento, y después de ello una descripción más detallada de los diversos tipos de ingredientes Los vehículos típicos incluyen pero no están limitados de ninguna de las maneras a composiciones para intercambio de iones, alúmina estearato de aluminio, lecitina, proteínas de suero, p ej , albumina de suero humano fosfatos, glicina, ácido sórbico sorbato de potasio mezclas de glicéridos parciales de ácidos grasos vegetales saturados, aceites de palma hidrogenados, agua, sales o electrolitos p ej , sulfato de protamina, hidrógeno-fosfato de disodio, hidrogeno-fosfatode dipotasio, cloruro de sodio, y sales de zinc, sílice coloidal, trisilicato de magnesio, poli(vinil-pirrolidona), sustancias basadas en celulosa p ej , carboximetil-celulosa de sodio, polietilen-glicol, poliacrilatos ceras polímeros de bloques de poli(oxietileno) y poli(oxipropileno), y grasa de lana

Más particularmente, los vehículos usados en las composiciones farmacéuticas del presente invento comprenden diversas clases y especies de aditivos que son miembros independientemente seleccionados entre los grupos que constan esencialmente de los citados en los párrafos siguientes

Se añaden agentes de acidificación y alcalinización con el fin de obtener un valor del pH deseado o predeterminado, y éstos comprenden agentes de acidificación, p ej , ácido acético, ácido acético glacial, ácido málico y ácido propiónico Se pueden usar, pero son menos prefendos acidos más fuertes tales como ácido clorhídnco, ácido nítnco y ácido sulfurico Los agentes de alcalinización incluyen, p ej , edetol, carbonato de potasio, hidróxido de potasio, borato de sodio, carbonato de sodio, e hidróxido de sodio Se pueden usar también agentes de alcalinización que contienen grupos amino activos tales como dietanol-amina y trolamina

Se requieren agentes propulsores de aerosoles cuando la composición farmaceutica ha de suministrarse en forma de un aerosol bajo una presion importante Dichos agentes propulsores incluyen, p ej , hidrocarburos fluoro-clorados aceptables tales como dicloro-difluoro-metano, dicloro-tetrafluoro-etano y tricloro-monofluoro-metano, nitrógeno, o un hidrocarburo volátil tal como butano, propano, isobutano o sus mezclas

Los agentes antimicrobianos incluyen agentes antibacterianos, antifungicos y

antiprotozoarios que se añaden cuando la composicion farmacéutica es aplicada por vía tópica a zonas de la piel que son susceptibles de haber sufrido condiciones desfavorables o abrasiones o cortes prolongados que exponen la piel a una infección por bacterias, hongos o protozoos Los agentes antimicrobianos incluyen compuestos tales como alcohol bencílico clorobutanol, alcohol fenil-etílico, acetato fenil-mercunco, sorbato de potasio y acido sórbico Los agentes antifungicos incluyen compuestos tales como ácido benzoico, butil-parabeno, etil-parabeno, metil-parabeno, propil-parabeno y benzoato de sodio

Se añaden agentes conservantes antimicrobianos a las composiciones farmacéuticas del presente invento con el fin de protegerlas contra el crecimiento de microorganismos potencialmente perjudiciales, que usualmente invaden a la fase acuosa, pero en algunos casos pueden también crecer en la fase oleosa de una composición Por lo tanto, son deseables agentes conservantes con solubilidad tanto en agua como en lípidos Apropiados agentes conservantes antimicrobianos incluyen, p ej , ésteres de alquilo con ácido *p*-hidroxibenzoico, sales propionatos, fenoxi-etanol, metil-parabeno de sodio, propil-parabeno de sodio, deshidroacetato de sodio, cloruro de benzalconio, cloruro de bencetonio alcohol bencílico, derivados de hidantoína, compuestos de amonio cuaternario y polimeros catiónicos, imidazolidinil-urea, diazolidinil-urea y etilen-diamina-tetraacetato de trisodio (EDTA) Preferiblemente, los agentes conservantes se emplean en unas cantidades que fluctuan entre aproximadamente 0,01% y aproximadamente 2,0% en peso de la composición total

Se añaden agentes antioxidantes para proteger a la totalidad de los ingredientes de la composicion farmacéutica con respecto del daño o de la degradación por agentes oxidantes presentes en la composición propiamente dicha o el entorno de uso, p ej , anoxómero, palmitato de ascorbilo, hidroxi-anisol butilado, hidroxi-tolueno butilado, ácido hipofosforoso, metabisulfito de potasio, galatos de propilo, octilo y dodecilo, metabisulfito de sodio dióxido de azufre, y tocoferoles

Los agentes de tamponamiento se usan para mantener un valor del pH deseado de una composición una vez que ésta se haya establecido, a partir de los efectos de agentes externos y desplazar equilibnos de componentes de la composición El agente de tamponamiento se puede seleccionar entre los que resultan familiares para un profesional experto en la preparación de composiciones farmacéuticas, p ej , acetato de calcio, metafosfato de potasio, fosfato de potasio monobásico, y ácido tartárico

Se usan agentes de quelación para ayudar a mantener la fuerza iónica de la composición farmacéutica y fijarse a, y eliminar eficazmente, compuestos y metales destructores, y éstos incluyen, p ej , edetato de dipotasio edetato de disodio, y ácido edético

Se añaden agentes activos dermatológicamente a las composiciones farmacéuticas del presente invento cuando estas se han de aplicar por vía tópica, y estos incluyen, p ej , agentes para la curación de heridas tales como derivados de péptidos, una levadura, pantenol hexil-resorcinol, fenol, hidrocloruro de tetraciclina lamina y cinetina retinoides para tratar un cáncer de piel p ej , retinol tretinoina, isotetrinoína, etretinato, acitretina y arotinoide, agentes antibacterianos suaves para tratar infecciones de piel, p ej , resorcinol ácido salicílico, peróxido de benzoílo una mezcla de eritromicina y peroxido de benzoílo eritromicina y clindamicina, agentes antifungicos para tratar tiña corporal (circinada), tiña del pie (pie de atleta) candidiasis y tiña (pitiriasis) versicolor, p ej , griseofulvina, azoles tales como miconazol econazol, itraconazol, fluconazol y ketoconazol, y alilaminas tales como naftifina y terfinafina, agentes antivíricos para tratar el herpes simple cutáneo, el herpes zoster y la varicela, p ej , aciclovir, famciclovir y valaciclovir, agente antihistamínicos para tratar el prurito las dermatitis atópica y por contacto p ej , difenhidramina, terfenadina, astemizol, loratadina cetirizina, acrivastina y temelastina, agentes anestésicos tópicos para aliviar dolor irritación y comezon, p ej , benzocaina, lidocaina, dibucaína e hidrocloruro de pramoxina, agentes analgésicos tópicos para aliviar el dolor y la inflamación, p ej , salicilato de metilo, alcanfor, mentol y resorcinol, agentes antisépticos tópicos para prevenir una infección, p ej , cloruro de benzalconio y povidona-yodo, y vitaminas y sus derivados tales como tocoferol, acetato de tocoferol, ácido retinoico y retinol

Se usan agentes dispersantes y suspendedores como agentes auxiliares para la preparación de formulaciones estables y éstos incluyen, p ej , poligeenano, povidona y dióxido de silicio

Los emolientes son agentes preferiblemente no oleosos y solubles en agua, que ablandan y apaciguan a la piel, especialmente una piel que se ha vuelto seca por causa de una excesiva pérdida de agua Dichos agentes se usan con composiciones farmacéuticas del presente invento que están destinadas a aplicaciones tópicas, e incluyen, p ej , aceites y ceras de hidrocarburos, ésteres de triglicéridos, monoglicéridos acetilados ésteres metílicos y otros ésteres alquílicos de ácidos grasos C_{10}-C_{20}, ácidos grasos C_{10}-C_{20}, alcoholes grasos C_{10}-C_{20}, lanolina y sus derivados, ésteres de alcoholes polivalentes tales como polietilen-glicol (200-600) poli(oxietilen)-ésteres de ácidos grasos de sorbitán, esteres cerosos, fosfolípidos, y esteroles, agentes emulsionantes que se usan para preparar emulsiones del tipo de aceite en agua, excipientes, p ej , laurocapramo y polietilen-glicol-monometil-éter agentes humectantes, p ej , sorbitol, glicerol y ácido hialurónico, bases para ungüentos, p ej , petrolato, polietilen-glicol, lanolina y un poloxámero, agentes intensificadores de la penetración, p ej , dimetil-isosorbida, dietil-glicol-monoetil-éter, 1-dodecil-aza-cicloheptan-2-ona y dimetil-sulfóxido

(DMSO), agentes conservantes, p ej , cloruro de benzalconio, cloruro de bencetonio, esteres de alquilo de ácido p-hidroxi-benzoico, derivados de hidantoína, cloruro de cetil-pindinio propil-parabeno, compuestos de amonio cuaternario tales como benzoato de potasio y timerosal agentes secuestrantes que comprenden ciclodextrinas, disolventes, p ej , acetona, alcohol etílico hidrato de amileno alcohol butílico, aceite de maíz, aceite de semilla de algodón, acetato de etilo, glicerol hexilen-glicol, alcohol isopropílico, alcohol isoestearílico, alcohol metílico cloruro de metileno, un aceite mineral, aceite de cacahuete, ácido fosfónico, polietilen-glicol poli(oxipropilen)-15-esteanl-éter, propilen-glicol, diacetato de propilen-glicol aceite de sésamo, y agua purificada, agentes estabilizadores p ej sacarato de calcio y timol, agentes tensioactivos, p ej , cloruro de lapino, laureth 4, es decir, α-dodecil-ω-hidroxi-poli(oxi-1,2-etanodilo) o polietilen-glicol-monododecil-éter

Los agentes emulsionantes, inclusive agentes emulsionantes y espesantes y auxiliares para emulsión se usan para preparar emulsiones del tipo de aceite en agua cuando éstas constituyen la base de las composiciones farmacéuticas del presente invento Dichos agentes emulsionantes incluyen, p ej , emulsionantes no iónicos tales como alcoholes grasos C_{10}-C_{20} y dichos alcoholes grasos condensados con 2 a 20 moles de óxido de etileno u óxido de propileno alquil (C_6-C_{12})-fenoles condensados con 2 a 20 moles de óxido de etileno mono- y di-ésteres con ácidos grasos C_{10}-C_{20} de etilen-glicol, un monoglicéndo de un ácido graso C_{10}-C_{20} dietilen-glicol, polietilen-glicoles con un P M (peso molecular) de 200-6 000, polipropilen-glicoles con un P M de 200-3 000 y particularmente sorbitol sorbitan, poli(oxietilen)-sorbitol, poli(oxietilen)-sorbitán, ésteres cerosos hidrófilos, alcohol ceto-estearílico, alcohol oleílico, alcoholes de lanolina, colesterol mono- y di-glicéndos monoestearato de glicerilo, monoestearato de polietilen-glicol, ésteres mixtos mono- y di-esteáncos de etilen-glicol y polioxietilen-glicol monoestearato de propilen-glicol e hidroxipropil-celulosa Se pueden usar también agentes emulsionantes que contienen grupos amino activos y éstos incluyen típicamente emulsionantes aniónicos tales como jabones de ácidos grasos, p ej , jabones de sodio, potasio y tnetanol-amina de ácidos grasos C_{10}-C_{20}, alquil (C_{10}-C_{30})-sulfatos de metales alcalinos, amonio o amonio sustituido alquil (C_{10}-C_{30})-sulfonatos y alquil (C_{10}-C_{30})-etoxi-éter-sulfonatos Otros apropiados agentes emulsionantes incluyen aceite de ricino y aceite de ricino hidrogenado, lecitina, y polímeros de ácido 2-propenoico juntamente con polímeros de ácido acrílico, ambos reticulados con alil-éteres de sacarosa y/o pentaeritritol, que tienen viscosidades variables y se identifican por los nombres de productos carbomer 910 934 934P 940, 941 y 1 342 Se pueden usar también emulsionantes catiónicos que tienen grupos amino activos, inclusive los basados en compuestos de amonio cuaternario, morfolinio y pindinio Similarmente, se pueden usar

emulsionantes anfóteros que tienen grupos amino activos tales como coco-betaínas, lauril-óxido de dimetil-amina y cocoíl-imidazolina Los agentes emulsionantes y espesantes utiles incluyen también alcohol cetílico y estearato de sodio y auxiliares de emulsion tales como acido oleico ácido estearico y alcohol estearílico

Los excipientes incluyen, p ej , laurocapramo y polietilen-glicol-monometil-éter

Cuando la composición farmacéutica del presente invento ha de ser aplicada por vía tópica, se pueden usar agentes intensificadores de la penetración que incluyen, p ej , dimetil-isosorbida, dietil-glicol-monoetil-éter, 1-dodecil-aza-cicloheptan-2-ona, y dimetil-sulfóxido (DMSO) Tales composiciones incluirán típicamente también bases para ungüentos, p ej , petrolato, polietilen-glicol, lanolina y un poloxámero, que es un copolímero de bloques de poli(oxietileno) y poli(oxipropileno), que puede servir también como un agente tensioactivo o emulsionante

Se usan agentes conservantes para proteger a las composiciones farmacéuticas del presente invento con respecto del ataque degradante de microorganismos del ambiente, y estos incluyen, p ej , cloruro de benzalconio, cloruro de bencetonio, ésteres alquílicos de ácido p-hidroxi-benzoico, derivados de hidantoína, cloruro de cetil-pindinio, monotioglicerol, fenol, fenoxi-etanol, metil-parabeno, imidazolidinil-urea, deshidroacetato de sodio, propil-parabeno compuestos de amonio cuaternario, especialmente polímeros tales como cloruro de polixetonio, benzoato de potasio, formaldehído-sulfoxilato de sodio, propionato de sodio y timerosal

Se usan agentes secuestrantes para mejorar la estabilidad de las composiciones farmacéuticas del presente invento y éstos incluyen, p ej , las ciclodextrinas que son una familia de oligosacáridos cíclicos naturales capaces de formar complejos de inclusión con una diversidad de materiales, y son de tamaños variables de los anillos siendo citados los residuos de 6-, 7- y 8-glucosa en un anillo comúnmente como α-ciclodextrinas, β-ciclodextrinas y γ-ciclodextrinas, respectivamente Las apropiadas ciclodextrinas incluyen, p ej , α-ciclodextrina, β-ciclodextrina, γ-ciclodextrina, δ-ciclodextrina y ciclodextrinas cationizadas

Los disolventes que se pueden usar para preparar las composiciones farmacéuticas del presente invento incluyen, p ej , acetona, alcohol etílico, hidrato de amileno, alcohol butílico, aceite de maíz, aceite de semilla de algodón, acetato de etilo, glicerol, hexilen-glicol, alcohol isopropílico, alcohol isoestearílico, alcohol metílico, cloruro de metileno, un aceite mineral, aceite de cacahuete, ácido fosfónico, polietilen-glicol, poli(oxipropilen)-15-estearil-éter, propilen-glicol, diacetato de propilen-glicol, aceite de sésamo y agua purificada

Los estabilizadores que son apropiados para su uso incluyen, p ej , sacarato de calcio y timol

Los agentes espesantes se usan típicamente en formulaciones destinadas a aplicaciones por vía tópica con el fin de proporcionar la viscosidad y las características de manipulación deseadas e incluyen, p ej , cera de ésteres cetílicos, alcohol miristílico parafina, parafina sintética, cera emulsionante, cera microcristalina, cera blanca y cera amarilla

Con frecuencia se usan azucares para conferir una diversidad de deseadas características a las composiciones farmacéuticas del presente invento y con el fin de mejorar los resultados obtenidos, e incluyen, p ej , monosacáridos, disacaridos y polisacáridos tales como glucosa, xilosa, fructosa, reosa, ribosa, pentosa, arabinosa, alosa, talosa, altrosa, manosa, galactosa, lactosa sacarosa, eritrosa, gliceraldehído, o cualquier combinación de ellos

Se emplean agentes tensioactivos para proporcionar estabilidad a composiciones farmacéuticas de componentes multiples del presente invento, intensificar las propiedades existentes de esas composiciones, y conferir características nuevas deseables a dichas composiciones Los agentes tensioactivos se usan como agentes humectantes, agentes antiespumantes, para reducir la tensión superficial del agua, y como agentes emulsionantes dispersantes y penetrantes, e incluyen, p ej , cloruro de lapirio laureth 4 es decir α-dodecil-ω-hidroxi-poli(oxi-1,2-etanodiilo) o polietilen-glicol-monododecil-éter, laureth 9, es decir, una mezcla de polietilen-glicol-monododecil-éteres que tienen en promedio aproximadamente 9 grupos de óxido de etileno por molécula, monoetanol-amina, nonoxinoles 4, 9 y 10, es decir polietilen-glicol-mono(p-nonil-fenil)-éteres, nonoxinol 15, es decir α-(p-nonil-fenil)-ω-hidroxi-pentadeca(oxietileno), nonoxinol 30, es decir es decir α-(p-nonil-fenil)-ω-hidroxi-triaconta(oxietileno), poloxaleno, es decir un polímero no iónico del tipo de polietilen-polipropilen-glicol, con un P M = aproximadamente 3 000 un poloxámero, que se ha citado en la discusión de las bases para ungüentos más arriba en este texto, estearatos de polioxilos 8, 40 y 50, es decir poli(oxi-1 2-etanodiil) α-hidro-ω-hidroxi-,octadecanoato, polioxil-10-oleil-éter, es decir poli(oxi-1 2-etanodiil), α-[(Z)-9-octadecenil-ω-hidroxi-, polisorbato 20, es decir sorbitán, monododecanoato poli(oxi-1,2-etanodiilo) polisorbato 40, es decir sorbitán, monohexa-decanoato, poli(oxi-1,2-etanodiilo), polisorbato 60, es decir sorbitán, monooctadecanoato, poli(oxi-1,2-etanodiilo), polisorbato 65, es decir sorbitán, trioctadecanoato, poli(oxi-1 2-etanodiilo), polisorbato 80, es decir sorbitán, mono-9-monodecenoato, poli(oxi-1,2-etanodiilo) polisorbato 85, es decir sorbitán, tri-9-octadecenoato, poli(oxi-1,2-etanodiilo), lauril-sulfato de sodio, monolaurato de sorbitán, monooleato de sorbitán, monopalmitato de sorbitán, monoestearato de sorbitán, sesquioleato de sorbitán, trioleato de sorbitán, y triestearato de sorbitán

Las composiciones farmacéuticas del presente invento se pueden preparar

utilizando una metodologia muy directa que es bien comprendida por un profesional con experiencia ordinaria Cuando las composiciones farmacéuticas del presente invento son simples soluciones en agua y/o en otros disolventes los diversos componentes de la composición global son reunidos en cualquier orden práctico, que será dictado ampliamente por consideraciones de conveniencia Los componentes que tienen solubilidad reducida en agua, pero suficiente estabilidad en el mismo disolvente conjunto con agua, pueden ser disueltos en dicho disolvente conjunto después de lo cual la solución en el disolvente conjunto será añadido a la porción de agua del vehículo con lo cual los solutos allí existentes resultarán disueltos en el agua Para ayudar en este proceso de dispersión/disolución se puede emplear un agente tensioactivo

Cuando las composiciones farmacéuticas del presente invento han de estar en la forma de emulsiones los componentes de la composicion farmacéutica serán reunidos de acuerdo con los siguientes procedimientos generales La fase de agua, continua es primeramente calentada a una temperatura situada en el intervalo de aproximadamente 60° a aproximadamente 95°C, preferiblemente desde alrededor de 70° hasta alrededor de 85°C, dependiendo la elección de la temperatura que se haya de usar de las propiedades fisicas y quimicas de los componentes que constituyen la emulsión del tipo de aceite en agua Una vez que la fase de agua, continua, ha alcanzado su temperatura seleccionada, los componentes de la composición final, que se han de añadir en esta etapa, se mezclan con el agua y se dispersan en ella mediando agitación a alta velocidad A continuación, la temperatura del agua es devuelta a aproximadamente su nivel original, después de lo cual los componentes de la composición que constituye la siguiente etapa se añaden a la mezcla de la composición mediando agitación moderada y se continua el mezclamiento durante un periodo de tiempo de aproximadamente 5 a aproximadamente 60 minutos, con preferencia de aproximadamente 10 a aproximadamente 30 minutos, dependiendo de los componentes de las dos primeras etapas Despues de ello la mezcla de la composición se enfría de modo pasivo o activo a una temperatura de aproximadamente 20° a aproximadamente 55°C, para la adición de cualesquiera componentes en las etapas remanentes, después de lo cual se añade agua en cantidad suficiente para alcanzar su concentración predeterminada original en la composición global

De acuerdo con el presente invento las composiciones farmaceuticas pueden estar en la forma de una preparacion inyectable estéril, por ejemplo una suspensión acuosa u oleaginosa inyectable estéril Esta suspensión se puede formular de acuerdo con técnicas conocidas en el sector tecnológico usando apropiados agentes dispersantes o humectantes y agentes suspendedores La preparación inyectable estéril puede ser tambien una solucion o suspensión inyectable esteril en un diluyente o disolvente no

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tóxico, aceptable parenteralmente por ejemplo en forma de una solución en 1,3-butanodiol Entre los vehiculos y disolventes aceptables que se pueden emplear se encuentran agua, la solución de Ringer y una solución isotónica de cloruro de sodio Ademas se emplean convencionalmente aceites fijos, esténles, como medio disolvente o de suspensión Para esta finalidad se puede emplear cualquier aceite fijo suave, inclusive mono- o di-glicéridos sintéticos Ciertos ácidos grasos, tales como ácido oleico y sus derivados de glicéndos son utiles en la preparación de inyectables, al igual que lo son ciertos aceites naturales farmaceuticamente aceptables, tales como aceite de oliva o aceite de ricino, especialmente en sus versiones poli(oxietiladas) Estas soluciones o suspensiones en aceites pueden contener también un agente diluyente o dispersante del tipo de alcohol de cadena larga tal como *Rh*, HCIX o un alcohol similar

Las composiciones farmacéuticas del presente invento se pueden administrar por vía oral en cualquier forma de dosificacion aceptable oralmente que incluye, pero no se limita a, cápsulas, tabletas y suspensiones o soluciones acuosas En el caso de tabletas para uso oral, los vehiculos que se usan corrientemente incluyen lactosa y un almidón de maíz Los agentes lubricantes tales como estearato de magnesio, se añaden también típicamente Para una administración por vía oral en una forma de cápsula, los diluyentes utiles incluyen lactosa y almidón de maíz secado Cuando se requieren suspensiones acuosas para uso oral, el ingrediente activo se combina con agentes emulsionantes y suspendedores Si se desea se pueden añadir también ciertos agentes edulcorantes, saboreantes o colorantes Alternativamente las composiciones farmacéuticas de este invento se pueden administrar en la forma de supositorios para administración rectal Éstos se pueden preparar mezclando el agente con un apropiado excipiente no irritante que sea sólido a la temperatura ambiente pero líquido a la temperatura rectal, y por lo tanto se funda dentro del recto para poner en libertad el fármaco Dichos materiales incluyen manteca de cacao cera de abejas y polietilen-glicoles

Las composiciones farmacéuticas del presente invento se pueden administrar también por via tópica especialmente cuando la diana del tratamiento incluye zonas u órganos fácilmente accesibles mediante aplicación por vía tópica, inclusive enfermedades de los ojos, de la piel o del tracto intestinal inferior Las apropiadas formulaciones tópicas se preparan con facilidad para cada una de estas zonas o cada uno de estos órganos

La aplicacion por vía tópica para el tracto intestinal inferior se puede efectuar en una formulación de supositorio rectal, tal como antes se ha descrito, o en una apropiada formulación de enema Se pueden usar también parches transdérmicos activos por via tópica

Para aplicaciones por via tópica las composiciones farmacéuticas se pueden formular en un apropiado ungüento que contiene el componente activo suspendido o

disuelto en uno o más vehículos Los vehículos para la administracion por vía tópica de los compuestos de este invento incluyen, pero no se limitan a, un aceite mineral, un petrolato liquido petrolato blanco, propilen-glicol, poli(oxietileno), un compuesto de poli(oxipropileno), una cera emulsionante y agua Alternativamente, las composiciones farmacéuticas se pueden formular en una apropiada locion o crema que contenga los componentes activos suspendidos o disueltos en uno o más vehículos farmacéuticamente aceptables Los vehiculos apropiados incluyen, pero no se limitan a, un aceite mineral, monoestearato de sorbitán, un polisorbato, una cera de ésteres cetílicos alcohol cetearílico 2-octil-dodecanol, alcohol bencílico y agua

Las composiciones farmacéuticas que se encuentran dentro del alcance del presente invento incluyen aquéllas en las que la cantidad terapéuticamente efectiva de un ingrediente activo que comprende un compuesto del presente invento requerido para tratar o prevenir enfermedades, trastornos y condiciones mediados/as por, o asociados/as con una modulación de la actividad de las PDE4, especialmente de las PDE4D como aquí se describe se proporciona en una forma de dosificación apropiada para la administración por vía sistémica Dicha composición farmacéutica contendrá dicho ingrediente activo en una apropiada forma líquida para suministro por (1) una inyección o infusión que es intraarterial, intra- o trans-dérmica, subcutánea, intramuscular, intraespinal, intratecal o intravenosa, en que dicho ingrediente activo (a) está contenido en solución como un soluto, (b) está contenido en la fase discontinua de una emulsión o en la fase discontinua de una emulsión inversa que se invierte después de inyección o infusión, conteniendo dichas emulsiones apropiados agentes emulsionantes, o (c) está contenido en una suspensión como un sólido suspendido en forma coloidal o de microparticulas, conteniendo dicha suspensión apropiados agentes suspendedores, (2) una inyección o infusión dentro de apropiados tejidos o cavidades corporales como un depósito, en que dicha composición proporciona el almacenamiento de dicho ingrediente activo y posteriormente una liberación retardada, prolongada y/o controlada de dicho ingrediente activo para la distribución por vía sistémica, (3) instilación, inhalación o insuflación dentro de apropiados tejidos o cavidades corporales de dicha composición farmacéutica en una forma sólida apropiada, en que dicho ingrediente activo (a) está contenido en una composición de implante sólido que proporciona una liberación retardada, prolongada y/o controlada de dicho ingrediente activo, (b) está contenido en una composición en forma de partículas que se ha de inhalar dentro de los pulmones, o (c) está contenido en una composición en particulas que se ha de insuflar dentro de tejidos o cavidades corporales y adecuados/as, en que dicha composición proporciona opcionalmente una liberación retardada, prolongada y/o controlada de dicho ingrediente activo, o (4) ingestión de dicha composición farmacéutica

en una forma sólida o liquida apropiada para el suministro por vía peroral de dicho ingrediente activo, en que dicho ingrediente activo está contenido en una forma de dosificación sólida, o (b) está contenido en una forma de dosificación liquida

Formas de dosificación particulares de las composiciones farmacéuticas antes descritas, incluyen (1) supositorios como un tipo especial de implante, que comprende bases que son sólidas a la temperatura ambiente pero que se funden a la temperatura corporal, liberando lentamente el ingrediente activo con el que están impregnados dentro del tejido circundante del cuerpo, en que el ingrediente activo resulta absorbido y transportado para efectuar la administracion por vía sistemica, (2) formas de dosificación peroral sólidas seleccionadas entre el grupo que consta de (a) tabletas, cápsulas, capletas, trociscos, rombos y materiales en partículas multiples, orales de liberación retardada, (b) tabletas y cápsulas revestidas entéricamente, que impiden la liberación y absorción en el estómago para facilitar el suministro a una parte distante con respecto al estómago del paciente que está siendo tratado (c) tabletas, cápsulas y micropartículas orales de liberación prolongada, que proporcionan el suministro sistémico del ingrediente activo de una manera controlada durante un período hasta de 24 horas, (d) tabletas de disolución rápida, (e) soluciones encapsuladas, (f) una pasta oral, (g) una forma granular incorporada o que se ha de incorporar en el alimento de un paciente que está siendo sometido a tratamiento, y (h) formas de dosificación perorales líquidas, seleccionadas entre el grupo que consta de soluciones, suspensiones, emulsiones emulsiones inversas elixires extractos, tinturas y concentrados

Las composiciones farmacéuticas situadas dentro del alcance del presente invento incluyen aquéllas en las que la cantidad terapéuticamente eficaz de un ingrediente activo que comprende un compuesto del presente invento requerido para tratar o prevenir enfermedades, trastornos y condiciones mediadas por, o asociadas con, la modulación de la actividad de las PDE4, especialmente de la PDE4D como aquí se describe, es proporcionada en una forma de dosificación apropiada para administración por vía local a un paciente que está siendo sometido a tratamiento, en que dicha composición farmacéutica comprende dicho ingrediente activo en una apropiada forma liquida para suministrar dicho ingrediente activo (1) por inyección o infusión dentro de un sitio local que es intraarterial, intraarticular, intracondral, intracostal, intraquístico, intra- o trans-dérmico intrafascicular, intraligamentoso, intramedular, intramuscular, intranasal, intraneural, intraocular es decir por administración oftálmica, intraosteal, intrapélvica, intrapericárdica, intraespinal, intraesternal intrasinovial, intratarsal o intratecal, inclusive componentes que proporcionan una liberación retardada una liberación controlada y/o una liberación prolongada de dicho ingrediente activo dentro de dicho sitio local, en que dicho ingrediente activo está contenido (a) en solución como un soluto, (b) en la fase

discontinua de una emulsión, o en la fase discontinua de una emulsión inversa que se invierte después de inyección o infusion, conteniendo dichas emulsiones unos apropiados agentes emulsionantes o (c) en una suspensión como un sólido suspendido en forma coloidal o de micropartículas, conteniendo dicha suspensión apropiados agentes suspendedores, o (2) por inyección o infusión como un depósito para suministrar dicho ingrediente activo a dicho sitio local, en que dicha composición proporciona un almacenamiento de dicho ingrediente activo y después de ello una liberación retardada prolongada y/o controlada de dicho ingrediente activo dentro de dicho sitio local y en que dicha composición incluye también componentes que aseguran que dicho ingrediente activo tenga predominantemente una actividad local, con poca actividad de acarreo sistémico, o en que dicha composición farmacéutica contiene dicho ingrediente activo en una forma sólida apropiada para suministrar dicho agente inhibidor (3) por instilación, inhalación o insuflacion a dicho sitio local en que dicho ingrediente activo está contenido (a) en una composición de implante sólido que es instalada en dicho sitio local, proporcionando dicha composición opcionalmente una liberación retardada, prolongada y/o controlada de dicho ingrediente activo a dicho sitio local, (b) en una composición en partículas que es inhalada dentro de un sitio local que comprende los pulmones, o (c) en una composición en partículas que es insuflada dentro de un sitio local, en que dicha composición incluye componentes que asegurarán que dicho ingrediente activo tenga predominantemente una actividad local, con una insignificante actividad de acarreo sistémico, y opcionalmente proporciona una liberación retardada, prolongada y/o controlada de dicho ingrediente activo a dicho sitio local Para uso oftálmico, las composiciones farmacéuticas se pueden formular como una suspensión reducida a tamaño de micrómetros en una solucion salina estéril isotónica ajustada en su pH, o, prefenblemente en forma de soluciones en una solucion salina estéril isotónica, ajustada en su pH, ya sea con o sin un agente conservante tal como cloruro de benzalconio Alternativamente, para usos oftálmicos, las composiciones farmacéuticas se pueden formular en un ungüento tal como un petrolato

Las composiciones farmacéuticas del presente invento se pueden administrar también mediante un aerosol o una inhalación nasal por medio del uso de un nebulizador, un inhalador de polvos secos o un inhalador de dosis medidas Dichas composiciones se preparan de acuerdo con técnicas bien conocidas en el sector tecnológico de la formulación farmacéutica y se puede preparar en forma de soluciones en una solución salina, empleando alcohol bencílico u otros apropiados conservantes, promotores de la absorción para intensificar la biodisponibilidad, hidrocarburos fluorados y/u otros agentes solubilizantes o dispersantes convencionales

Como ya se mencionado, los ingredientes activos de Fórmula (1 0 0) del presente

invento se pueden administrar por via sistémica a un paciente que se ha de someter a tratamiento como una composición farmacéutica en una forma liquida apropiada por inyección o infusión Existen cierto numero de sitios y sistemas de órganos en el cuerpo del paciente que permitirán que la composición farmacéutica apropiadamente formulada una vez que haya sido inyectada o infundida, penetre por todo el cuerpo y por todo el sistema de órganos del paciente que esté siendo sometido a tratamiento Una inyección es una unica dosis de la composición farmacéutica introducida forzadamente, usualmente mediante una jeringa dentro del tejido implicado Los tipos más comentes de inyecciones son las intramusculares, intravenosas y subcutáneas En contraste con ello, una infusión es la introducción gradual de la composición farmacéutica dentro del tejido implicado El tipo más comente de infusión es la intravenosa Otros tipos de inyección o infusión comprenden las intraarteriales, intra- o trans-dermicas (inclusive las subcutáneas) o intraespinales, especialmente intratecales En estas composiciones farmacéuticas líquidas, el ingrediente activo puede estar contenido en solución como el soluto Éste es el tipo más comente y más preferido de una de tales composiciones, pero requiere un ingrediente activo en una forma de sal que tenga una solubilidad en agua razonablemente buena El agua (o una solución salina) es con mucho el disolvente más preferido para dichas composiciones Ocasionalmente, se pueden utilizar soluciones sobresaturadas, pero éstas plantean problemas de estabilidad que las hacen impracticables para su uso sobre una base de cada día

Si no es posible obtener una forma de algun compuesto de Fórmula (1 0 0) que tenga el grado requendo de solubilidad en agua, como puede ocurrir algunas veces, está dentro del alcance de un profesional el recurso de preparar una emulsión, que es una dispersión de pequeños glóbulos de un líquido, la fase discontinua o interna, a través de un segundo líquido, la fase continua o externa, con la que es inmiscible Los dos líquidos se mantienen en un estado emulsionado por el uso de emulsionantes que son farmacéuticamente aceptables Por lo tanto, si el ingrediente activo es un aceite insoluble en agua, puede ser administrado en una emulsión de la que es la fase discontinua También cuando el ingrediente activo es insoluble en agua, pero puede ser disuelto en un disolvente que es inmiscible con agua, se puede usar una emulsión Mientras que el ingrediente activo se usaría lo más comentemente como la fase discontinua o interna de lo que es citado como una emulsion del tipo de aceite en agua, también se podría utilizar como la fase discontinua o interna de una emulsión inversa, que es citada comentemente como una emulsión del tipo de agua en aceite Aquí, el ingrediente activo es soluble en agua y se podría administrar como una simple solución acuosa Sin embargo, las emulsiones inversas se invierten después de su inyección o infusión en un medio acuoso tal como la sangre y ofrecen la ventaja de proporcionar una dispersión más rápida y

eficiente del ingrediente activo dentro de ese medio acuoso que se puede obtener usando una solución acuosa Las emulsiones inversas se preparan usando apropiados agentes emulsionantes farmacéuticamente aceptables, que son bien conocidos en el sector tecnológico Cuando el ingrediente activo tiene una limitada solubilidad en agua, también se puede administrar como un sólido suspendido en forma coloidal o en una forma de microparticulas en una suspensión preparada usando apropiados agentes suspendedores farmacéuticamente aceptables Los sólidos suspendidos que contienen el ingrediente activo se pueden formular también como composiciones de liberación retardada, prolongada y/o controlada

Mientras que la administración por via sistémica se llevará a cabo con la máxima frecuencia por inyeccion o infusión en un liquido, existen muchas situaciones en las cuales será ventajoso o incluso necesario suministrar el ingrediente activo como un sólido La administración por vía sistémica de sólidos se lleva a cabo por instilación, inhalación o insuflación de una composición farmacéutica en una forma sólida apropiada que contiene el ingrediente activo La instilación del ingrediente activo puede implicar el recurso de instalar una composicion de implante sólido dentro de apropiados tejidos o cavidades corporales El implante puede comprender una matriz de materiales bio-compatibles y bio-erosionables en la que están dispersadas partículas de un ingrediente activo sólido o en que, posiblemente, se atrapan glóbulos o celdillas aisladas de un ingrediente activo líquido Deseablemente, la matriz será rota y absorbida completamente por el cuerpo La composición de la matriz se selecciona también preferiblemente para proporcionar una liberación controlada prolongada y/o retardada del ingrediente activo durante prolongados períodos de tiempo, incluso hasta de varios meses

El término "implante" designa con la mayor frecuencia una composición farmacéutica sólida que contiene el ingrediente activo, mientras que el término "depósito" implica usualmente una composición farmacéutica liquida que contiene el ingrediente activo, que se deposita en cualesquiera apropiados tejidos o cavidades corporales para formar un recipiente (reservorio) o una agrupación que migra lentamente hacia los tejidos y órganos circundantes, y finalmente resulta distribuido/a sistémicamente Sin embargo, estas distinciones no son siempre mantenidas rígidamente en el sector tecnológico y, consiguientemente, se considera que se incluyen dentro del alcance del presente invento los implantes líquidos y los depósitos sólidos e incluso formas sólidas y líquidas mixtas para cada uno de ellos Los supositorios pueden ser considerados como un tipo de implante, puesto que comprenden bases que son sólidas a la temperatura ambiente pero que se funden a la temperatura del cuerpo de un paciente, liberando con lentitud el ingrediente activo con el que están impregnados, dentro del tejido circundante del cuerpo de un paciente, en que el ingrediente activo resulta absorbido y transportado para

efectuar una administracion por via sistémica

La administración por via sistémica se puede conseguir también por inhalación o insuflación de un polvo es decir, de una composición en forma de particulas que contiene el ingrediente activo Por ejemplo, el ingrediente activo en forma de un polvo se puede inhalar dentro de los pulmones usando convencionales dispositivos para convertir en aerosoles las formulaciones en partículas El ingrediente activo es una formulación en particulas que también se puede administrar por insuflación, es decir se puede soplar o dispersar de otro modo dentro de apropiados tejidos o cavidades corporales por simple espolvoreo o usando dispositivos convencionales para convertir en aerosoles las formulaciones en particulas Estas composiciones en partículas se pueden formular también para proporcionar una liberación retardada, prolongada y/o controlada del ingrediente activo de acuerdo con principios bien comprendidos y materiales conocidos

Otros medios de administración por vía sistémica, que pueden utilizar los ingredientes activos del presente invento en forma ya sea líquida o sólida incluyen las rutas transdérmica, intranasal y oftalmica En particular, los parches transdérmicos preparados de acuerdo con una tecnología bien conocida de suministro de fármacos, se pueden preparar y aplicar a la piel de un paciente que ha de ser sometido a tratamiento, después de lo cual el agente activo, por razón de sus caracteristicas formuladas de solubilidad, migra a través de la epidermis y dentro de las capas dérmicas de la piel de un paciente, en donde es recogido como una parte de la circulación general del paciente, proporcionando a fin de cuentas una distribucion por vía sistémica del ingrediente activo durante un deseado período de tiempo prolongado También se incluyen implantes que son colocados por debajo de la capa epidérmica de la piel, es decir entre la epidermis y la dermis de la piel del paciente que está siendo sometido a tratamiento Dicho implante se formulará de acuerdo con principios y materiales bien conocidos que se utilizan corrientemente en esta tecnologia de suministro y se pueden preparar de una manera tal que se proporcione una liberación controlada, prolongada y/o retardada del ingrediente activo dentro de la circulación sistémica del paciente Dichos implantes subepidérmicos (subcuticulares) proporcionan la misma facilidad de instalación y la misma eficiencia de suministro que los parches transdérmicos, pero sin la limitación de estar sujetos a degradacion, deterioro o eliminación accidental como una consecuencia de estar expuestos sobre la capa superior de la piel de un paciente

En la descripción anterior de composiciones farmacéuticas que contienen un ingrediente activo de Fórmula (1 0 0), las expresiones equivalentes "administración", "administración de", "administrar" y "administrar una", se han usado con respecto a dichas composiciones farmacéuticas Tal como se emplean de este modo, se pretende que estas expresiones signifiquen proporcionar a un paciente que necesite de un

tratamiento una composicion farmacéutica del presente invento por cualquiera de las rutas de administración aquí descritas, en que el ingrediente activo es un compuesto de Fórmula (1 0 0) o un profármaco, derivado o metabolito del mismo, que es util para tratar una enfermedad un trastorno o una condición que es mediada/o por o está asociada/o con la modulación de la actividad de las PDE4 especialmente de las PDE4D en dicho paciente Correspondientemente, se incluye dentro del alcance del presente invento cualquier otro compuesto que, después de su administración a un paciente, sea capaz de proporcionar directa o indirectamente un compuesto de Fórmula (1 0 0) Dichos compuestos son reconocidos como profármacos y están disponibles cierto numero de procedimientos consagrados para preparar dichas formas de profármacos de los compuestos de Fórmula (1 0 0)

El régimen de dosificación y dosis de los compuestos de Fórmula (1 0 0) eficaces para tratar o prevenir una enfermedad un trastorno o una condición mediada/o por o asociada/o con la modulación de la actividad de las PDE4, especialmente de la PDE4D, dependerán de una diversidad de factores, tales como la naturaleza del agente inhibidor, el tamaño del paciente, la meta del tratamiento la naturaleza de la patología que se ha de someter a tratamiento la composición farmacéutica específica usada, y las observaciones y conclusiones del médico que esté realizando el tratamiento

Por ejemplo, cuando la forma de dosificación es oral, p ej , una tableta o cápsula, los apropiados niveles de dosificación de los compuestos de Fórmula (1 0 0) estarán entre aproximadamente 0 1 µg/kg y aproximadamente 50,0 mg/kg de peso corporal por día, con preferencia entre aproximadamente 5,0 µg/kg y aproximadamente 5,0 mg/kg de peso corporal por día, con mayor preferencia entre aproximadamente 10,0 µg/kg y aproximadamente 1,0 mg/kg de peso corporal por día, y con la mayor preferencia entre aproximadamente 20,0 µg/kg y aproximadamente 0,5 mg/kg de peso corporal por día del ingrediente activo

Cuando la forma de dosificación es administrada por vía tópica a los bronquios y pulmones, p ej , por medio de un inhalador o nebulizador de polvos, los niveles apropiados de dosificacion de los compuestos de Fórmula (1 0 0) estarán entre aproximadamente 0,001 µg/kg y aproximadamente 10,0 mg/kg de peso corporal por dia, con preferencia entre aproximadamente 0,5 µg/kg y aproximadamente 0,5 mg/kg de peso corporal por día, con mayor preferencia entre aproximadamente 1,0 µg/kg y aproximadamente 0,1 mg/kg de peso corporal por día, y con la máxima preferencia entre aproximadamente 2 0 µg/kg y aproximadamente 0,05 mg/kg de peso corporal por día del ingrediente activo

Usando pesos corporales representativos de 10 kg y 100 kg con el fin de ilustrar la gama de dosificaciones tópicas convertidas en aerosoles dianamente, que se pueden

usar como antes se ha descrito, los apropiados niveles de dosificación de los compuestos de Fórmula (1 0 0) estaran entre aproximadamente 1,0 - 10,0 µg y 500,0 - 5 000,0 mg por dia, con preferencia entre aproximadamente 5 0 - 50 0 µg y 5 0 - 50 0 mg por día, con mayor preferencia entre aproximadamente 100,0 - 1 000,0 µg y 10,0 - 100,0 mg por día, y con la mayor preferencia entre aproximadamente 200,0 - 2 000,0 µg y aproximadamente 5,0 - 50,0 mg por dia del ingrediente activo que comprende un compuesto de Fórmula (1 0 0) Estos intervalos de cantidades de dosificación representan cantidades de dosificación totales del ingrediente activo por día para un paciente dado El numero de veces por día en que se administra una dosis dependerá de factores farmacológicos y farmacocinéticos tales como la semivida del ingrediente activo, que refleja su régimen de catabolismo y aclaramiento, así como los niveles minimos y óptimos en plasma sanguíneo u otros fluidos corporales de dicho ingrediente activo que se alcanzan en el paciente y que se requieren para obtener una eficacia terapéutica

Otros numerosos factores deben también ser considerados para decidir el numero de dosis por día y la cantidad de ingrediente activo por dosis que se administrará No es el menos importante de dichos otros factores la respuesta individual del paciente que está siendo sometido a tratamiento Por lo tanto, por ejemplo, cuando el ingrediente activo se usa para tratar o prevenir el asma, y se administra por vía tópica a través de una inhalación de aerosol dentro de los pulmones se administrarán cada día de una a cuatro dosis que consisten en actuaciones de un dispositivo dispensador, es decir, "bocanadas" de un inhalador, conteniendo cada dosis desde aproximadamente 50,0 µg hasta aproximadamente 10,0 mg de ingrediente activo

Los compuestos de Formula (1 0 0) se pueden administrar en una formulación de liberación controlada tal como una formulación de liberación lenta o de liberación rápida (inmediata) Dichas formulaciones de liberación controlada de los compuestos de Fórmula (1 0 0) se pueden preparar usando métodos bien conocidos por los expertos en el sector tecnológico Por ejemplo, se puede preparar la formulación de un producto terapeutico que tiene hasta tres o incluso cuatro formas de dosificación con diferentes perfiles de liberación Con respecto al componente de liberación inmediata, en una realización, el componente forma de dosificación de liberación inmediata proporciona de aproximadamente 20% a aproximadamente 50% de la dosificación total del agente terapéutico que se ha de suministrar por el producto Con respecto al componente de liberación retardada, el tiempo de liberacion se puede controlar por medio de la concentración del agente terapéutico en el revestimiento y/o el espesor del revestimiento Estas formas de dosificación remanentes suministran el resto del agente terapéutico Si se usa más de una forma de dosificación de liberación retardada, cada una de las formas

de dosificación de liberacion retardada puede proporcionar cantidades aproximadamente iguales de agente terapéutico, pero éstas se pueden formular tambien para proporcionar cantidades diferentes Cada una de las formas de dosificación puede contener el mismo agente terapéutico, pero cada una de las formas de dosificación puede contener también más de un agente terapéutico, o un agente terapéutico diferente

La porción de liberación inmediata de la formulación de liberación controlada puede ser una mezcla de ingredientes que se descomponga con rapidez después de la administración, para liberar el agente terapéutico Ésta puede adoptar la forma o bien de un comprimido o gránulo discreto que se incorpora y mezcla con, o se comprime con, los otros componentes de la formulación Los materiales para el componente de liberación inmediata incluyen p ej , celulosa microcristalina, almidón de maíz, almidón previamente gelatinizado almidón de patata almidón de arroz, carboximetil-almidón de sodio hidroxipropil-celulosa, hidroxipropil-metil-celulosa, hidroxietil-celulosa, etil-celulosa, quitosana, hidroxi-quitosana, quitosana hidroximetilado, quitosana reticulado, hidroximetil-quitosana reticulado, maltodextrina, manitol, sorbitol, dextrosa, maltosa, fructosa, glucosa, levulosa, sacarosa, poli(vinil-pirrolidona) (PVP), derivados de ácido acrílico, p ej , Carbopol y Eudragit, polietilen-glicoles, p ej los PEG's de bajo peso molecular PEG2 000-10 000, y los PEG's de alto peso molecular p ej Polyox, con unos pesos moleculares situados por encima de 20 000 dalton Estos materiales estarán presentes usualmente en el intervalo de 1,0 a 60% (p/p = peso/peso)

Puede ser deseable tener otros ingredientes en la formulación de liberación controlada como una ayuda en la disolución del agente terapéutico, o en la descomposición de algun otro componente después de ingestión o administración Dichos ingredientes incluyen agentes tensioactivos, p ej , lauril-sulfato de sodio, monoglicerato de sodio, monooleato de sorbitán, monooleato de sorbitán, poli(oxietilen)-monooleato de sorbitán, monoestearato de glicerilo, monooleato de glicerilo, monobutirado de glicerilo, un agente tensioactivo no iónico, p ej tomado de Pluronic, u otros materiales con propiedades de actividad superficial Todos estos ingredientes se pueden usar en combinación y usualmente estarán presentes en el intervalo de 0,05-15% (p/p)

Un componente de liberación retardada, no sensible al pH, de las formulaciones de liberación controlada que se usan en el presente invento, puede tener los mismos ingredientes que el componente de liberación inmediata que antes se ha descrito, pero con polimeros adicionales integrados en la composición, o aplicados como revestimientos sobre el comprimido o gránulo que se forma Los materiales usados para obtener un retraso en la liberación apropiados para este componente, son, p ej polietilen-glicol (PEG) con un peso molecular por encima de 4 000 dalton, p ej , Carbowax y Polyox, ceras, p ej cera blanca o cera de abejas, parafina, derivados de ácido acrílico p ej ,

Eudragit, propilen-glicol y etil-celulosa Típicamente estos materiales están presentes en el intervalo de 0,5-25% (p/p) de este componente

Un componente sensible al pH, es decir, de liberación entérica de las formulaciones de liberación controlada, usadas en el presente invento, puede tener los mismos ingredientes que el componente de liberación inmediata que antes se ha descrito, pero con polímeros adicionales integrados en la composición o aplicados como revestimiento sobre el comprimido o gránulo que se forma La clase de materiales que son utiles para esta finalidad son acetato-ftalato de celulosa, Eudragit L, y otras sales ftalatos de derivados de celulosa, que pueden estar presentes en concentraciones de 4-20% (p/p)

Un componente de liberación prolongada de las formulaciones de liberación controlada usadas en el presente invento, puede tener los mismos ingredientes que el componente de liberación inmediata que antes se ha descrito, pero con polímeros adicionales integrados en la composición, o aplicados como revestimientos sobre el comprimido o gránulo que se forma La clase de materiales utiles para esta finalidad son etil-celulosa, hidroxipropil-metil-celulosa, hidroxipropil-celulosa, hidroxietil-celulosa, carboximetil-celulosa, metil-celulosa, nitro-celulosa Eudragit R y Eudragit RL, Carbopol y polietilen-glicoles con pesos moleculares por encima de 8 000 dalton, que pueden estar presentes en concentraciones de 4-20% (p/p)

Las unidades en forma de partículas que forman la base para las formulaciones de liberación controlada usadas en el presente invento pueden estar en la forma de comprimidos o gránulos discretos o partículas contenidos/as en una cápsula, o en la forma de partículas embebidas en una tableta o suspendidas en una suspensión líquida La formulación de liberación controlada se puede administrar, p ej , por una ruta sublingual transmucosal, transdérmica o parenteral, y preferiblemente se administra por vía oral

En una realización particular de la formulación de liberación controlada usada en el presente invento, la formulación de un compuesto de Fórmula (1 0 0) se basa preferiblemente en comprimidos activos que tienen un nucleo que forma un componente inerte que puede comprender nucleos de siembra de azucar *non-pareil* (esferas de azucar, USP XXII) que tienen un tamaño medio de mallas 14 a 35 El componente inerte que forma el nucleo es revestido con una formulación que comprende un compuesto de Fórmula (1 0 0) e hidroxipropil-metil-celulosa Una suficiente cantidad del revestimiento se aplica para proporcionar la deseada dosificación de un compuesto de Fórmula (1 0 0), es decir con preferencia entre aproximadamente 5,0 µg/kg y aproximadamente 5,0 mg/kg de peso corporal por día

Para formar un comprimido designado por A el comprimido activo es revestido

seguidamente con un revestimiento de cierre hermético que puede comprender una mezcla de hidroxipropil-metil-celulosa y polietilen-glicol El polietilen-glicol puede tener un peso molecular medio numénco comprendido entre 200 y 2 000 Generalmente, se puede aplicar una relación de 2 1 a 6 1 de la hidroxipropil-metil-celulosa al polietilen-glicol en forma de una solución al 3 hasta 7 % en peso en un disolvente tal como etanol, alcohol isopropílico, agua y sus mezclas El revestimiento de cierre hermético es luego revestido con un revestimiento modificador de la liberación que comprende una mezcla de una resina acrílica que es soluble en medios de carácter ácido, y un polímero insoluble en agua, p ej un polímero celulósico tal como etil-celulosa o acetato de celulosa, en una relación en peso de aproximadamente 1 4, respectivamente Dicho revestimiento modificador de la liberacion se aplica a partir de una solución al 3 hasta 7% en peso de alcohol isopropílico, etanol, acetona o mezclas de estos compuestos Una resina acrílica util que es soluble en medios ácidos es la Eudragit E que consiste en un copolímero catiónico de metacrilato de dimetilamino-etilo y ésteres neutros de ácido metacrílico que tienen un peso molecular medio ponderado de 150 000

Para formar un comprimido designado por B el comprimido A es revestido con un primer revestimiento de hidroxipropil-metil-celulosa, después de lo cual se aplica un revestimiento entérico, donde el polimero de revestimiento entérico es goma laca, copolímeros de ácido metacrílico (Eudragit S ó L), acetato-ftalato de celulosa ftalato de hidroxipropil-metil-celulosa, acetato-succinato de hidroxipropil-metil-celulosa, trimelitato-acetato de celulosa, poli(acetato-ftalato de vinilo), o mezclas de ellos, particularmente acetato-ftalato de celulosa El espesor del revestimiento se selecciona para proporcionar el deseado régimen de liberación, que depende del espesor de los constituyentes del revestimiento

Se pueden utilizar ayudas de revestimiento auxiliares, p ej 1-5 % en peso basado en el componente de nucleo activo y en el peso total del revestimiento final, de un plastificante tal como acetil-citrato de tributilo, triacetina un monoglicérido acetilado, aceite de colza, aceite de oliva, aceite de sésamo, acetil-citrato de trietilo, glicerol-sorbitol, oxalato de dietilo, maleato de dietilo, fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dioctilo, sebacato de dibutilo, citrato de trietilo citrato de tributilo, tributirato de glicerol, polietilen-glicol (con un peso molecular de 380 a 420), propilen-glicol y mezclas de ellos, en combinación con uno o más agentes antiadherentes, p ej , un estearato de metal alcalino-térreo tal como estearato de magnesio o estearato de calcio, o talco

Los nucleos se forman proyectando los nucleos de semillas *non-pareil* con una suspensión acuosa o no acuosa que contiene un compuesto de Fórmula (1 0 0) e hidroxipropil-metil-celulosa El medio para suspensión puede comprender cualquier

disolvente con baja viscosidad, p ej alcohol isopropílico, etanol, agua o mezclas de ellos Se prefiere secar cada uno de los revestimientos antes de aplicar un segundo revestimiento Los comprimidos A y los comprimidos B se mezclan conjuntamente para obtener un producto acabado que tiene el siguiente perfil de liberación *in vitro* de 50 a 80 % en peso liberado después de 2 horas en SGF (pH 1,5) de 70 a 95 % en peso liberado después de 4 horas en SGF (pH 1 5) y no menos de 80 % en peso liberado después de 6 horas en SGF (pH 1,5), tal como se determina en un aparato USPXXII del Tipo 2, a 37°C y 50 rpm

Los comprimidos o gránulos se pueden colocar dentro de una cápsula de gelatina o se pueden convertir en tabletas añadiendo primeramente de 25 a 40 % en peso de un excipiente sólido para tabletas, farmacéuticamente aceptable, p ej lactosa, dextrosa, manitol, fosfato de calcio, celulosa microcristalina, caolín, sacarosa en polvo o sus mezclas que formarán una mezcla compresible con los comprimidos A y B, preferiblemente sin triturar a los comprimidos A o B y opcionalmente una cantidad eficaz de un agente desintegrante de tabletas, p ej , crospovidona, croscarmelosa de sodio, almidón seco o almidón-glicolato de sodio, y un lubricante

En otra realización de una formulación de liberación controlada que se usa en el presente invento, se preparan microesferas de poli(alcohol vinílico) (PVA) reticulado que contienen un compuesto de Fórmula (1 0 0) a partir de una solución acuosa de PVA que contiene diversas concentraciones de glutaraldehído dispersado en forma de gotitas en una parafina líquida, usando un agente de encolamiento apropiado La reticulación de las gotitas de PVA con glutaraldehído es inducida por un catalizador de carácter ácido, HCl, que se produce por la adición de pequeñas cantidades de cloruro de benzoílo al medio para dispersión Se preparan microesferas que contienen un compuesto de Fórmula (1 0 0) llevando a cabo la reacción de reticulación en la presencia de dicho compuesto de Fórmula (1 0 0) En otra realización, se preparan microesferas de policarbonato cargadas con un compuesto de Fórmula (1 0 0) mediante una técnica de evaporación del disolvente que da como resultado un alto grado de carga con fármaco de > 50%

Una realización adicional de las formulaciones de liberación controlada destinadas a usarse en el presente invento, comprende tabletas de liberación controlada que tienen una fase interna que contiene un fármaco y una fase externa que comprende un polímero de polietilen-glicol (PEG) que tiene un peso molecular medio ponderado de 3 000-10 000 Un compuesto de Fórmula (1 0 0) en forma cristalina se carga dentro de una bandeja para revestir y se reviste por proyección con una suspensión que contiene Eudragit L30D, acetil-citrato de trietilo, talco y agua a 54-60°C, hasta que se formen los cristales revestidos de dicho compuesto de Fórmula (1 0 0) Los cristales revestidos se mezclan con una igual cantidad de PEG (peso molecular medio 3 350) a 50°C para

formar una mezcla fundida que se conforma como tabletas

Otra realización de forma de dosificación sólida para vía oral de liberación prolongada destinada a usarse en el presente invento comprende una cantidad eficaz de un compuesto de Fórmula (1 0 0) que tiene una solubilidad de menos que aproximadamente 10 g/l, y un excipiente de liberación prolongada que comprende un agente de gelificación, un diluyente farmacéutico inerte, y una cantidad eficaz de un agente reticulante catiónico farmacéuticamente aceptable La relación del compuesto de Fórmula (1 0 0) al agente de gelificación es con preferencia de aproximadamente 1 3 a aproximadamente 1 8, y la tableta resultante proporciona un nivel en sangre terapéuticamente efectivo del compuesto de Fórmula (1 0 0) durante al menos aproximadamente 12 horas, y en realizaciones preferidas durante alrededor de 24 horas Preferiblemente dicho agente de gelificación es una goma de hetero-polisacárido y una goma de homo-polisacarido capaz de reticular a dicha goma de hetero-polisacárido cuando es expuesta a un fluido medioambiental y dicho diluyente farmacéutico inerte es granulado con una solución o una dispersion de un material hidrófobo en una cantidad eficaz para hacer más lenta la hidratación del agente de gelificación sin romper a la matriz hidrófila La combinación de goma de xantano con goma de algarrobo es un agente de gelificación preferido

El agente de reticulacion catiónico puede consistir en cationes de metales monovalentes o multivalentes Las sales preferidas son las sales inorgánicas, que incluyen diversos sulfatos, cloruros, boratos, bromuros, citratos, acetatos, lactatos de metales alcalinos y/o metales alcalino-térreos, etc Las sales preferidas son sulfato de calcio y cloruro de sodio El agente catiónico de reticulación es añadido en una cantidad eficaz para obtener un aumento deseado en la concentración del gel, típicamente en una cantidad de aproximadamente 1 a aproximadamente 20 % en peso del excipiente para liberación prolongada

El polímero hidrófobo está seleccionado entre una alquil-celulosa tal como etil-celulosa, otros materiales celulósicos hidrófobos, polímeros o copolímeros derivados de ésteres de ácido acrílico o metacrílico, copolímeros de ésteres de ácido acrílico y metacrílico, zeína, ceras, goma laca y aceites vegetales hidrogenados Alquil-celulosas comercialmente disponibles son Aquacoat, una dispersión acuosa de etil-celulosa disponible de FMC, y Surelease, una dispersión acuosa de etil-celulosa disponible de Colorcon), y los polímeros acrílicos incluyen Eudragit® RS y RL, que son copolímeros de ésteres de los ácidos acrílico y metacrílico que tienen un bajo contenido, p ej de 1 20 o 1 40 de compuestos de amonio cuaternario

Es importante incluir una cantidad eficaz de un agente humectante en la formulación de liberación controlada que antes se describe con el fin de aumentar la

biodisponibilidad de compuestos de Formula (1 0 0) con mala solubilidad El agente humectante se puede añadir p ej proyectando el granulado mientras que se está mezclando Los agentes humectantes apropiados incluyen polietilen-glicoles como ésteres o éteres, p ej , aceite de ricino polietoxilado aceite de ricino hidrogenado polioxietilado, un ácido graso polietoxilado procedente de aceite de ricino, o un ácido graso polietoxilado procedente de aceite de ricino hidrogenado Agentes humectantes comercialmente disponibles son Cremophor Myrj Polyoxyl 40 estearato, Emerest 2675 Lipal 395 y PEG 3350

Despues de ello, un técnico formulador sólo necesita mezclar el compuesto deseado de Fórmula (1 0 0) y un agente lubricante opcional con el excipiente y luego comprimir la mezcla para formar tabletas de liberación lenta El excipiente puede comprender una mezcla física de las gomas junto con un excipiente soluble tal como sacarosa, lactosa o dextrosa compresible aunque se prefiere granular o aglomerar las gomas con sacarosa, lactosa dextrosa pura, es decir cristalina, para formar un excipiente La forma de granulado tiene ciertas ventajas que incluyen el hecho de que puede ser optimizada en cuanto a fluidez y compresibilidad puede ser comprimido como tabletas, formulado en una cápsula, extrudido y esferonizado con un medicamento activo formar gránulos comprimidos etc

Los excipientes farmacéuticos preparados de acuerdo con el presente invento se pueden preparar de acuerdo con cualquier técnica de aglomeración para proporcionar un apropiado producto excipiente En técnicas de granulación en humedo, las cantidades deseadas de la goma de hetero-polisacárido, la goma de homo-polisacárido, y el diluyente inerte se mezclan conjuntamente y después de ello se añade un agente humectante tal como agua, propilen-glicol, glicerol, alcohol u otro similar para preparar una masa humedecida Seguidamente, la masa humedecida es secada La masa secada es luego molida con un equipo convencional para formar gránulos

En todavía otras realizaciones de las formulaciones de liberación controlada usadas en el presente invento un compuesto de Fórmula (1 0 0) que tienen una mala solubilidad en agua forma una dispersión sólida de un polimero poloxámero hidrófilo siendo mezclada dicha dispersión con una hidroxipropil-metil-celulosa hinchable con agua, de la que una solución al 2 % tiene una viscosidad en el intervalo de 100-100 000 centipoises, para formar una matriz de hidrogel, y uno o más ingredientes para compresión de tabletas a fin de formar un nucleo de tabletas, siendo eficaz dicho nucleo de tabletas, como tal o después de revestimiento del nucleo con un revestimiento polimérico, para conseguir niveles terapéuticos de dicho compuesto de Fórmula (1 0 0) durante prolongados períodos de tiempo después de una administración por vía oral

Se puede incluir un componente tensioactivo que es un agente tensioactivo

aniónico, catiónico o no iónico, seleccionado entre lauril-sulfato de sodio, un carboxilato de sodio, un alquil-sulfato, un éster de polietilen-glicol, un éter de polietileno, un éster de sorbitán, un éster de sorbitán etoxilado, un haluro de alquil-trimetil-amonio, y una mezcla de ellos La dispersión sólida puede incluir también un componente ácido seleccionado entre ácido adípico, ácido ascórbico ácido cítrico ácido fumárico, ácido málico, ácido succínico y ácido tartárico Además, la dispersión sólida puede incluir un componente de base seleccionado entre carbonato de calcio, hidróxido de calcio, hidróxido de magnesio bicarbonato de sodio, carbonato de sodio, citrato de sodio e hidróxido de sodio

Los polioles poloxameros son una serie de copolímeros de bloques de óxido de etileno y óxido de propileno estrechamente relacionados y, más especialmente, los polioles poloxámeros son copolímeros de bloques de α-hidro-ω-hidroxi-poli(oxietileno)-poli(oxipropileno)-poli(oxietileno), conocidos más generalmente como copolímeros de etilen-propilen-glicol o copolímeros de poli(oxietileno)-poli(oxipropileno) Los poloxámeros preferidos son los que contienen entre 60% y 90% más especialmente entre 70% y 80%, en peso de la porción de poli(oxietileno) El segmento de poli(oxietileno) es hidrófilo mientras que el segmento de poli(oxipropileno) es hidrófobo Los poloxámeros difieren solamente en las cantidades relativas de óxido de propileno y óxido de etileno que se añaden durante la producción Los polioles poloxamer (poloxámeros) son conocidos por los nombres comerciales Lutrol, Monolan y Pluronic Los compuestos mal solubles de Fórmula (1 0 0) son fácilmente dispersables en la forma fundida de los poloxámeros, y cuando se enfrían, la mezcla del compuesto de Fórmula (1 0 0), uno o varios agente(s) auxiliar(es) si está(n) presente(s), y un poloxámero forma un sólido duro y seco que puede ser triturado o molido con facilidad

La forma de dosificación oral sólida de la realización antes mencionada puede estar en la forma de una cápsula o de una tableta La tableta consta de un nucleo de tableta definido por una dispersión sólida como ya se ha descrito, dispersada en una matriz de hidrogel La dispersión sólida es comprimida en una forma de dosificación que contiene un polímero o una mezcla de polímeros, que cuando estén humedos se hincharán para formar un hidrogel El régimen de liberación de un compuesto de Fórmula (1 0 0) a partir de esta forma de dosificación se controla tanto por difusión a partir de la masa hinchada para tabletas como por erosión de la superficie de las tabletas a lo largo del tiempo El regimen de liberación de un compuesto de Fórmula (1 0 0) se puede controlar tanto por medio de la cantidad de polimero por tableta y mediante las viscosidades inherentes de los polímeros usados Un preferido polímero hinchable con agua es hidroxipropil-metil-celulosa (HPMC)

La dispersión sólida está en la forma de un nucleo de tabletas de liberación instantánea, que está adaptado para compresión directa seguida por revestimiento con

la membrana que controla el regimen Una consideración principal con dicha formulación es la selección de apropiados ingredientes de tabletas para confenr el efecto deseado mientras que se comprime con facilidad, correspondientemente, la dispersión sólida se mezcla de manera apropiada, con excipientes clásicos para tabletas, tales como una base de compresión clásica Un azucar compresible, un agente solubilizante y un agente lubricante En este tipo de forma de dosificacion, la liberación de un compuesto de Fórmula (1 0 0) se controla por medio de un mecanismo de difusión

Con el fin de obtener el deseado perfil de liberación, apropiado para la administración en una vez por día, la membrana que controla el régimen contendrá apropiadamente una proporción mayontaria de un polímero insoluble en agua formador de película farmacéuticamente aceptable, y opcionalmente una proporción minoritaria de un polímero soluble en agua, formador de pelicula farmacéuticamente aceptable Los polímeros solubles en agua incluyen polímeros que son libremente permeables para el agua, mientras que los polímeros insolubles en agua incluyen polímeros que son ligeramente permeables al agua Preferiblemente, el polimero soluble en agua existente en la membrana, si está presente, se selecciona entre poli(alcohol vinílico), poli(vinil-pirrolidona), metil-celulosa, hidroxipropil-celulosa, hidroxipropil-metil-celulosa, agar, carragenano, xantano, polietilen-glicol, y sus mezclas Se puede usar la incorporación de diversos agentes hidrófilos en el revestimiento polimérico de manera tal que se formen canales en dicho revestimiento, y en general conduce a un régimen de liberación más lineal Dichos agentes hidrófilos incluyen ácido fumárico, ácido cítrico, ácido tartárico, citrato de sodio bicarbonato de sodio, fumarato de sodio, carbonato de sodio, monosacáridos y disacáridos Un monosacárido especialmente apropiado es glucosa Alternativamente, el polímero soluble en agua existente en la membrana se puede reemplazar por un material polimérico que es permeable libremente para el ingrediente activo y el agua, y comprende un copolimero de esteres de los acidos acrílico y metacrílico Un polimero apropiado, que es libremente permeable para varios compuestos mal solubles de Fórmula (1 0 0) y para el agua, es el que se vende como Eudragit RL

Otros polímeros solubles en agua formadores de película farmacéuticamente aceptables, que se pueden usar, incluyen un acilato de celulosa, un diacilato de celulosa, un triacilato de celulosa, acetato de celulosa, diacetato de celulosa, triacetato de celulosa, acetato de beta-glicano, dimetil-acetato de acetaldehido, acetato-etil-carbamato de celulosa, una poliamida, un poliuretano, un poliestireno sulfonado, acetato-ftalato de celulosa, acetato-metil-carbamato de celulosa, acetato-succinato de celulosa, acetato-dimetilamino-acetato de celulosa, acetato-cloroacetato de celulosa, dipalmitato de celulosa, dioctanoato de celulosa, dicaprilato de celulosa, dipentanoato de celulosa,

acetato-valerato de celulosa, acetato-p-toluenosulfonato de celulosa, acetato-butirato de celulosa, y otros polímeros semi-permeables tales como los que se describen en la patente de los EE UU Nº 4 285 987 y polímeros selectivamente permeables formados por la co-precipitación de un policatión y un polianión como se describe en las patentes de los EE UU Nºs 3 173 876 3 276 586, 3 541 005 3 541 006 y 3 546 142

El polímero insoluble en agua se selecciona preferiblemente entre etil-celulosa, acetato de celulosa, propionato de celulosa (de peso molecular bajo, intermedio o alto), acetato-propionato de celulosa, acetato-butirato de celulosa, acetato-ftalato de celulosa, triacetato de celulosa poli(metacrilato de metilo) poli(metacrilato de etilo), poli(metacrilato de butilo), poli(metacrilato de isobutilo), poli(metacrilato de hexilo), poli(metacrilato de isodecilo), poli(metacrilato de laurilo) poli(metacrilato de fenilo), poli(acrilato de metilo), poli(acrilato de isopropilo), poli(acrilato de isobutilo), poli(acrilato de octadecilo), poli(etileno), poli(etileno) de baja densidad, poli(etileno) de alta densidad, poli(propileno), poli(óxido de etileno), poli(tereftalato de etileno), poli(vinil-isobutil-eter) poli(acetato de vinilo), poli(cloruro de vinilo) poliuretano y sus mezclas El polímero insoluble en agua de la membrana puede comprender también polímeros o resinas que se presentan en la naturaleza, p ej goma laca, quitosana, goma de enebro o junípero, una cera o una sustancia similar a una cera, zeína, aceites vegetales hidrogenados o una de sus mezclas

El polímero insoluble en agua existente en la membrana se puede reemplazar también por un material polimérico, que es ligeramente permeable para el ingrediente activo y el agua, y comprende un copolímero de ésteres de ácido acrílico y metacrílico, p ej , un polímero vendido como Eudragit RS o un polímero cuya permeabilidad es dependiente del pH y se vende como Eudragit L, Eudragit S o Eudragit E Se prefiere el Eudragit S Los polímeros Eudragit son sustancias de barnices poliméricos, basadas en acrilatos y/o metacrilatos Los Eudragit RL y Eudragit RS son resinas acrílicas que comprenden copolímeros de ésteres de los ácidos acrílico y metacrílico con un bajo contenido en grupos de amonio cuaternario, que están presentes en forma de sales y dan lugar a la permeabilidad de las películas de barniz El Eudragit es libremente permeable y el Eudragit RS es ligeramente permeable, ambos independientemente del pH El Eudragit S es un polímero aniónico sintetizado a partir de ácido metacrílico y el éster metílico de ácido metacrílico, que es insoluble en ácidos y en agua pura, pero se vuelve soluble en un medio desde neutro a débilmente alcalino formando sales con álcalis La permeabilidad del Eudragit S es dependiente del pH, puesto que por encima de un pH de 6 0, el polímero se vuelve crecientemente permeable

La solución/suspensión para revestimiento del material polimérico comprende uno o más polímeros disueltos o suspendidos en un apropiado disolvente o en una apropiada

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mezcla de disolventes La concentración del material polimérico en la solución/ suspensión de revestimiento se determina por la viscosidad de la solución/suspensión final La adición de un agente plastificante a la solución/suspensión polimérica puede ser necesaria, dependiendo de la formulación con el fin de mejorar la elasticidad y la estabilidad de la película polimérica y evitar cambios en la permeabilidad del polímero durante un almacenamiento prolongado Dichos cambios pueden afectar al régimen de liberación de un compuesto de Fórmula (1 0 0) Agentes plastificantes apropiados incluyen polietilen-glicol, propilen-glicol glicerol triacetina, ftalato de dimetilo, ftalato de dietilo, ftalato de dibutilo sebacato de dibutilo citrato de trietilo, citrato de tributilo, acetil-citrato de trietilo, aceite de ricino y porcentajes variables de monoglicéridos acetilados

Puesto que la etil-celulosa, que es un material polimérico hidrófobo preferido, tiene una alta temperatura de transición vítrea y no forma películas flexibles en condiciones normales de revestimiento, es necesario plastificar la etil-celulosa antes de usarla como un material para revestimiento La plastificación de la etil-celulosa se puede conseguir o bien por la denominada "plastificación interna" o bien por la "plastificación externa" La idoneidad de un plastificante depende de su afinidad o poder solvatante para el polímero y de su eficacia para interferir con fijaciones de polímero con polímero Dicha actividad confiere la deseada flexibilidad aliviando la rigidez molecular Generalmente, la cantidad del plastificante incluido en una solución para revestimiento está basada en la concentración del agente formador de película, p ej , con la mayor frecuencia de aproximadamente 1 a aproximadamente 50 % en peso del agente formador de película La concentración del plastificante sin embargo, puede solamente ser determinada apropiadamente después de una experimentación cuidadosa con la solución particular de revestimiento y el método particular de aplicación Lo más preferiblemente, se incluye alrededor de 20% de un plastificante en la dispersión acuosa de un polímero acrílico

Un parámetro importante en la determinación de un plastificante apropiado para un polímero está relacionado con la temperatura de transición vítrea (Tg) del polímero La temperatura de transición vítrea está relacionada con la temperatura o el intervalo de temperaturas en el que hay un cambio fundamental en las propiedades físicas del polímero Este cambio no refleja un cambio de estado, sino más bien un cambio en la movilidad macromolecular del polímero Por debajo de la Tg, la movilidad de la cadena del polímero es gravemente restringida Por lo tanto, para un polímero dado, si su Tg está por encima de la temperatura ambiente, el polímero se comportará como un material vítreo, siendo duro, no plegable y más bien frágil, propiedades que son demasiado restrictivas en el revestimiento con películas puesto que la forma de dosificación revestida puede ser sometida a una cierta cantidad de tensión externa La incorporación de apropiados plastificantes en la matriz del polímero reduce efectivamente la Tg, de

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manera tal que en condiciones del ambiente las películas son más blandas, más plegables y con frecuencia más duras y por lo tanto mejor capaces de resistir tensiones mecánicas

Otros aspectos de plastificantes apropiados incluyen la capacidad del plastificante para actuar como un buen "agente de hinchamiento" para la etil-celulosa y el perfil de solubilidad de la película de polímero en agua Ejemplos de apropiados plastificantes para la etil-celulosa incluyen sebacato de dibutilo, ftalato de dietilo, citrato de trietilo y citrato de tributilo, aunque se pueden usar otros plastificantes p ej monoglicéridos acetilados, ésteres ftalatos y aceite de ricino Ejemplos de plastificantes apropiados para los polímeros acrílicos antes descritos incluyen ésteres de ácido cítrico tales como citrato de trietilo NF XVI, citrato de tributilo, ftalato de dibutilo y 1,2-propilen-glicol Otros plastificantes que han demostrado ser apropiados para intensificar la elasticidad de las películas formadas a partir de polímeros acrílicos tales como soluciones de barnices Eudragit RL y RS, incluyen polietilen-glicoles, propilen-glicol, ftalato de dietilo, aceites de ricino y triacetina

Una dispersión acuosa apropiada de etil-celulosa es el Aquacoat vendido por FMC Corp , que se prepara disolviendo la etil-celulosa en un disolvente orgánico inmiscible con agua y luego emulsionándola en agua en la presencia de un agente tensioactivo y un estabilizador Después de homogeneización para generar gotitas de tamaño inferior al micrómetro, el disolvente orgánico es evaporado en vacío para formar un pseudo-látex El plastificante no es incorporado en el pseudo-látex durante la fase de producción, consiguientemente, antes de usarlo como revestimiento, es necesario mezclar íntimamente el Aquacoat con un plastificante apropiado Otra apropiada dispersion acuosa de etil-celulosa es la Surelease vendida por Colorcon, Inc , que se prepara incorporando un plastificante en la dispersión durante el proceso de producción Una masa termofusible de un polímero, un plastificante (sebacato de dibutilo) y un estabilizador (ácido oleico) se prepara como una mezcla homogénea, que luego es diluida con una solución alcalina para obtener una dispersión acuosa que puede ser aplicada directamente sobre substratos

Se ha encontrado además que la adición de una pequeña cantidad de talco reduce la tendencia de la dispersión acuosa a adherirse durante el tratamiento, y actua como un agente de pulimentación

El revestimiento del nucleo activo de tableta con una membrana permeable diferencialmente permite una disolución y una difusión activas a partir del micro-entorno del nucleo activo Polímeros especialmente apropiados para esta finalidad son celulosa y polímeros basados en poli(metacrilatos), y el revestimiento se realiza de manera apropiada en un aparato granulador C F 360 Disolventes preferidos para su uso en la

aplicación y el revestimiento con polímeros incluyen acetona, alcohol isopropílico y esencia mineral industrial metilada Una dispersión acuosa plastificada de un polímero hidrófobo se puede aplicar sobre un nucleo de tableta por proyección, usando cualquier apropiado equipo de proyección conocido en el sector tecnológico En un método preferido se usa un sistema de lecho fluidizado Wurster en el que un chorro de aire, inyectado desde abajo fluidifica al material de nucleo y efectua la desecación mientras que el revestimiento de polímero acrílico se está proyectando sobre él Se aplica preferiblemente una cantidad suficiente de la dispersión acuosa de polímero hidrófobo para obtener una liberación controlada predeterminada de un compuesto de Fórmula (1 0 0) cuando el substrato revestido es expuesto a soluciones acuosas, p ej , un fluido gástrico tomando en cuenta las caracteristicas físicas de dicho compuesto de Fórmula (1 0 0), la manera de incorporar el plastificante, etc Después de haber revestido con el polímero hidrófobo, un revestimiento superior adicional de un compuesto formador de película, tal como hidroxipropil-metil-celulosa p ej , Opadry, es aplicado opcionalmente a las tabletas Este revestimiento superior es proporcionado, si es que lo es, con el fin de reducir sustancialmente la aglomeración de las tabletas

El problema de la estabilidad de las formulaciones farmacéuticas de liberación controlada usando dispersiones acuosas de polímeros hidrófobos, es decir que los cambios de perfil de liberación y disolución al envejecer, se pueden superar curando la tableta revestida a una temperatura mayor que la temperatura de transición vítrea de la dispersión acuosa de un polímero hidrófobo plastificado y con una necesaria humedad relativa hasta que se alcanza un punto final en el que dicho substrato alcanza un perfil de disolución que está sustancialmente sin afectar por exposición a condiciones de almacenamiento aceleradas, p ej , de aproximadamente 37°-40°C, y una humedad relativa de aproximadamente 75-80% durante tres meses o un período de tiempo más largo

Los revestimientos de liberación controlada para compuestos de Fórmula (1 0 0) pueden incluir también agentes modificadores de la liberación, tales como acetato-ftalato de celulosa, descritos en la patente de los EE UU N° 2 196 768, goma laca, zeína, ftalato de hidroxipropil-metil-celulosa, goma de sandáraca, goma laca modificada, etc Los apropiados agentes modificadores de la liberación pueden abarcar también agentes favorecedores de la erosión tales como almidón inclusive almidón de maíz, almidón de arroz, carboximetil-almidon, almidón de patata, y otros almidones vegetales, un almidón modificado, y derivados de almidón Esta categoría incluye otros agentes favorecedores de la erosión tales como gomas, p ej , goma de xantano, ácido algínico, otros alginatos bentonita, Veegum, agar, guar, goma de algarrobo, goma arábiga, membrillo de pulguera (*psyllium*), semillas de lino goma de quimbombó arabinogiactina, pectina, tragacanto,

esclerogluçano, dextrano, amilosa, amilopectina, dextrina, etc poli(vinil-pirrolidona) reticulada, resinas de intercambio de iones, tales como un poli(metacrilato de potasio), carragenano κ-carragenano λ-carragenano, goma de carajá (karaya) una goma biosintética, etc

Los revestimientos de liberación controlada para compuestos de Fórmula (1 0 0) pueden incluir también materiales que sean utiles para producir láminas microporosas en el entorno de uso Los materiales utiles para producir las láminas microporosas incluyen policarbonatos que se componen de poliésteres lineales de ácido carbónico en los que los grupos de carbonato vuelven a aparecer en la cadena del polímero, materiales microporosos preparados por la fosgenación de un compuesto aromático dihidroxílico tal como bisfenol, un poli(cloruro de vinilo) microporoso, poliamidas microporosas tales como poli(hexametilen-adipamida) copolímeros modacrílicos microporosos que incluyen los formados a partir de poli(cloruro de vinilo) y acrilonitrilo, copolímeros microporosos de estireno y acrilato y sus copolímeros, polisulfonas porosas caracterizadas por la difenilen-sulfona en una de sus cadenas lineales, un poli(vinilideno) halogenado, poli(cloro-éteres) polímeros de acetales poliésteres preparados por esterificación de un acido o anhídrido dicarboxílico con un alquilen-poliol, poli(sulfuros de alquileno), compuestos fenólicos, poliésteres, polisacáridos microporosos que tienen unidades de anhidro-glucosa sustituidas, que exhiben una permeabilidad disminuida al paso del agua y de fluidos biológicos, polímeros porosos asimétricos, polímeros - reticulados de olefinas homopolímeros microporosos hidrofobos o hidrófilos copolímeros o interpolímeros que tienen una densidad aparente reducida, y materiales descritos en los documentos de Patente de los EE UU Nºs 3 595 752, 3 643 178, 3 654 066, 3 709 774, 3 718 532, 3 803 601, 3 852 224, 3 852 388, y 3 853 601, en la Ppatente Británica 1 126 849 y en Chem Abst volumen 71, 427F, 22573F, 1969

Materiales microporosos adicionales para formar láminas microporosas incluyen poli(uretanos), poli(uretanos) reticulados, prolongados en su cadena, poli(imidas), poli(bencimidazoles), colodión proteinas regeneradas, poli(vinil-pirrolidona) reticulada semi-sólida, materiales microporosos preparados por difusión de cationes multivalentes en soles de polielectrólitos, derivados microporosos de poli(estireno) tales como poli(estireno-sulfonato de sodio), poli(vinil-bencil-cloruro de trimetil-amonio), acrilatos celulósicos microporosos y polímeros microporosos similares tales como los descritos en las patentes de los EE UU Nºs 3 524 753, 3 565 259 3 276 589, 3 541 055, 3 541 006, 3 546 142 3 615 024, 3 646 178, y 3 852 224 Agentes formadores de poros, utiles para formar las láminas microporosas en el entorno de uso, incluyen materiales sólidos y líquidos formadores de poros

El término "agente formador de poros" abarca también agentes formadores de

micro-trayectorias y la eliminación de los poros y de los agentes formadores de poros conduce a ambas realizaciones La expresión de "líquidos formadores de poros" abarca genéricamente fluidos semi-sólidos y viscosos Los agentes formadores de poros pueden ser inorgánicos u orgánicos El término "agente formador de poros" tanto para sólidos como para líquidos incluye sustancias que se pueden disolver, extraer o lixiviar a partir de la pared microporosa precursora por un fluido presente en el entorno de uso para formar láminas microporosas de tipo de celdillas abiertas Los materiales sólidos formadores de poros tienen un tamaño, p ej de aproximadamente 0 1 a 200 µm e incluyen sales de metales alcalinos, tales como carbonato de litio, cloruro de sodio, bromuro de sodio cloruro de potasio, sulfato de potasio fosfato de potasio acetato de sodio, citrato de sodio, sales de calcio apropiadas, y similares Los compuestos orgánicos incluyen polisacáridos tales como sacarosa glucosa fructosa, manitol, manosa galactosa, sorbitol y similares Los sólidos formadores de poros pueden ser polímeros solubles en el entorno de uso, tales como los Carbowaxes, Carbopol y similares Los agentes formadores de poros abarcan dioles, polioles, alcoholes polivalentes, polialquilen-glicoles, poliglicoles, poli(a-w)alquilen-dioles y similares Los agentes formadores de poros no son tóxicos y al ser eliminados desde las láminas, se forman canales y poros a través de las láminas, que se llenarán con el fluido presente en el entorno de uso

Los revestimientos de liberación controlada usados para suministrar compuestos de Fórmula (1 0 0) pueden incluir también unos medios de salida que comprenden por lo menos un pasaje, un orificio o una entidad similar El pasaje se puede formar por métodos tales como los que se describen en las patentes de los EE UU Nºs 3 845 770, 3 916 889, 4 063 064, y 4 088 864 El pasaje puede tener cualquier conformación tal como redonda, triangular, cuadrada, elíptica, irregular, etc

Para administrar los compuestos de Fórmula (1 0 0) se pueden usar otras clases de sistemas de suministro con liberación controlada Por ejemplo, ciertos dispositivos osmóticos han demostrado tener utilidad para suministrar agentes terapéuticos a un entorno de uso en una manera controlada durante prolongados períodos de tiempo Dispositivos conocidos de este tipo incluyen tabletas, píldoras y cápsulas El sector tecnológico se ha esforzado en desarrollar nuevas membranas que suministren agentes activos mediante difusión y/o bombeo osmótico Por ejemplo, la patente de los EE UU Nº 4 235 236 describe un dispositivo osmótico que suministra un agente terapéutico mediante los mecanismos combinados de difusión y bombeo osmótico El dispositivo comprende una pared microporosa que rodea a un compartimiento que contiene un agente activo y un miembro expansible El miembro expansible consta de una película semipermeable, flexible o expansible que rodea a un miembro seleccionado entre el grupo que consta de un soluto efectivo osmóticamente, un par generador de gas y un

polímero hinchable La pared externa del dispositivo está formada por un material microporoso a través del que se suministra el agente activo que permite la liberación del agente activo en un caudal permanente, la denominada liberación de orden cero Dispositivos apropiados de estos y otros tipos relacionados se pueden usar para suministrar un compuesto de Fórmula (1 0 0)

La patente de los EE UU Nº 4 327 725 describe un dispositivo osmótico que comprende una pared semipermeable que rodea a dos capas, una capa que contiene un agente activo y otra capa que contiene un hidrogel expansible Un pasaje en la pared comunica la capa de agente activo con el entorno de uso Un acilato de celulosa se usa para producir la membrana semipermeable Las patentes de los EE UU Nºs 5 612 059 y Nº 5 698 220 describe el uso de membranas asimétricas en dispositivos de suministro Estas membranas pueden ser permeables, semipermeables, perforadas o sin perforar y pueden suministrar una sustancia activa mediante los mecanismos combinados de difusión y bombeo osmótico Las membranas asimétricas se pueden producir con el acetato de celulosa 398-10 procedente de Eastman Los documentos de patente europea EP 636366 y EP 553392 describen una composicion de agente activo, revestida con una dispersión acuosa de un polímero acrílico plastificado, que se somete a un proceso de curado particular La resultante formulación de liberación controlada tiene un perfil estable de disolución a pesar de una exposición a una diversidad de condiciones de almacenamiento La patente de los EE UU Nº 5 543 155 describe un nucleo a base de una composición farmacéutica de suministro controlado, rodeada por una pared que comprende un copolímero de metacrilato de amonio que es permeable para moléculas de bajo peso molecular Esta composición farmacéutica de suministro controlado contiene un compuesto farmacéutico activo e hidroxipropil-metil-celulosa (HPMC) como el polímero hidrófilo Las tabletas que tienen un nucleo de dos capas se preparan con una capa de polimero hidrófilo que comprende una HPMC de alto peso molecular que tiene una viscosidad mayor que 1 000 cP en una solucion acuosa al 2% Dispositivos y formulaciones apropiados/as de estos y otros tipos relacionados se pueden usar para suministrar un compuesto de Fórmula (1 0 0)

Los dispositivos osmóticos de este tipo tienen un nucleo de dos capas, una capa que contiene el agente activo y la otra que es una capa de placebo hinchable, rodeada por una membrana semipermeable La capa de placebo consiste principalmente en un polímero hinchable y/o en un hidrogel que, mientras que absorbe un fluido desde el entorno de uso, se expande y ejerce presión sobre la capa que contiene el agente activo, liberando con ello el agente activo a través de un pasaje existente en la pared La técnica enseña que la perforación de la membrana semipermeable debería llevarse a cabo selectivamente en la cara de la membrana que está adyacente a la capa que comprende

el agente activo De hecho, si la membrana es perforada adyacentemente a la capa de placebo, el agente activo no será liberado Si se llevan a cabo dos perforaciones, una adyacente a la capa de agente activo y la otra adyacente a la capa de polímero hinchable citada como la capa de "empuje", se liberan tanto el agente activo como el polímero hinchable, dando como resultado una pérdida del efecto de "empuje" La patente de los EE UU Nº 5 543 155 describe también la perforación de la membrana adyacentemente a ambas capas del nucleo, sin embargo, se requiere un polímero especifico de alto peso molecular para impedir la pérdida de la capa de empuje, lo que deja a un numero importante de polímeros hidrófilos indisponibles para usarse en estos dispositivos La patente de los EE UU Nº 5 516 527 describe un dispositivo que puede incluir un pasaje previamente formado y numerosos poros El dispositivo requiere la formación de un revestimiento separado en fases, que finalmente forma una membrana porosa

Otro dispositivo que podría ser apropiado para la liberación controlada de un compuesto de Fórmula (1 0 0), comprende a) un nucleo situado aproximadamente en el centro del dispositivo, que consta de un polímero hidrófilo expansible y opcionalmente un agente osmótico, siendo capaz el nucleo de absorber y/o embeber fluidos a partir del entorno de uso, b) una composición que rodea inmediatamente al nucleo, y que consta de un compuesto de Fórmula (1 0 0) y, opcionalmente, de un agente osmótico y/o de un polímero osmótico, c) una membrana que rodea inmediatamente a la composición, y que consta de una mezcla de un acilato (éster) de celulosa, un copolímero de una sal metacrilato y un plastificante, en que la membrana permite el suministro de un compuesto de Fórmula (1 0 0) por medio de una combinación de difusión y bombeo osmótico, y d) por lo menos un pasaje previamente formado y numerosos microporos en la membrana, que comunican a la composición con el exterior del dispositivo Los microporos en la pared se forman durante la producción de la pared o durante la exposición a fluidos en un entorno de uso pretendido Los métodos de producir paredes, en que los microporos se forman en el entorno de uso, son bien conocidos y se describen, entre otras, en las patentes de los EE UU Nºs 3 845 770 3 916 899 4 063 064, 4 088 864, 4 816 263, 4 200 098, 4 285 987, y 5 912 268

Los agentes osmóticos o compuestos osmóticamente eficaces son generalmente solubles en el fluido que entra en un dispositivo del tipo antes descrito a través de una de sus paredes, creando un gradiente de presion osmotica a traves de la pared El fluido y los componentes de la capa del dispositivo formarán generalmente una solución o suspensión que comprenderá un compuesto de Fórmula (1 0 0) que se ha de suministrar Agentes osmóticos dados como ejemplo incluyen compuestos de peso molecular alto o bajo, compuestos orgánicos e inorgánicos tales como sales, ácidos, bases, agentes

quelantes, cloruro de sodio cloruro de litio, cloruro de magnesio sulfato de magnesio, sulfato de litio, cloruro de potasio sulfito de sodio, bicarbonato de calcio, sulfato de sodio, sulfato de calcio, lactato de calcio d-manitol, urea, ácido tartárico, rafinosa, sacarosa, alfa-d-lactosa monohidrato, glucosa, combinaciones de estos y otros materiales similares o equivalentes conocidos en el sector tecnológico Agentes osmóticos preferidos incluyen cloruro de potasio, tartrato de sodio glucosa, manitol, acetato de sodio cloruro de sodio, sulfato de sodio, citrato de sodio, tartrato de potasio, sorbitol, sacarosa y sus combinaciones La capa del dispositivo que comprende un compuesto de Fórmula (1 0 0) puede comprender también un polímero osmótico, tal como los que se usan para el nucleo, preferiblemente un poli(óxido de alquileno) y, más preferiblemente, un poli(óxido de etileno) con un peso molecular medio comprendido entre aproximadamente 100 000 y 8 000 000

Es conocido en el sector tecnológico que es deseable disponer de un método para reducir la gravedad de, o eliminar o evitar la presentación de, uno o más efectos colaterales de un agente terapéutico que inhibe a las PDE4, y que uno de estos métodos comprende administrar el agente terapéutico en una formulación de liberación controlada lo que da como resultado un retraso en la aparicion en el plasma de cantidades detectables de dicho agente terapéutico y da como resultado también una reducción del régimen de aumento en la concentración en plasma de dicho agente terapéutico por al menos aproximadamente 10% como se compara con el de una formulación de liberación inmediata que contiene la misma cantidad de agente terapéutico administrado por la misma ruta Al menos un retraso de 10 minutos en el comienzo de la presentación concentraciones crecientes en plasma es una práctica preferida aunque unos retrasos con una duración entre 10 y 45 minutos por ejemplo de 30 minutos, o mayor (de 1 hora o más) son también utiles y practicables Esta temporizacion del retardo se puede medir haciendo referencia al comienzo de la absorción, como se mide frente a una tableta de liberación inmediata (LI), aunque una formulación de LI es solamente uno de los patrones posibles

Una reducción de 10% en el régimen de aumento de la concentración en plasma de un agente terapéutico es un umbral para eliminar o reducir su aparición o la gravedad de los efectos colaterales con una dosis dada de agente terapéutico, o para aumentar la cantidad de agente terapéutico que se administra, ya sea en un unico momento en el tiempo o cuando se usa una técnica de dosificación gradual o infusión Dicha reducción es determinada por comparación con una preparación de liberación inmediata, administrada por la misma ruta Por ejemplo, si la ruta oral de administración se escoge como el enfoque se ha de adoptar, entonces una tableta o cápsula de liberación inmediata es el patrón frente al cual se ha de medir la reducción de 10% en el régimen

de aumento

Una metodología preferida para reducir el régimen de aumento y/o retrasar el comienzo de la absorción consiste en las tecnologías de liberación controlada Esto implica formular el agente terapéutico con excipientes, que modulan y prolongan el período de tiempo durante el cual el ingrediente activo es liberado desde el vehículo Este tipo de formulación es descrito algunas veces como una formulacion de liberación prolongada o como un sistema de suministro con liberacion no inmediata El término "liberacion controlada" está destinado a cubrir cualquier formulación que se pueda caracterizar como poseedora de un perfil de liberación en el que una porción de su carga con fármaco es liberada en el curso del tiempo, o bien episódicamente o bien continuamente en el curso del tiempo Éste incluye tambien preparaciones en las que la liberación inicial del agente terapéutico es retrasada como resultado de una barrera externa o un revestimiento externo que es selectivamente soluble en el entorno en el que se dispone la formulación o una preparación en la que el revestimiento no se descompone en el entorno en el que la formulación es introducida inicialmente, pero entonces migra a otro entorno en el que el revestimiento externo es soluble o es descompuesto, después de lo cual el farmaco es liberado en el curso del tiempo Por vía de ilustración y explicación adicionales, estos sistemas de suministro pueden ser caracterizados como de i) liberación retardada, ii) liberación controlada o prolongada, iii) liberación especifica para un sitio, o iv) liberación de receptores

Una explicación más detallada de estos diferentes sistemas está disponible en las relacionadas por Remington's Pharmaceutical Sciences, 18ª Edición, Mack Publishing Co Easton, Pensylvania, EE UU 18042, o adiciones posteriores de Drugs and Pharmaceutical Sciences, v 29, "Suministro controlado de fármacos aspectos fundamentales y aplicaciones, Segunda Edición", compilado por Joseph R Robinson y Vincent H Lee publicado por Marcel Dekker Inc Estos sistemas pueden ser dependientes de la disolución, como se ilustra por productos de disolución encapsulados o productos de disolución en matriz O bien éstos pueden ser formulados usando sistemas osmóticos o resinas de intercambio de iones El enfoque más preferido es el de proporcionar un producto de liberación controlada oral, basado en una tecnología de disolución en matriz

Un retraso en el comienzo de la absorción y un régimen reducido de absorción se pueden correlacionar con efectos colaterales reducidos cuando un conocido inhibidor de las PDE4 se administra a pacientes en una preparación de liberación controlada oral que contiene una cantidad de agente terapéutico tres veces mayor que la de una tableta de liberación inmediata que no era bien tolerada También se observará que la tableta de liberación controlada da como resultado un régimen reducido de absorción, que se

refleja en un régimen reducido de aumento en las concentraciones en plasma pero proporciona varias horas más tarde una Cmax (concentración máxima) que supera a la Cmax asociada con efectos colaterales desfavorables en una tableta de liberación inmediata Esto es, cuando una tableta de liberación inmediata es administrada a un paciente, la Cmax y los efectos colaterales se correlacionan en gran manera Esta correlación no se observaba con la formulación de liberacion controlada, incluso aunque diese como resultado una Cmax mas alta No está claro si los resultados observados con una preparación de liberación controlada son dependientes de, o están relacionados con, una o ambas de estas observaciones, o con otro factor o con otra combinación de factores, tales como Tmax (tiempo máximo) ka (constante de absorción), Tretardo (tiempo de retardo en la absorción), o alguno otro factor o fenómeno Independientemente de cual sea el mecanismo subyacente, el resultado es que ahora se ha hecho posible aumentar de manera importante la cantidad del agente inhibidor de las PDE4 que se administra en un momento particular y evitar los retos de tolerabilidad, asociados con los inhibidores de TDE4 en ciertos segmentos de la población

Las preparaciones de liberación controlada se pueden producir seleccionando excipientes tomados entre cualquier numero o tipo de materiales que proporcionen el requerido perfil de liberacion controlada, que se necesita para evitar los efectos colaterales, mientras que permitan un aumento significativo en la cantidad de agente terapéutico contenido en la formulación, en comparación con una preparación de liberación inmediata Un enfoque preferido consiste en usar una tecnologia de disolución en matriz basada en polímeros de ácido acrilico Carbomer es el nombre sin propietario para estos materiales Éstos son polímeros de alto peso molecular preparados por reticulación de ácidos acrílicos con los semejantes de alquil-sacarosa o alil-éteres de pentaeritritol Dichos polímeros pueden presentarse tambien por el nombre de acritamer o carbopol El nombre químico y el numero de registro en el CAS para esta clase son carboxipolimetileno [54182-57-91] Carbómeros ejemplificadores son carbomer 910 [91315-32-1], carbomer 934 [9007-16-3], carbomer 934P [9003-01-4] y carbomer 940 [76050-42-5] Estos polímeros contienen entre 56 y 68% de grupos de ácido carboxílico, calculado sobre una base seca Una mezcla de dos o más carbómeros de diferente peso molecular se puede usar para modificar y manipular el régimen de liberación

Los excipientes preferidos para afectar al régimen de liberación son carbómeros, particularmente una combinación de dos o más diferentes carbómeros Se prefieren especialmente los carbómeros conocidos como Carbopoles y producidos por BF Groodrich Carbómeros preferidos son carbomer 934P (Carbopol 974P) y carbomer 94 1 P (Carbopol 97 1 P)

Una formulación preferida tendrá entre aproximadamente 1 y 25% en peso de un

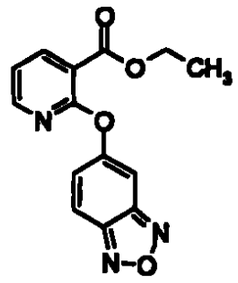
agente terapéutico, con preferencia una cantidad entre 3 y 20% y opcionalmente una cantidad entre aproximadamente 5 y 15%

DESCRIPCIÓN DETALLADA DEL INVENTO

11 0 Preparaciones y Ejemplos de realización

Preparación 1a

Éster etílico de ácido 2-[benzo[2,1 3]oxadiazol-5-iloxi]-nicotínico de Fórmula (5 0 1)



(5.0 1)

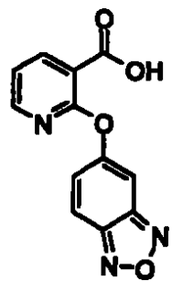
Una mezcla de 5,5 g (29,4 mmol) del éster etílico de ácido 2-cloro-nicotínico, 4,0 g (29,4 mmol) de 5-hidroxi-benzofurazano y 20,1 g (61,7 mmol) de carbonato de cesio en 125 ml de dimetil-formamida seca se calentó a 90°C durante cinco días La mezcla se vertió en agua y se extrajo con acetato de etilo Los extractos en acetato de etilo se combinaron, se lavaron sucesivamente con una solución de bicarbonato de sodio, con agua y con salmuera, luego se secaron (sobre Na_2SO_4) y se concentraron en vacío para dar un material sólido La recristalización en una mezcla de dietil-éter y pentano dio 2,2 g (26%) de un material sólido

^{1}H-NMR ($CDCl_3$) δ 8.3 (m, 2H), 7 8 (d, 1H, J=10 Hz), 7 2 (m, 3H), 4.4 (q, 2H, J=7 Hz), 1.4 (t, 3H J=7 Hz)

GC-MS (m/z) 285 (M^+, 20), 122 (100)

Preparación 1b

Ácido 2-[benzo[2,1,3]oxadiazol-5-iloxi]-nicotínico de Fórmula (5 0 2)



(5 0.2)

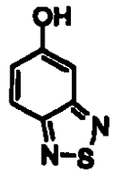
Una mezcla de 2,2 g (7,7 mmol) del éster etílico de ácido 2-[benzo[2,1,3]oxadiazol-5-iloxi]-nicotínico y 23,1 ml (23 1 mmol) de LiOH 1 M en 75 ml de tetrahidrofurano se agitó durante una noche a la temperatura ambiente El tetrahidrofurano se evaporó en vacío y la mezcla acuosa se acidificó con HCl 1 N El precipitado resultante se filtró y secó para dar 1,9 g (96%) de un material sólido

^{1}H-NMR (CH_3OD) δ 8 4 (d, 1H, J=8 Hz), 8 3 (dd, 1H, J=2, 5 Hz), 8 0 (d, 1H, J=9 Hz), 7 6 (s, 1H), 7 5 (d, 1H J=9 Hz), 7.2 (dd, 1H, 5, 8 Hz)

MS (m/z) 257 (M^+, 20), 258 (100)

Preparación 2

Benzo[2,1,3]tiadiazol-5-ol de Fórmula (5 0 3)



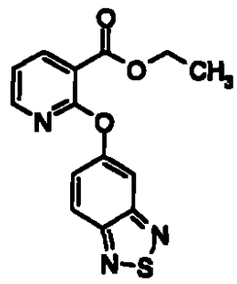
(5.0.3)

El 5-metoxi-benzo-2,1,3-tiadiazol (4,09 g, 24,6 mmol) se agitó con ácido bromhídrico (60 ml, 165 mmol, al 30% en ácido acético) a 80ºC durante 5 días La mezcla se enfrió a 10ºC y se filtró Los materiales sólidos se purificaron por cromatografía en columna corta (con una mezcla de 50% de acetato de etilo y hexano) Los disolventes se separaron por arrastre en vacío para proporcionar 1,0 g de un material sólido de color amarillo (con un rendimiento de 27%)

^{1}H NMR (CD_3OD) δ 7 81 (d, 1H, J= 2 Hz), 7 79 (d, 1H, J= 2 Hz), 7 30 (s, 1H)

Preparación 3

Éster etílico de ácido 2-(benzo[2,1,3]tiadiazol-5-iloxi)-nicotínico de Fórmula (5 0 4)



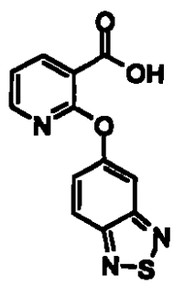
(5 0.4)

Una mezcla del éster etílico de ácido 2-cloro-nicotínico (0 516 g, 3 mmol), benzo[2,1,3]-tiadiazol-5-ol) (0 46 g, 3 mmol) y carbonato de cesio (2,07 g, 6,3 mmol) se agitó en 40 ml de N N-dimetil-formamida a 80°C durante 48 horas La mezcla de color anaranjado oscuro se enfrió y vertió en agua (600 ml) y se extrajo con acetato de etilo Las capas orgánicas combinadas se lavaron con agua y con salmuera, y se secaron (sobre Na_2SO_4) La mezcla se concentró en vacio para dar 0,74 g de un material sólido de color amarillo (con un rendimiento de 82%)

MS (m/z) 302 (M^+, 20), 227 (100)

Preparación 4

Ácido 2-(benzo[2 1 3]tiadiazol-5-iloxi)-nicotínico de Fórmula (5 0 5)



(5.0 5)

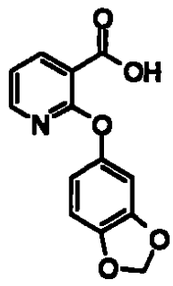
Una solución del éster etílico de ácido 2-(benzo[2 1 3]tiadiazol-5-iloxi)-nicotínico (0 74 g,

2,5 mmol) en tetrahidrofurano (2,78 ml) y LiOH 1 M (2,7 ml) se agitó durante una noche La mezcla se diluyó con agua y se acidificó a un pH de 1 con ácido clorhídrico 2 N y se filtró para dar un material sólido de color amarillo pálido (160 mg)

^{1}H NMR (CD_3OD) δ 8 37 (d, 1H, J= 6 Hz), 8 26 (dd, 1H J= 2 Hz, 5 Hz), 8 00 (d, 1H, J= 9 Hz), 7 60 (t 1H J= 2 Hz), 7 50 (t, 1H J= 2 Hz), 7 26 (d 1H J= 8 Hz)

Preparación 5

Ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico de Fórmula (5 0 6)



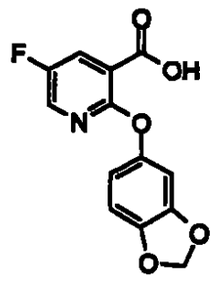
(5.0 6)

El éster etílico de ácido 2-cloro-nicotínico (10 g), el benzo[1,3]dioxol-5-ol) (sesamol, 8,2 g) y el carbonato de cesio (21 g) se mezclaron en dioxano anhidro (40 ml) y la suspensión resultante se calentó a reflujo durante 16 h En un matraz dispuesto por separado, se disolvió hidróxido de litio (12,9 g) en agua (80 ml) con calentamiento moderado y luego se añadió a la mezcla puesta a reflujo, que se calentó durante 4 h adicionales La mezcla se enfrió a la temperatura ambiente y se concentró en vacío para eliminar el dioxano El ácido clorhídrico concentrado se añadió gota a gota hasta que el pH fuese = 3 La solución acidificada se extrajo luego con acetato de etilo para proporcionar el compuesto purificado del título (10,8 g)

^{1}H NMR (CD_3OD) δ 8.28 (dd, J = 8 y 2 Hz, 2H), 7 13 (m, 1H), 6 79 (d, J = 8Hz, 1H) 6.62 (s, J = 2Hz, 1H), 6 53 (dd, J = 8 y 2Hz, 1H), 5 95 (s, 2H)

Preparación 6

Ácido 2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-nicotínico de Fórmula (5 0 7)



(5.0 7)

El ácido 2-cloro-5-fluoro-nicotínico (sintetizado de acuerdo con los procedimientos descritos en el documento de patente europea EP 0634413 A1) se convirtió en el correspondiente éster etílico con etanol anhidro y cloruro de tionilo en exceso, y luego se trató de la manera usual Al éster etílico de ácido 2-cloro-5-fluoro-nicotínico (5 0 g) en un matraz de 250 ml de capacidad, secado en estufa, se le añadieron carbonato de cesio (9,60 g), sesamol (4 07 g) y 50 ml de dioxano anhidro La mezcla de reacción se agitó durante una noche a 100°C Se añadió hidróxido de litio (2,94 g) en 10 ml de agua y la mezcla de reacción se dejó de nuevo en agitación durante una noche a 100°C El dioxano se evaporó luego bajo una corriente de nitrógeno El residuo se recogió luego en 50 ml de agua, se acidificó con ácido clorhídrico concentrado a un pH = 3, y se extrajo con acetato de etilo (3 x 100 ml) Los extractos organicos combinados se secaron sobre sulfato de magnesio, se filtraron y se concentraron en vacio El residuo secado se lavó con acetato de etilo (20 ml) y se secó en alto vacío, proporcionando el compuesto del título (2,96 g)

^{1}H NMR (CD_3OD) δ 8 09-8 04 (m, 2H), 6 76 (d, J = 9Hz, 1H), 6 61 (s, 1H), 6 51 (d, J = 7, 1H), 5 93 (s, 2H)

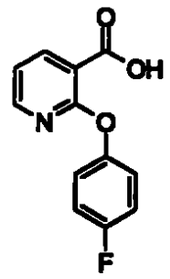
MS *m/z* 278 $(M + H)^+$

541

00545

Preparación 7

Ácido 2-(4-fluoro-fenoxi)-nicotínico de Fórmula (5 0 8)



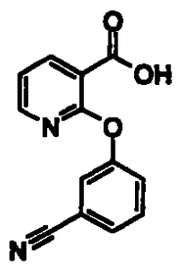
(5.0.8)

El éster etílico de ácido 2-cloro-nicotínico el 4-fluoro-fenol y el carbonato de cesio se mezclaron en dioxano anhidro y la suspensión resultante se calentó a reflujo durante aproximadamente 16 h En un matraz dispuesto por separado se disolvió hidróxido de litio en agua con calentamiento moderado y luego se añadió a la mezcla puesta a reflujo, que se calentó durante 4 h adicionales La mezcla se enfrió a la temperatura ambiente y se concentró en vacío para eliminar el dioxano Se añadió gota a gota ácido clorhídrico concentrado hasta que el pH fuese = 3 La solución acidificada se extrajo luego con acetato de etilo para proporcionar un producto bruto, que se recristalizó en acetato de etilo para proporcionar el compuesto purificado del título (10,8 g)

MS *m/z* 232 $(M-H)^+$

Preparación 8

Ácido 2-(3-ciano-fenoxi)-nicotínico de Fórmula (5 0 9)

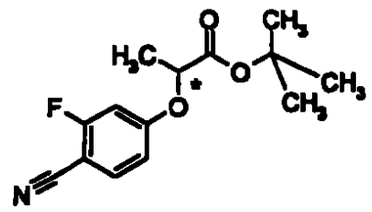


(5.0 9)

El compuesto de Fórmula (5 0 9) se preparó de una manera análoga a la descrita en la Preparación 7 anterior reemplazando el 4-fluoro-fenol por el 3-ciano-fenol

Preparación 9

(±)-Éster *terc* -butílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 10)



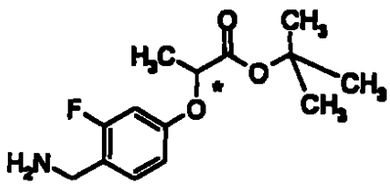
(5.0 10)

El 2-fluoro-4-hidroxi-benzonitrilo (1 g, 7,29 mmol) se disolvió en *N,N*-dimetil-formamida (20 ml) y se agitó con carbonato de potasio (1,1 g, 8,0 mmol) a TA (temperatura ambiente) durante 2 h Se añadió el (±)-éster *terc* -butílico de ácido 2-bromo-propiónico (1,67 g, 8,0 mmol) y la mezcla de reacción se agitó a TA durante 72 h La mezcla de reacción se sofocó en ácido clorhídrico acuoso diluido y se extrajo 2 veces con acetato de etilo Los materiales orgánicos agrupados se secaron (sobre Na_2SO_4) y se adsorbieron sobre gel de sílice, seguido por purificación mediante cromatografía en columna de resolución rápida (con una mezcla de 20% de acetato de etilo y hexano) para proporcionar 1,8 g de un aceite incoloro (con un rendimiento de 93%)

^{1}H NMR ($CDCl_3$) δ 7 48 (t, 1H, J= 7 5 Hz), 6 68 (d, 1H, J= 9 Hz), 6 64 (d, 1H, J= 11 Hz), 4 55 (q, 1H, J= 7 Hz) 1 58 (d 3H J= 7 Hz), 1 41 (s, 9H)

Preparación 10

(±)-Éster *terc* -butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 11)



(5.0 11)

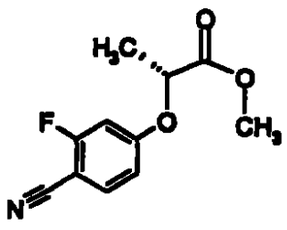
El (±)-éster *terc* -butílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico (1,77 g, 6,7 mmol) se sacudió sobre un aparato sacudidor de Parr bajo 40 psi (2,8 kg/cm^2) durante 30 min, usando hidróxido de paladio sobre carbón (1 g, con 30% de Pd en peso) en 200 ml de metanol anhidro La mezcla de reacción se filtró a través de vidrio sinterizado, y los disolventes se eliminaron en vacío para proporcionar 1,71 g de un aceite incoloro (con

un rendimiento de 95%)

MS (m/z) 269 (M^+, 45), 168 (100)

Preparación 11

(R)-Éster metílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 12)



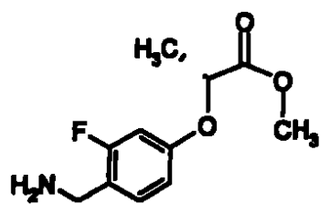
(5.0 12)

A una solución agitada de 2-fluoro-4-hidroxi-benzonitrilo (0,2 g, 1,5 mmol), (S)-(-)-lactato de metilo (0,14 ml, 1,5 mmol) y trifenil-fosfina (1,15 g, 4,4 mmol) a la temperatura ambiente se le añadió gota a gota azo-dicarboxilato de dietilo (0,67 ml 4,4 mmol) La mezcla se agitó a la temperatura ambiente durante una noche, se diluyó con acetato de etilo y se lavó sucesivamente con hidróxido de sodio acuoso diluido, con ácido clorhídrico acuoso diluido, con salmuera, y se secó (sobre Na_2SO_4) Los disolventes se separaron por arrastre en vacío El aceite resultante se lavó con dietil-éter y el precipitado se separó por filtración Las aguas madres se adsorbieron sobre gel de sílice y el producto se purificó por cromatografía en columna de resolución rápida (con una mezcla de 20% de diclorometano y hexano), proporcionando 0,12 g de un aceite de color rosa (con un rendimiento de 36%)

^{1}H NMR ($CDCl_3$) δ 7 51 (t, 1H, J= 7 5 Hz), 6 71 (d, 1H, J= 9 Hz), 6 67 (d, 1H, J= 10 Hz), 4 78 (q, 1H, J= 7 Hz) 3 77 (s 3H) 1 64 (d, 3H, J= 7 Hz)

Preparación 12

(R)-Éster metílico de acido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico de Formula (5 0 13)



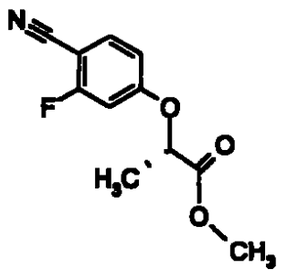
(5.0 13)

El compuesto de Fórmula (5 0 13) se preparó de una manera análoga a la que se describe en la Preparación 10, reemplazando el (R)-éster metílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico al correspondiente material de éster *terc* -butílico

^{1}H NMR ($CDCl_3$) δ 7 41 (t, 1H, J= 8 Hz), 6 90 (br, 2H), 6 58 (m, 2H), 4 69 (q, 1H, J= 7 Hz), 4 00 (s 2H), 3 71 (s 3H) 1 56 (d, 3H J= 7 Hz)

Preparación 13

(S)-Éster metílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 14)



(5.0 14)

El compuesto de Fórmula (5 0 14) se preparó de una manera análoga a la que se describe en la Preparación 11, reemplazando el (R)-(+)-lactato de metilo por el (S)-(-)-lactato de metilo

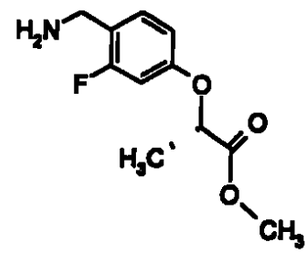
^{1}H NMR ($CDCl_3$) δ 7 51 (t, 1H, J= 7 5 Hz), 6 72 (d, 1H, J= 9 Hz), 6 67 (d, 1H, J= 10 Hz), 4 78 (q, 1H, J= 7 Hz), 3 77 (s, 3H), 1 64 (d, 3H, J= 7 Hz)

00549

545

Preparación 14

(S)-Éster metílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 15)



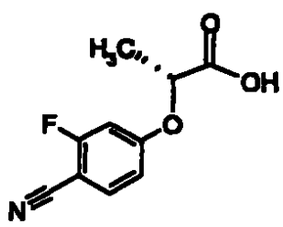
(5.0 15)

El compuesto de Fórmula (5 0 15) se preparó de una manera análoga a la que se describe en la Preparación 12, basada en la Preparación 10, reemplazando el éster metílico de ácido (-)-2-(4-ciano-3-fluoro-fenoxi)-propiónico al correspondiente material (+)

^{1}H NMR ($CDCl_3$) δ 7 41 (t, 1H J= 8 Hz), 6 90 (br, 2H), 6 58 (m, 2H), 4 69 (q, 1H, J= 7 Hz), 4 00 (s 2H), 3 71 (s, 3H), 1 56 (d, 3H, J= 7 Hz)

Preparación 15

(R)-Ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 16)



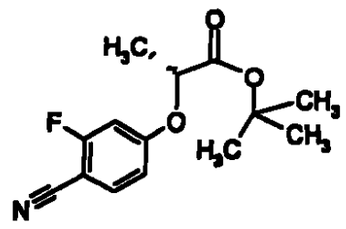
(5 0 16)

A una solución agitada del (R)-éster metílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propionico (0,40 g, 1,8 mmol) en 50 ml de una mezcla 1 1 de tetrahidrofurano y metanol a la temperatura ambiente se le añadió hidróxido de litio (5 5 ml de una solución acuosa 1 M, 5 5 mmol) y la solución se agitó durante una noche La mezcla de reacción se sofocó en ácido clorhídrico acuoso diluido y se extrajo con acetato de etilo Las capas orgánicas se reunieron y se lavaron con salmuera, se secaron (sobre Na_2SO_4) y se concentraron en vacío para proporcionar un aceite incoloro (0,37 g, 98%)

^{1}H NMR ($CDCl_3$) δ 7 50 (t, 1H, J= 7 Hz), 6 69 (m, 2H), 4 81 (q, 1H, J= 7 Hz), 1 68 (d, 3H, J= 7 Hz)

Preparación 16

(R)-Éster *terc* -butílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 17)



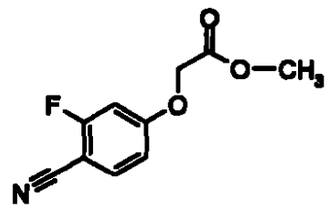
(5.0 17)

Una solución de (R)-ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico (55 mg, 0,26 mmol) en tolueno seco (30 ml) y del di-*terc* -butil-acetal *N N*-dimetil-formamida (0,25 ml 1,05 mmol) se agitó a 90°C durante 1 hora La mezcla de reacción se adsorbió sobre gel de sílice y se purificó por cromatografía en columna de resolución rápida (con una mezcla de 30% de acetato de etilo y hexano) para proporcionar 51 mg de un sólido de color blanco (con un rendimiento de 74%)

^{1}H NMR ($CDCl_3$) δ 7.48 (t, 1H, J= 7 Hz), 6 65 (m, 2H), 4 61 (q, 1H, J= 7 Hz), 1 58 (d, 3H, J= 7 Hz), 1 41 (s, 9H)

Preparación 17

Éster metílico de acido (4-ciano-3-fluoro-fenoxi)-acético de Fórmula (5 0 18)



(5 0 18)

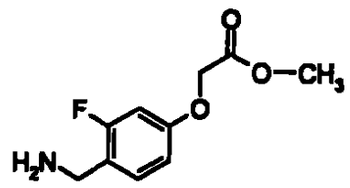
El compuesto de Fórmula (5 0 18) se preparó de una manera análoga a la que se describe en la Preparación 9, reemplazando el éster metílico de ácido bromo-acético al material de éster *terc* -butílico de ácido bromo-propiónico

00551/547

MS (m/z) 209 (M^+, 100)

Preparación 18

Éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético de Fórmula (5 0 19)



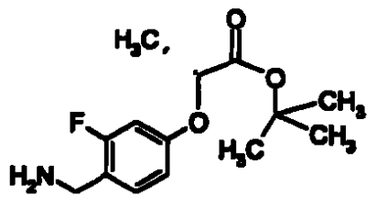
(5.0 19)

El compuesto de Fórmula (5 0 19) se preparó de una manera análoga a la que se describe en la Preparación 10 reemplazando el ester metílico de ácido (4-ciano-3-fluoro-fenoxi)-acético al correspondiente material de éster *terc* -butílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico

MS (m/z) 212 (M^+, 100)

Preparación 19

(R)-Éster *terc* -butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico de Fórmula (5 0 20)



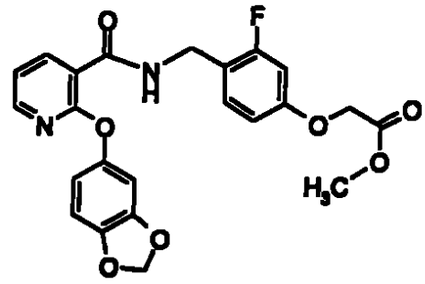
(5.0.20)

El compuesto de Fórmula (5 0 20) se preparó de una manera análoga a la que se describe en la Preparación 10, reemplazando el (R)-éster *terc* -butílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico al correspondiente material de (±)-éster *terc* -butílico de ácido 2-(4-ciano-3-fluoro-fenoxi)-propiónico

^{1}H NMR ($CDCl_3$) δ 7 17 (t, 1H, J= 9 Hz), 6 55 (t, 2H J= 8 Hz), 4 53 (q, 1H J= 7 Hz), 3 78 (s, 2H), 2 57 (br, 2H), 1 52 (d, 3H, J= 7 Hz), 1 39 (s, 9H)

Preparación 20

Éster metílico de ácido [4-({[2-(benzo[1 3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético de Fórmula (5 0 21)



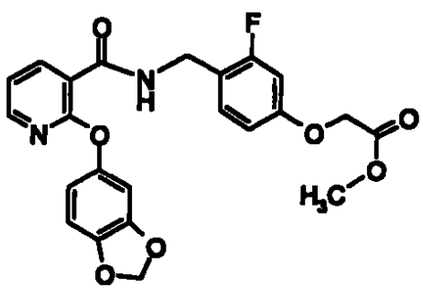
(5.0.21)

El ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico (0 31 g, 1 1 mmol), el ester metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético (0,46 g, 2,15 mmol), el hidrato de 1-hidroxi-benzotriazol (0,16 g, 1,2 mmol), y el hidrocloruro de 1-[3-(dimetil-amino)propil]-3-etil-carbodiimida (0,23 g, 1,2 mmol) se disolvieron en una mezcla 1 1 de *N,N*-dimetil-formamida y diclorometano (40 ml) y se agitaron a la temperatura ambiente durante una noche Los disolventes se eliminaron en vacío El residuo se recogió en acetato de etilo y se lavó consecutivamente con ácido clorhídrico acuoso diluido, con hidróxido de sodio acuoso diluido y con salmuera, y se secó (sobre Na_2SO_4) El producto se purificó por cromatografía en columna de resolución rápida (con una mezcla de 20% de acetato de etilo y hexano) para proporcionar un aceite de color amarillo (0,19 g, 38%)

MS (m/z) 455 (M^++1, 100)

Preparación 21

(±)-Éster *terc*-butílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 22)



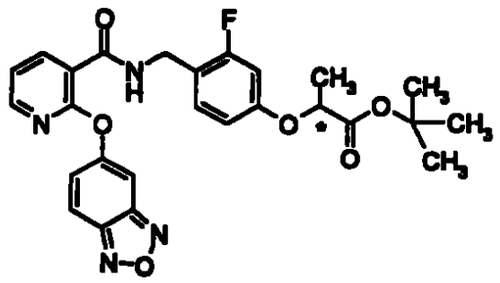
(5.0.21)

El compuesto de Fórmula (5 0 22) se preparó de una manera analoga a la que se descnbe en la Preparacion 20, reemplazando el (±)-éster *terc* -butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico al matenal de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético

^{1}H NMR ($CDCl_3$) δ 8 58 (dd, 1H, J= 2 Hz 8 Hz), 8 19 (dd 2H, J= 2 Hz, 5 Hz), 7 26 (m, 1H), 7 10 (m, 1H), 6 78 (d, 1H, J= 8 Hz), 6 63 (d, 1H, J= 2 Hz), 6 55 (m, 2H), 5 99 (s, 2H), 4 62 (d, 2H, J= 5 Hz) 4 51 (q, 1H, J= 7 Hz), 1 53 (d 3H, J= 7 Hz), 1 40 (s, 9H)

Preparación 22

(±)-Éster *terc* -butílico de ácido 2-[4-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 23)



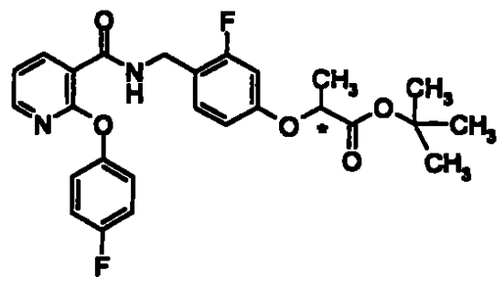
(5.0.23)

El compuesto de Fórmula (5 0 23) se preparó de una manera análoga a la que se descnbe en la Preparación 20 reemplazando el ácido 2-(benzo[2,1,3]oxadiazol-5-iloxi)-nicotínico y el (±)-éster *terc* -butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

^{1}H NMR ($CDCl_3$) δ 8 62 (dd, 1H, J= 2 Hz, 5 Hz), 8 18 (dd 1H, J= 2 Hz, 5 Hz) 7 88 (t, 1H J= 5 Hz), 7 85 (dd, 1H, J= 1 Hz, 9 Hz), 7 54 (s 1H), 7 23 (m, 2H), 6 55 (m, 2H), 4 64 (d, 2H, J= 6 Hz), 4 52 (q, 1H J= 7 Hz) 1 53 (d 3H, J= 7 Hz), 1 39 (s, 9H)

Preparacion 23

(±)-Éster *terc*-butílico de ácido 2-[3-fluoro-4-({[2-(4-fluoro-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 0 24)



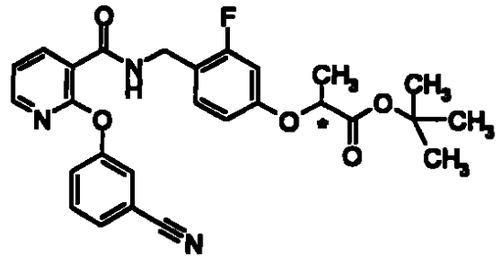
(5 0 24)

El compuesto de Fórmula (5 0 24) se preparo de una manera análoga a la que se describe en la Preparación 20, reemplazando el ácido 2-(4-fluoro-fenoxi)-nicotínico y el (±)-éster *terc*-butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de acido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

MS (m/z) 484 (M^+, 100)

Preparación 24

(±)-Éster *terc*-butílico de ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-fenoxi]-propionico de Fórmula (5 0 25)



(5.0.25)

El compuesto de Fórmula (5 0 25) se preparo de una manera análoga a la que se describe en la Preparación 20, reemplazando el ácido 2-(3-ciano-fenoxi)-nicotínico y el (±)-éster *terc*-butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

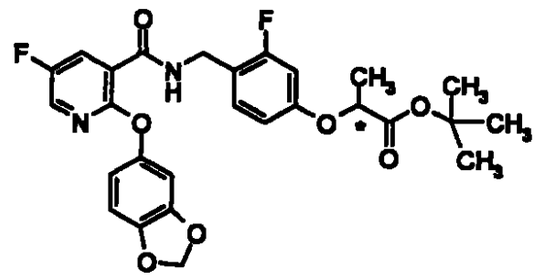
MS (m/z) 491 (M^+, 100)

551

00855

Preparación 25

(±)-Éster *terc* -butílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 26)



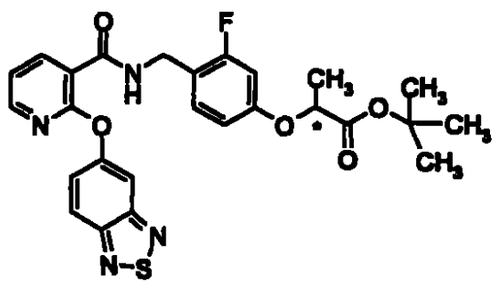
(5 0.26)

El compuesto de Fórmula (5 0 26) se preparó de una manera análoga a la que se describe en la Preparación 20, reemplazando el ácido 2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-nicotínico y el (±)-éster *terc* -butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propionico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

MS (*m/z*) 529 (M^+ 100)

Preparación 26

(±)-Éster *terc.*-butílico de ácido 2-[4-({[2-(benzo[2,1 3]tiadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 27)



(5 0.27)

El compuesto de Fórmula (5 0 27) se preparó de una manera análoga a la que se describe en la Preparación 20, reemplazando el ácido 2-(benzo[2,1,3]tiadiazol-5-iloxi)-nicotínico y el (±)-éster *terc* -butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

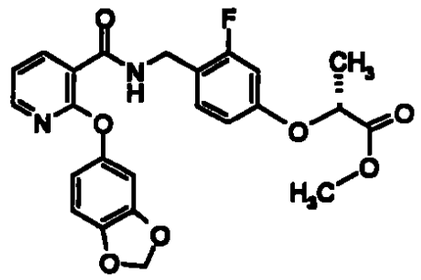
552

MS (m/z) 524 (M^+, 100)

00536

Preparación 27

(R)-Éster metílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 28)



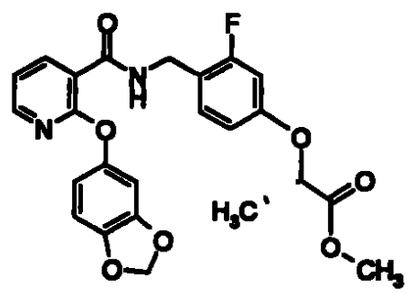
(5.0.28)

El compuesto de Fórmula (5 0 28) se preparó de una manera análoga a la que se describe en la Preparación 20, reemplazando el (R)-éster metílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico al correspondiente material de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético

MS (m/z) 469 (M^++1, 20), 455 (M^+-14, 100)

Preparación 28

(S)-Éster metílico de ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 29)



(5.0.29)

El compuesto de Fórmula (5 0 29) se preparó de una manera análoga a la que se describe en la Preparación 20, reemplazando el (S)-éster metílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico al correspondiente material de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético

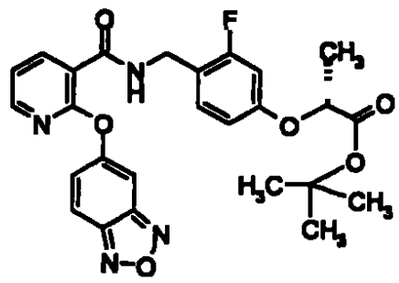
553

00857

^{1}H NMR ($CDCl_3$) δ 8 55 (dd, 1H, J= 2, 7 Hz), 8 26 (t, 1H, J= 5 Hz), 8 19 (dd, 1H, J= 2, 5 Hz), 7.27 (t, 1H, J= 9 Hz), 7 10 (m, 1H) 6 79 (d, 1H, J= 8 Hz), 6 55 (m, 3H), 5 98 (s, 2H), 4 68 (q, 1H, J= 6 Hz), 4 61 (d, 2H, J= 6 Hz), 3 71 (s, 3H), 1 57 (d, 3H, J= 7 Hz)

Preparación 29

(R)-Éster *terc* -butílico de ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Formula (5 0 30)



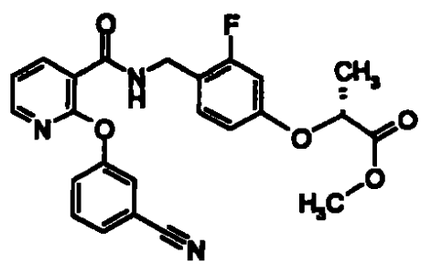
(5 0.30)

El compuesto de Fórmula (5 0 30) se preparó de una manera análoga a la que se describe en la Preparacion 20, reemplazando el acido 2-(benzo[2 1,3]oxadiazol-5-iloxi)-nicotínico y el (R)-éster *terc* -butílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1-3]dioxol-5-iloxi)-nicotínico y de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

^{1}H NMR ($CDCl_3$) 8 61 (dd, 1H, J= 2, 8 Hz), 8 18 (dd, 1H, J= 2, 5 Hz), 7 88 (t, 1H, J= 9 Hz), 7 84 (d, 1H, J= 10 Hz), 7 53 (s, 1H), 7 23 (m, 2H), 6 55 (m, 2H) 4 63 (d, 2H, J= 6 Hz), 4 52 (q, 1H, J= 7 Hz), 1 52 (d, 3H, J= 7 Hz), 1 38 (s, 9H)

Preparación 30

(R)-Éster metílico de ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-pirdina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 0 31)



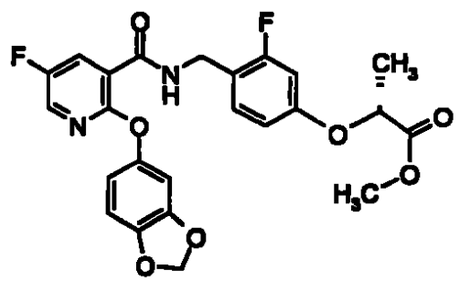
(5 0 31)

El compuesto de Fórmula (5 0 31) se preparó de una manera análoga a la que se describe en la Preparación 20, reemplazando el ácido 2-(3-ciano-fenoxi)-nicotínico y el (R)-éster metílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

^{1}H NMR ($CDCl_3$) δ 8 59 (dd, 1H, J= 2, 8 Hz), 8 15 (dd, 1H, J= 2, 5 Hz), 8 00 (t, 1H, J= 5 Hz), 7 35 (m, 5H), 6 56 (m 2H), 4 68 (q, 1H, J= 7 Hz), 4 62 (d, 2H, J= 6 Hz), 3 71 (s, 3H), 1 57 (d, 3H, J= 7 Hz)

Preparación 31

(R)-Éster metílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 32)



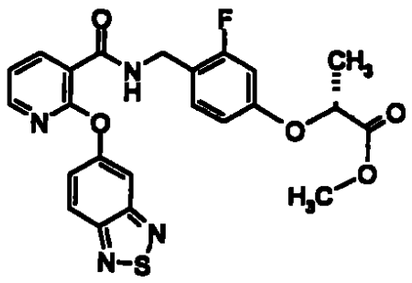
(5 0 32)

El compuesto de Fórmula (5 0 32) se preparó de una manera análoga a la que se descnbe en la Preparación 20, reemplazando el ácido 2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-nicotínico y el (R)-éster metílico de acido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

^{1}H NMR ($CDCl_3$) δ 8 32 (dd, 1H, J= 3, 8 Hz), 8 26 (s, 1H), 8 02 (d, 1H, J= 3 Hz), 7.28 (t, 1H, J= 8 Hz), 6 80 (d, 1H, J= 8 Hz) 6 56 (m, 3H), 6 00 (s, 2H), 4 68 (q, 1H, J= 7 Hz), 4 61 (d, 2H, J= 6 Hz), 3 72 (s, 3H), 1 57 (d, 3H, J= 7 Hz)

Preparación 32

(R)-Éster metílico de ácido 2-[4-({[2-(benzo[2,1 3]tiadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 0 33)



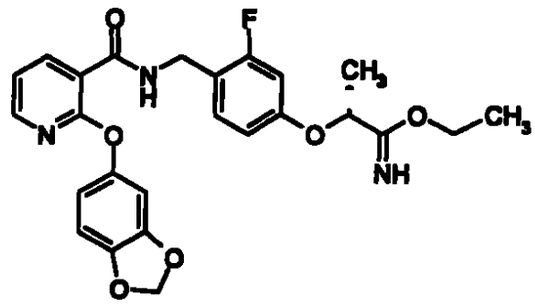
(5 0.33)

El compuesto de Fórmula (5 0 33) se preparó de una manera análoga a la que se describe en la Preparación 20 reemplazando el ácido 2-(benzo[2,1 3]tiadiazol-5-iloxi)-nicotínico y el (R)-éster metílico de ácido 2-(4-aminometil-3-fluoro-fenoxi)-propiónico a los correspondientes materiales de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico y de éster metílico de ácido (4-aminometil-3-fluoro-fenoxi)-acético, respectivamente

^{1}H NMR ($CDCl_3$) δ 8 62 (dd, 1H J= 2 8 Hz), 8 17 (dd, 1H, J= 2, 5 Hz), 8 10 (t, 1H, J= 5 Hz), 8 00 (dd, 1H, J= 1, 10 Hz), 7 74 (d, 1H, J= 3 Hz), 7 39 (dd, 1H, J= 2, 9 Hz), 7 30 (t, 1H, J= 9 Hz), 7 20 (m, 1H), 6 56 (m, 2H), 4 66 (m, 3H), 3 70 (s, 3H), 1 56 (d, 3H, J= 7 Hz)

Preparación 33

(R)-Éster etílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propionimídico de Fórmula (5 0 34)



(5.0.34)

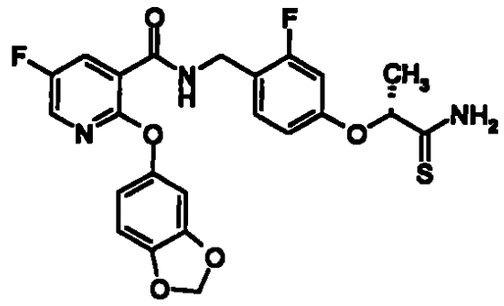
A una solución agitada de (R)-2-(benzo[1,3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida (0,4 g, 0,88 mmol) en diclorometano (20 ml) se le añadió tetrafluoroborato de trietil-oxonio (0,17 g, 0,88 mmol) La mezcla de reacción se agitó a la temperatura ambiente durante 16 h La mezcla de reacción se adsorbió sobre una pequeña cantidad de gel de sílice y la cromatografía en columna (con una mezcla de 2%

de metanol y diclorometano) proporcionó 160 mg del deseado producto como un aceite incoloro (con un rendimiento de 38%)

MS (m/z) 481 (M^+, 100)

Preparación 34

(R)-2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(1-tiocarbamoil-etoxi)-bencil]-nicotinamida de Fórmula (5 0 35)



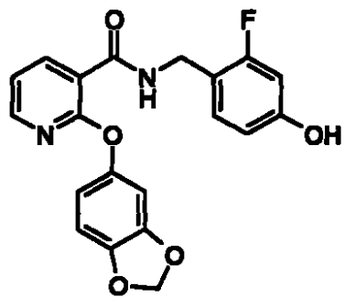
(5.0.35)

Una solución de (R)-2-(benzo[1,3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-5-fluoro-nicotinamida (1 0 g, 2 12 mmol) y del reactivo de Lawesson (0,52 g, 1,27 mmol) en tetrahidrofurano seco (10 ml) se agitó a la temperatura ambiente durante 2 h El disolvente se eliminó en vacío El residuo se adsorbió sobre gel de sílice y se purificó por cromatografía en columna (con una mezcla de 20% de acetato de etilo y hexano) para proporcionar 1 01 g de un sólido de color amarillo (con un rendimiento de 98%)

MS (m/z) 486 (M^+, 100)

Preparación 35

2-(benzo[1,3]dioxol-5-iloxi)-N-(2-fluoro-4-hidroxi-bencil)-nicotinamida de Fórmula (5 0 36)



(5 0 36)

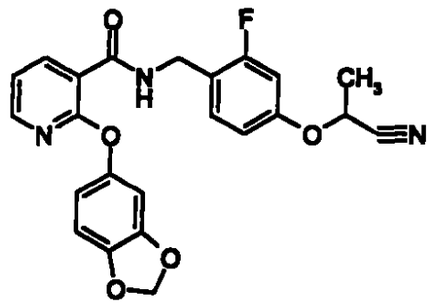
Una solución del hidrocloruro de 4-aminometil-3-fluoro-fenol (4,75 g, 27 mmol) en *N,N*-dimetil-formamida (20 ml) se añadió a una solución agitada de ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico (14 g, 54 mmol) hidrato de 1-hidroxi-benzotriazol (7,29 g, 54 mmol), hidrocloruro de 1-[3-(dimetilamino)propil]-3-etil-carbodiimida (10,37 g, 54 mmol) y trietil-amina (3,76 ml, 27 mmol) en *N,N*-dimetil-formamida (130 ml) a la temperatura ambiente y se agitó durante una noche La mezcla de reacción se sofocó en ácido clorhídrico acuoso diluido y se extrajo con dietil-éter y luego con acetato de etilo Las capas orgánicas agrupadas se lavaron sucesivamente con una solución acuosa diluida de hidróxido de sodio, con agua y con salmuera Los disolventes se separaron por arrastre en vacío para proporcionar 12,2 g de un material bruto El residuo se disolvió en metanol (100 ml) y se agitó con hidróxido de litio (10 ml 1 M) durante 1 h para hidrolizar el éster del producto *bis*-acilado Los disolventes se separaron por arrastre en vacío, el residuo se diluyó con agua (200 ml) y se saponificó a un pH de 12 con hidróxido de sodio El material precipitado se separó por filtración, y el material filtrado se acidificó a un pH de 1 con ácido clorhídrico concentrado y se extrajo con acetato de etilo (2 x 200 ml) Los materiales orgánicos agrupados se lavaron con carbonato de sodio 2 N, luego con salmuera y se secaron (sobre $MgSO_4$) Los disolventes se separaron por arrastre en vacío para proporcionar el producto puro (5,7 g, 14,9 mmol) con un rendimiento de 55%

^{1}H NMR ($CDCl_3$) 8 53 (dd, 1H, J= 2 Hz, 8 Hz), 8 16 (dd, 1H, J= 2 Hz, 5 Hz), 7 11 (m, 2H), 6 78 (d, 1H, J= 8 Hz), 6 61 (d, 1H, J= 2 Hz), 6 52 (m 3H), 5 97 (s, 2H), 4 57 (s, 2H)

MS (m/z) 383 (M^++1 10)

Preparación 36

(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(1-ciano-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 0 37)



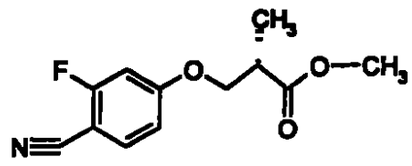
(5.0 37)

A una solución agitada de 2-(benzo[1,3]dioxol-5-iloxi)-N-(2-fluoro-4-hidroxi-bencil)-nicotinamida (5 g, 13,1 mmol) (±)-lactonitrilo (0,93 g, 13 1 mmol) y trifenil-fosfina (3,78 g, 14,4 mmol) en tetrahidrofurano (200 ml) a la temperatura ambiente, se le añadió gota a gota con agitación azo-dicarboxilato de dietilo (2 3 ml, 14 4 mmol) La mezcla se agitó a la temperatura ambiente durante una noche Los disolventes se separaron por arrastre en vacío se diluyeron con acetato de etilo y se lavaron con una solución acuosa diluida de hidróxido de sodio, con salmuera y se secaron (sobre $MgSO_4$) Los disolventes se separaron por arrastre en vacío El aceite resultante se lavó con dietil-éter y el material precipitado se separó por filtración Las aguas madres se purificaron por cromatografía en columna de resolución rápida (con una mezcla de 35% de acetato de etilo y hexano), proporcionando 1,5 g de un material sólido de color blanco (con un rendimiento de 26%)

^{1}H NMR ($CDCl_3$) 8 59 (d, 1H, J=8 Hz), 8 28 (t, 1H, J= 6 Hz) 8 21 (dd, 1H, J= 2 Hz, 4 Hz), 7 40 (t, 1H, J= 8 Hz), 7 12 (dd, 1H, J= 5 Hz, 8 Hz), 6 82 (d, 1H J= 8 Hz), 6 66 (m, 3H), 6 00 (s, 2H), 4 83 (q, 1H, J= 7 Hz), 4 66 (d, 2H, J= 6 Hz), 1 76 (d, 3H, J= 7 Hz)

Preparación 37

(S)-Éster metílico de ácido 3-(4-ciano-3-fluoro-fenoxi)-2-metil-propiónico de Fórmula (5 0 38)



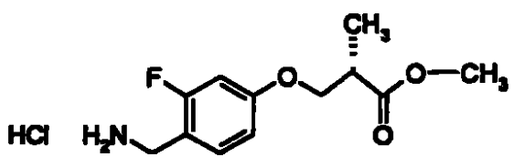
(5.0 38)

A una solución agitada de 2-fluoro-4-hidroxi-benzonitrilo (1,0 g, 7,3 mmol), (S)-éster metílico de ácido 3-hidroxi-2-metil-propiónico (0 8 ml 7,3 mmol) y trifenil-fosfina (2,3 g, 8,8 mmol) a la temperatura ambiente se le añadió gota a gota azo-dicarboxilato de dietilo (1,4 ml, 8,8 mmol) La mezcla se agitó a la temperatura ambiente durante una noche, se diluyó con acetato de etilo y se lavó sucesivamente con una solución acuosa diluida de hidróxido de sodio, con una solución acuosa diluida de ácido clorhídrico, con salmuera y se secó (sobre $MgSO_4$) Los disolventes se separaron por arrastre en vacío El aceite resultante se lavó con dietil-éter y el material precipitado se separó por filtración Las aguas madres se adsorbieron sobre gel de sílice y el producto se purificó por cromatografía en columna de resolución rápida (con una mezcla de 40% de acetato de etilo y hexano), proporcionando 0,14 g de un aceite de color amarillo (con un rendimiento de 8%)

^{1}H NMR ($CDCl_3$) 7 49 (t, 1H, J= 8 Hz), 6 73 (d, 1H, J= 9 Hz), 6 70 (d, 1H, J= 9 Hz), 4.21 (dd, 1H, J= 7, 9 Hz), 4 01 (dd, 1H, J= 6, 9 Hz), 3 71 (s, 3H), 2 95 (m, 1H) 1.29 (d, 3H J= 7 Hz)

Preparación 38

(S)-Hidrocloruro del éster metílico de ácido 3-(4-aminometil-3-fluoro-fenoxi)-2-metil-propiónico de Fórmula (5 0 39)



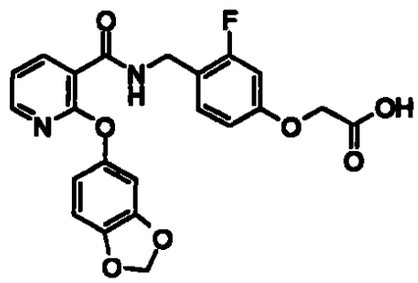
(5 0.39)

El (S)-éster metílico de ácido 3-(4-ciano-3-fluoro-fenoxi)-2-metil-propiónico (0,14 g) se sacudió sobre un aparato sacudidor de Parr bajo 50 psi (3 5 kg/cm^2) de hidrógeno durante 16 h, usando hidróxido de paladio sobre carbono (0,01 g, con 30% de Pd en peso) en metanol anhidro (20 ml) y ácido clorhídrico concentrado (0,5 ml) La mezcla de reacción se filtró a través de vidrio sinterizado y los disolventes se eliminaron en vacío para proporcionar 0,18 g de un material sólido de color blanco (con un rendimiento de 95%)

MS (m/z) 241 (M$^+$, 100)

Ejemplo 1

Ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético de Fórmula (5 5 1)



(5.5 1)

A una solución agitada del éster metílico de ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético (0,40 g, 0,88 mmol) en tetrahidrofurano (10 ml) y metanol (2 ml) se le añadió hidróxido de litio acuoso (2 ml, 1 M, 2 mmol) La mezcla de reacción se agitó a la temperatura ambiente durante 1 hora Los disolventes se separaron por arrastre en vacío y el residuo se repartió entre una solución acuosa diluida de ácido clorhídrico y acetato de etilo La fase acuosa se extrajo con 2 partes alícuotas de acetato de etilo y los materiales orgánicos agrupados se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentraron en vacío para proporcionar un material sólido de color amarillo El producto bruto se recristalizó en acetato de etilo para proporcionar 80 mg de un material sólido cristalino de color blanco (0,18 mmol, rendimiento 21%)

P f 180°C

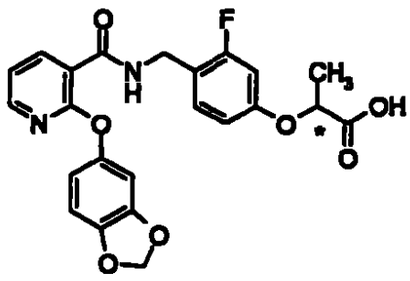
561

00535

^{1}H NMR (CD_3OD) δ 8 52 (dd, 1H, J= 2, 8 Hz), 8 24 (br, 1H), 8 16 (dd, 1H, J= 2, 5 Hz), 7.29 (t, 1H, J= 4 Hz), 7 09 (dd, 1H, J= 5, 8 Hz), 6 77 (d, 1H, J= 8 Hz), 6 55 (m 3H), 5 98 (s 2H) 4 59 (d, 2H, J= 6 Hz), 4 52 (s, 2H)

Ejemplo 2

(±)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propionico de Fórmula (5 5 2)



(5 5.2)

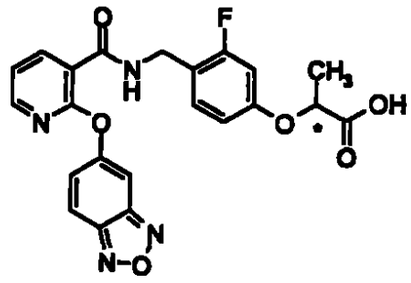
El compuesto de Fórmula (5 5 2) se preparó de una manera análoga a la que se describe en el Ejemplo 1, reemplazando el (±)-éster *terc* -butílico de ácido 2-[4-({[2-(benzo[1,3]-dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de éster metílico de ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético

P f = 136,4-138,0°C

^{1}H NMR ($CDCl_3$) δ 8 59 (dd, 1H, J= 2, 8 Hz), 8 30 (t, 1H J= 6 Hz), 8 21 (dd, 1H J= 2, 5 Hz), 7 30 (t, 1 J= 8 Hz) 7 12 (dd 1H, J= 5 8 Hz) 6 81 (d, 1H J= 8 Hz) 6 60 (s 2H), 4 74 (q, 1H, J= 7 Hz), 4 63 (d 2H J= 6 Hz), 1 63 (d, 3H, J= 7 Hz)

Ejemplo 3

(±)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 3)



(5.5.3)

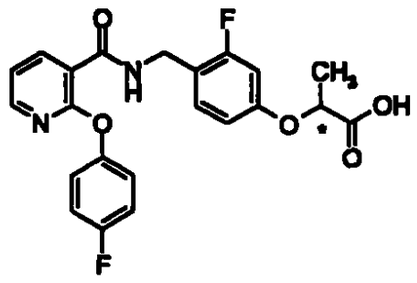
El (±)-éster *terc* -butílico de ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propionico 0,17 g, 0,33 mmol) se agitó en ácido fórmico (5 ml) a la temperatura ambiente durante 2 horas El ácido fórmico se eliminó en vacío y el producto se almacenó durante una noche en alto vacío para proporcionar un material sólido de color blanco (0,12 g, rendimiento 80%)

^{1}H NMR ($CDCl_3$) δ 8 36 (dd, 1H, J= 2, 7 Hz), 8 09(dd, 1H, J= 2 5 Hz), 8 03 (br, 1H), 7 75 (d, 1H, J= 9 Hz), 7 42 (s, 1H), 7 13 (m, 2H), 6 50 (m, 2H), 4 54 (q, 1H, J= 7 Hz), 4.49 (d, 1H, J= 6 Hz), 1 46 (d, 3H J= 7 Hz)

MS (m/z) 452 (M^+, 100)

Ejemplo 4

(±)-Ácido 2-[3-fluoro-4-({[2-(4-fluoro-fenoxi)-pirídina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 4)



(5 5.4)

El compuesto de Fórmula (5 5 4) se preparo de una manera análoga a la que se describe en el Ejemplo 3, reemplazando el (±)-éster *terc* -butílico de ácido 2-[3-fluoro-4-({[2-(4-

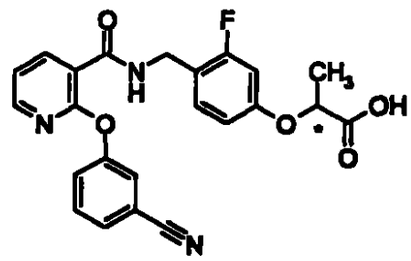
fluoro-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico al correspondiente material de (±)-éster *terc*-butílico de ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$) δ 8 58 (d, 1H, J= 7 Hz), 8 26 (s, 1H), 8 16 (d, 1H, J= 4 Hz), 7 10 (m, 4H), 6 60 (m, 2H), 4 72 (q, 1H, J= 7 Hz), 4 61 (d, 2H, J= 6 Hz), 1 62 (d, 3H, J= 7 Hz)

MS (m/z) 428 (M^+, 100)

Ejemplo 5

(±)-Ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 5)



(5 5.5)

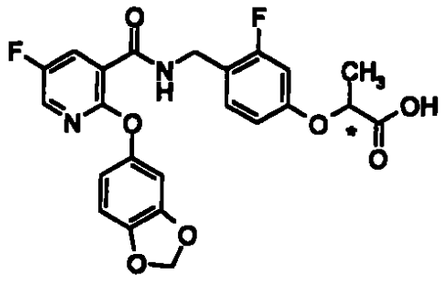
El compuesto de Fórmula (5 5 5) se preparó de una manera analoga a como se describe en el Ejemplo 3 reemplazando el (±)-éster *terc*-butílico de ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico al correspondiente material de (±)-éster *terc*-butílico de ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$)· δ 8 58 (d, 1H, J= 7 Hz), 8.26 (s, 1H), 8 16 (d, 1H, J= 4 Hz), 7 10 (m, 4H), 6 60 (m, 2H), 4 72 (q, 1H, J= 7 Hz), 4 61 (d, 2H, J= 6 Hz), 1 62 (d, 3H, J= 7 Hz)

MS (m/z) 428 (M^+, 100)

Ejemplo 6

(±)-Ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-5-fluoro-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propionico de Formula (5 5 6)



(5 5 6)

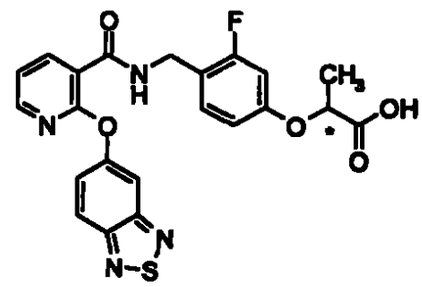
El compuesto de Fórmula (5 5 6) se preparó de una manera análoga a como se describe en el Ejemplo 3 reemplazando el (±)-ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propionico al correspondiente material de (±)-éster *terc* -butílico de acido 2-[4-({[2-(benzo[2 1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$) δ 8 31 (dd 1H, J= 3, 8 Hz), 8 02 (d 1H, J= 3 Hz), 7 28 (t, 1H, J= 9 Hz), 7.23 (m, 1H), 6 79 (d, 1H, J= 8 Hz), 6 55 (m, 3H), 5 99 (s, 2H), 4 73 (q, 1H, J= 7 Hz), 4 60 (d, 2H, J= 6 Hz), 1 62 (d, 3H, J= 7 Hz)

MS (m/z) 472 (M^+, 100)

Ejemplo 7

(±)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Formula (5 5 7)



(5.5.7)

El compuesto de Fórmula (5 5 7) se preparó de una manera análoga a la que se describe en el Ejemplo 3, reemplazando el (±)-éster *terc* -butílico de ácido 2-[4-({[2-(benzo-

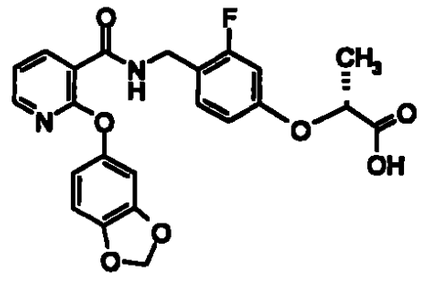
[2,1,3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de (±)-éster *terc* -butílico de ácido 2-[4-({[2-(benzo-[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$) δ 8 61 (d, 1H, J= 7 Hz), 8 18 (d, 1H, J= 5 Hz), 8 06 (s, 1H), 7 99 (d, 1H, J= 10 Hz), 7 64 (s, 1H), 7 43 (d, 1H, J= 9 Hz), 7 29 (t, 1H, J= 9 Hz) 6 60 (m, 2H), 4 72 (q, 1H, J= 7 Hz), 4 63 (d, 2H, J= 6 Hz), 1 61 (d, 3H, J= 7 Hz)

MS (m/z) 468 (M^+, 100)

Ejemplo 8

(R)-Ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 8)



(5.5.8)

El compuesto de Fórmula (5 5 8) se preparó de una manera análoga a la que se describe en el Ejemplo 1 reemplazando el (R)-éster metílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de éster metílico de ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético

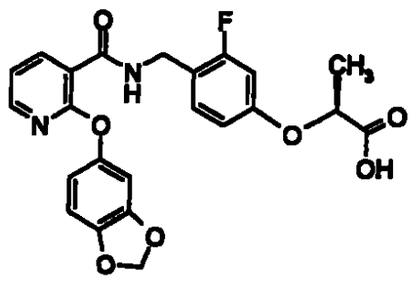
^{1}H NMR ($CDCl_3$) δ 8 59 (dd, 1H, J= 2, 8 Hz), 8 31 (t 1H, J= 6 Hz), 8 21 (dd, 1H, J= 2, 5 Hz), 7 30 (t, 1H, J= 8 Hz), 7 12 (dd, 1H, J= 5, 8 Hz), 6 81 (d, 1H, J= 8 Hz), 6 61 (m, 3H), 6 00 (s, 2H), 4 74 (q, 1H, J= 7 Hz), 4 63 (d, 2H, J= 6 Hz), 1 64 (d, 3H, J= 7 Hz)

566

00570

Ejemplo 9

(S)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 9)



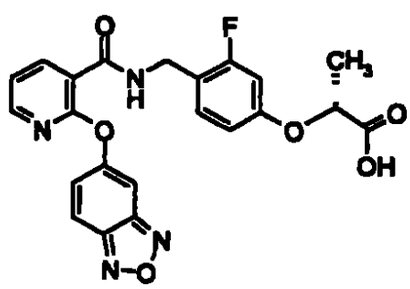
(5 5 9)

El compuesto de Fórmula (5 5 9) se preparó de una manera análoga a la que se describe en el Ejemplo 1, reemplazando el (S)-éster metílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de éster metílico de ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético

^{1}H NMR ($CDCl_3$) δ 8 59 (dd, 1H, J= 2, 8 Hz), 8 31 (t, 1H, J= 6 Hz), 8 21 (dd 1H, J= 2, 5 Hz), 7 30 (t, 1H, J= 8 Hz), 7 12 (dd, 1H, J= 5, 8 Hz), 6 81 (d 1H J= 8 Hz), 6 61 (m, 3H), 6 00 (s, 2H) 4 74 (q, 1H, J= 7 Hz), 4 63 (d, 2H, J= 6 Hz), 1 64 (d 3H J= 7 Hz)

Ejemplo 10

(R)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 10)



(5 5 10)

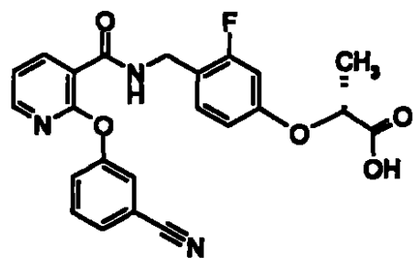
El compuesto de Formula (5 5 10) se preparo de una manera análoga a la que se describe en el Ejemplo 1 reemplazando el (R)-éster metílico de ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de éster metílico de ácido [4-({[2-(benzo-[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acetico

^{1}H NMR ($CDCl_3$) δ 8 36 (dd 1H, J= 2, 7 Hz), 8 09(dd, 1H, J= 2, 5 Hz), 8 03 (br, 1H), 7 75 (d, 1H, J= 9 Hz), 7 42 (s, 1H), 7 13 (m, 2H), 6 50 (m, 2H), 4 54 (q, 1H, J= 7 Hz), 4 49 (d, 2H, J= 6 Hz), 1 46 (d, 3H, J= 7 Hz)

MS (m/z) 452 (M^+ 100)

Ejemplo 11

(R)-Ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-pirdina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 11)



(5 5 11)

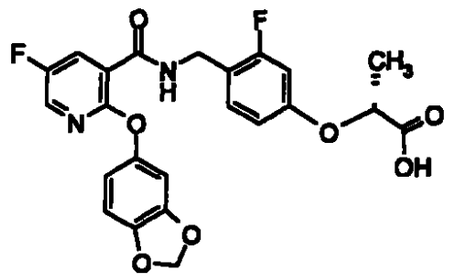
El compuesto de Fórmula (5 5 11) se preparó de una manera analoga a la que se describe en el Ejemplo 1 reemplazando el (R)-éster metílico de ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-pirdina-3-carbonil]-amino}-metil)-fenoxi]-propiónico al correspondiente material de éster metílico de ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético

^{1}H NMR ($CDCl_3$) δ 8 50(dd, 1H, J= 2, 6 Hz), 8 12 (dd, 1H, J= 2, 5 Hz), 8 03 (s, 1H), 7 35 (m, 4H), 7 15 (dd, 1H, J= 5, 8 Hz), 6 56 (m, 2H), 4 61 (q, 1H, J= 7 Hz), 4 57 (d, 2H, J= 6 Hz) 1 54 (d, 3H, J= 7 Hz)

MS (m/z) 435 (M^+, 100)

Ejemplo 12

(R)-Ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-5-fluoro-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 12)



(5 5.12)

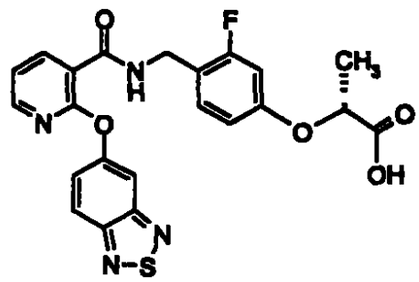
El compuesto de Fórmula (5 5 12) se preparó de una manera análoga a la que se describe en el Ejemplo 1, reemplazando el (R)-ester metílico de ácido 2-[4-({[2-(benzo-[1,3]dioxol-5-iloxi)-5-fluoro-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de éster metílico de acido [4-({[2-(benzo[1 3]dioxol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético

^{1}H NMR ($CDCl_3$) δ 8 33 (dd, 2H, J= 3, 8 Hz), 8 04 (d, 1H, J= 3 Hz), 7 30 (t, 1H, J= 8 Hz), 6 80 (d, 1H, J= 8 Hz), 8 62 (m, 3H), 6 56 (dd, 1H J= 2, 8 Hz), 6 01 (s, 2H), 4 74 (q, 1H, J= 7 Hz), 4 62 (d, 2H, J= 6 Hz), 1 65 (d, 3H, J= 7 Hz)

MS (m/z) 472 (M^+, 100)

Ejemplo 13

(R)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 13)



(5 5 13)

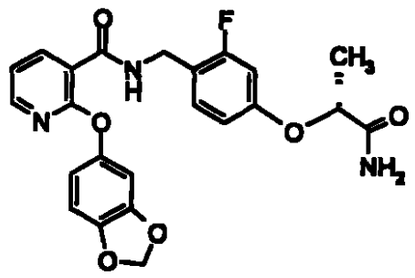
El compuesto de Fórmula (5 5 13) se preparó de una manera análoga a la que se describe en el Ejemplo 1 reemplazando el (R)-éster metílico de ácido 2-[4-({[2-(benzo-[2,1 3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de éster metílico de ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético

^{1}H NMR ($CDCl_3$) δ 8 60 (d, 1H, J= 7 Hz) 8 18 (d, 1H, J= 5 Hz), 8 06 (s, 1H), 7 99 (d, 1H, J= 10 Hz), 7 64 (s 1H), 7 43 (d, 1H, J= 9 Hz), 7 29 (t, 1H, J= 9 Hz), 6 60 (m, 2H), 4 72 (q, 1H, J= 7 Hz), 4 63 (d 2H, J= 6 Hz), 1 61 (d, 3H J= 7 Hz)

MS (m/z) 468 (M^+, 100)

Ejemplo 14

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 14)



(5.5 14)

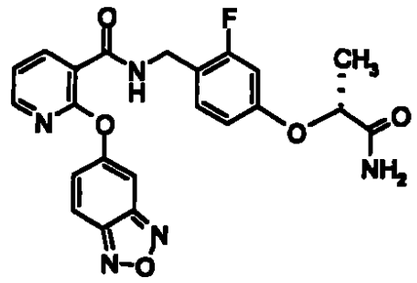
A una solución agitada de (R)-ácido2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico (0,25 g, 0,55 mmol) en etilen-glicol-dimetil-éter (20 ml) a -10ºC se le añadió N-metil-morfolina (0,06 ml, 0,55 mmol) lo cual fue seguido por la adicion gota de cloroformiato de isobutilo (0,071 ml, 0,55 mmol) La solución turbia se agitó a -10ºC durante 10 min Se burbujeó amoníaco gaseoso a través de la mezcla de reacción durante 10 min, que luego se calentó a la temperatura ambiente y se agitó durante 15 min adicionales La mezcla de reacción se repartió entre cloroformo y agua La capa orgánica se secó sobre sulfato de sodio y se concentró en vacío para proporcionar un sólido de color blanco La cromatografía en columna de resolución rápida (con una mezcla de 1% de metanol y diclorometano) proporcionó 0,15 g de un sólido de color blanco (con un rendimiento de 60%)

^{1}H NMR ($CDCl_3$) δ 8 57 (d, 1H J= 7 Hz) 8 24 (br, 1H), 8 19 (d 1H, J= 5 Hz), 7 33 (t, 1H, J= 9 Hz) 7 10 (m, 1H) 6 80 (d 1H, J= 8 Hz), 6 58 (m, 3H), 6 25 (br 1H) 5 99 (s, 2H) 5 38 (br 1H) 4 60 (m 3H), 1 55 (d, 3H, J= 7 Hz)

MS (m/z) 454 (M^++1, 100)

Ejemplo 15

(R)-2-(benzo[2,1,3]oxadiazol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 15)



(5.5.15)

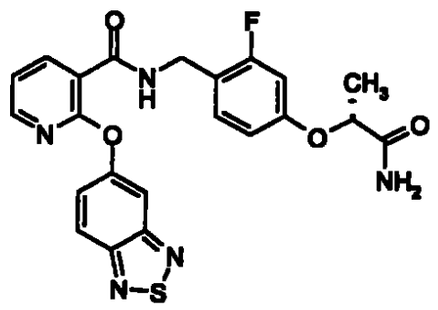
El compuesto de Fórmula (5 5 15) se preparó de una manera análoga a la que se describe en el Ejemplo 14, reemplazando el (R)-ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de (R)-ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$) δ 8 61 (dd, 1H, J= 2, 7 Hz) 8 19 (dd 1H, J= 2 5 Hz) 7.87 (t, 1H, J= 9 Hz), 7 52 (d, 1H, J= 2 Hz), 7 33 (s, 1H), 7 25 (t 1H, J=5 Hz), 6 63 (m, 2H), 6.26 (br, 1H), 5.47 (br, 1H), 4 64 (d, 2H, J= 6 Hz), 4 58 (q, 1H, J= 7 Hz), 1 54 (d, 3H, J= 7 Hz)

MS (m/z) 452 (M^++1, 100)

Ejemplo 16

(R)-2-(benzo[2,1,3]tiadiazol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 16)



(5 5 16)

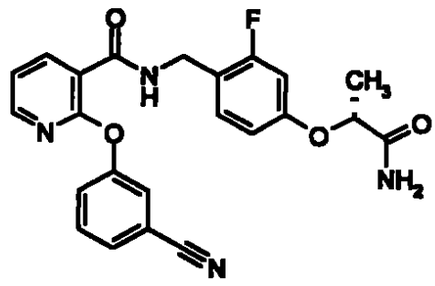
El compuesto de Fórmula (5 5 16) se preparo de una manera análoga a la que se describe en el Ejemplo 14, reemplazando el (R)-ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de (R)-ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$) δ 8 63 (dd, 1H, J= 2, 7 Hz), 8 19 (dd, 1H J= 2, 5 Hz), 7 87 (t, 1H, J= 9 Hz), 7 52 (d, 1H, J= 2 Hz), 7 33 (s, 1H), 7 25 (t, 1H J=5 Hz), 6 63 (m, 2H), 6 26 (br, 1H), 5 47 (br, 1H), 4 64 (d, 2H, J= 6 Hz), 4 57 (q, 1H, J= 7 Hz), 1 54 (d, 3H, J= 7 Hz)

MS (m/z) 468 (M^++1, 100)

Ejemplo 17

(R)-N-[4-(1-Carbamoil-etoxi)-2-fluoro-bencil]-2-(3-ciano-fenoxi)-nicotinamida de Fórmula (5 5 17)



(5.5 17)

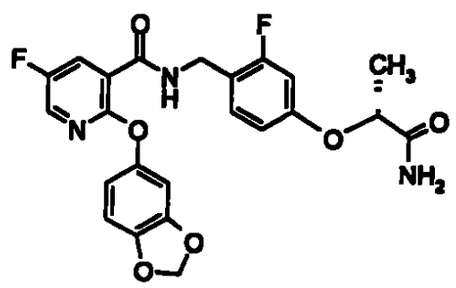
El compuesto de Fórmula (5 5 17) se preparó de una manera análoga a la que se descnbe en el Ejemplo 14, reemplazando el (R)-ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-pindina-3-carbonil]-amino}-metil)-fenoxi]-propionico al correspondiente material de (R)-ácido 2-[4-({[2-(benzo[1 3]dioxol-5-iloxi)-pindina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$)) δ 8 59 (dd, 1H, J= 2, 7 Hz), 8 16 (dd, 1H, J= 2, 5 Hz), 8 03 (t, 1H, J= 9 Hz), 7 38 (m 4H), 6 63 (m 2H) 6 27 (br, 1H), 5 48 (br 1H) 4 59 (m, 3H), 1 55 (d, 3H, J= 7 Hz)

MS (m/z) 435 (M^++1 100)

Ejemplo 18

(R)-2-(benzo[1 3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-5-fluoro-nicotinamida de Fórmula (5 5 18)



(5.5 18)

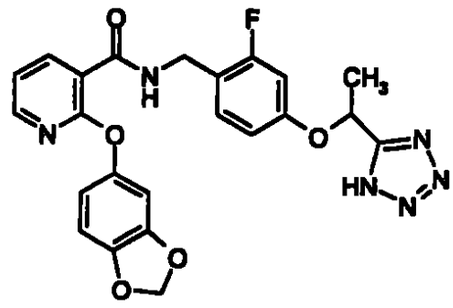
El compuesto de Fórmula (5 5 18) se preparó de una manera análoga a la que se describe en el Ejemplo 14 reemplazando el (R)-ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-pindina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico al correspondiente material de (R)-ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pindina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$) δ 8 31 (m, 2H), 8 02 (d, 1H, J= 3 Hz), 7 32 (t, 1H, J= 8 Hz), 6 80 (d, 1H, J= 8 Hz), 6 60 (m, 3H) 6 26 (br, 1H) 6 00 (s, 2H) 5 35 (br, 1H) 4 07 (m, 3H), 1 55 (d 3H, J= 7 Hz)

MS (m/z) 472 (M^++1 100)

Ejemplo 19

(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(1*H*-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 19)



(5 5 19)

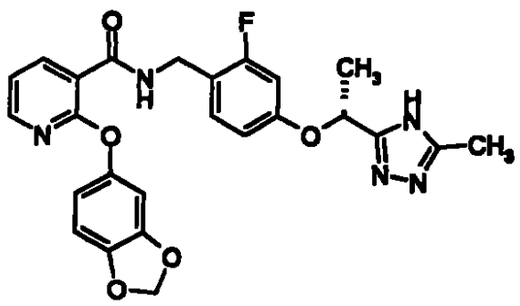
Una solución de (±)-2-(benzo[1,3]dioxol-5-iloxi)-N-[4-(1-ciano-etoxi)-2-fluoro-bencil]-nicotinamida (1,5 g, 3,5 mmol) en tolueno anhidro (5 ml) se transfirió a un matraz a una pequeña presión Se añadieron óxido de dibutil-estaño (0,53 g, 2,1 mmol) y azíduro de trimetil-sililo (1,7 ml, 21 mmol) El tubo se cerró herméticamente y se colocó detrás de un protector del escape de soplado La mezcla de reacción se agitó durante 15 min a 55°C, luego se calentó a 110°C con agitación durante una noche La mezcla de reacción de color negro se enfrió a 0-5°C, el matraz a presión se abrió y el residuo se recogió en metanol Los disolventes se eliminaron en vacío y el residuo se recogió en acetato de etilo La solución orgánica se lavó dos veces con carbonato de sodio acuoso saturado Las fases acuosas se agruparon y acidificaron con ácido clorhídrico concentrado, y se extrajeron dos veces con acetato de etilo Las fases orgánicas agrupadas se secaron (sobre $MgSO_4$), se concentraron y se cargaron sobre una columna con gel de sílice en forma de un aceite de color pardo La purificación por cromatografía en columna (con una mezcla de 5% de metanol y diclorometano) proporcionó un producto en forma de un material sólido de color blanco (0 46 g, 28%)

^{1}H NMR ($CDCl_3$) 8 58 (dd, 1H J=2 Hz, 8 Hz), 8 43 (t, 1H, J= 6 Hz), 8 21 (dd, 1H, J= 2 Hz, 5 Hz), 7 13 (m, 2H), 6 79 (d, 1H, J= 8 Hz), 6 61 (d, 1H, J= 2 Hz), 6.53 (m, 3H), 5.99 (s, 2H), 5 72 (q, 1H, J= 7 Hz), 4 57 (d, 2H, J= 5 Hz), 1 78 (d, 3H, J= 6 Hz)

MS (m/z) 479 (M^++1, 40)

Ejemplo 20

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 20)



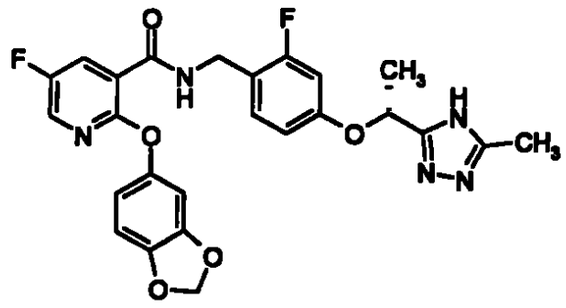
(5.5.20)

Una solución del (R)-éster etílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propionimídico (0,16 g, 0,33 mmol) e hidrazida acética (24 mg, 0,31 mmol) en *n*-butanol (20 ml) se agitó durante 20 h a 80ºC La mezcla de reacción se enfrió a la temperatura ambiente y se sofocó en una solución acuosa saturada de ácido oxálico, y luego se extrajo con acetato de etilo La solución orgánica se secó (sobre $MgSO_4$) y se concentró en vacio El residuo se purificó por cromatografía en columna (con una mezcla de 3% de metanol y diclorometano) para proporcionar un material sólido pegajoso de color amarillo (12 mg) El residuo se purificó adicionalmente mediante cromatografía de capa fina preparatoria (con una mezcla de 10% de metanol y diclorometano) para proporcionar 7 mg del deseado compuesto (con un rendimiento de 4%)

^{1}H NMR ($CDCl_3$) 8 52 (d, 1H, J= 7 8 Hz), 8 42 (s, 1H), 8 21 (dd, 1H, J= 5 0, 1 9 Hz), 7 19 (t, 1H, J= 8 3 Hz), 7 11 (m, 1H), 6 77 (m, 4H), 6 00 (s, 2H), 5 48 (d, 2H, J= 6 6 Hz), 4 80 (s, 2H), 2.45 (s, 3H), 1 75 (d, 3H, J= 6 7 Hz)

Ejemplo 21

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-{2-fluoro-4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 21)



(5.5.21)

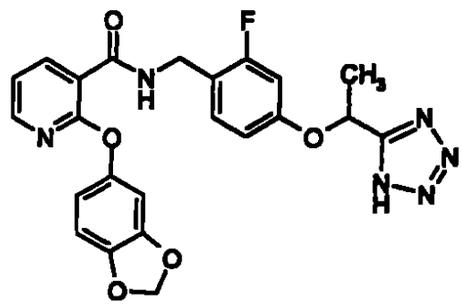
Una solución de (R)-2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(1-tiocarbamoil-etoxi)-bencil]-nicotinamida (0,1 g, 0,21 mmol) en piridina (5 ml) se calento con agitación a 70°C Se añadio hidrazina anhidra (1,5 ml, 50 mmol) con agitación a través de una jeringa La mezcla de reacción se agitó a 70°C durante 5 min y luego se enfrió a la temperatura ambiente El disolvente se eliminó en vacío y el residuo se almacenó bajo el vacío del alojamiento durante 1 h El residuo se recogió subsiguientemente en piridina de nueva aportación (5 ml) A esta solución se le añadió cloruro de acetilo (0,057 ml, 0,8 mmol) a la temperatura ambiente, y la mezcla de reacción se agitó durante 2 h La piridina se eliminó en vacio y se reemplazó por N N-dimetil-formamida (5 ml) y la solución resultante se agitó a 130°C durante 4 h La mezcla de reacción se enfrió a la temperatura ambiente, se sofocó en agua (50 ml) y se extrajo con dietil-éter Los extractos agrupados se secaron (sobre $MgSO_4$), se filtraron y se concentraron casi hasta sequedad, luego se cargaron sobre una columna de gel de silice y se purificaron por cromatografía en columna (con un gradiente desde una mezcla de 1% de metanol y diclorometano que cambian a una mezcla de 5% de metanol y diclorometano) para proporcionar un material sólido de color blanco (7,6 mg, rendimiento 7%)

MS (m/z) 509 (M^+ 20)

$[\alpha]_D$ = +24° ($CHCl_3$)

Ejemplo 22

(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[2-fluoro-4-[1-(1H-tetrazol-5-il)-etoxi]-bencil]-nicotinamida de Fórmula (5 5 22)



(5.5.22)

Una solucion de (±)-2-(benzo[1,3]dioxol-5-iloxi)-N-[4-(1-ciano-etoxi)-2-fluoro-bencil]-nicotinamida (1,5 g, 3 5 mmol) en tolueno anhidro (5 ml) se transfinó a un pequeño matraz a presión Se añadieron óxido de dibutil-estaño (0,53 g, 2,1 mmol) y aziduro de trimetil-sililo (1,7 ml 21 mmol) El tubo se cerró herméticamente y se colocó detrás de un protector del escape de soplado La mezcla de reaccion se agitó durante 15 min a 55°C, luego se calento a 110°C con agitación durante una noche La mezcla de reacción de color negro se enfnó a 0-5°C el matraz a presion se abrió y el residuo se recogio en metanol Los disolventes se eliminaron en vacio y el residuo se recogió en acetato de etilo La solución orgánica se lavó dos veces con una solución acuosa saturada de carbonato de sodio Las fases acuosas se agruparon y acidificaron con ácido clorhídnco concentrado y se extrajeron dos veces con acetato de etilo Las fases orgánicas agrupadas se secaron (sobre $MgSO_4$) se concentraron y se cargaron sobre una columna con gel de silice como un aceite de color pardo La purificación por cromatografia en columna (con una mezcla de 5% de metanol y diclorometano) porporcionó el producto como un material sólido de color blanco (0,46 g, 28%)

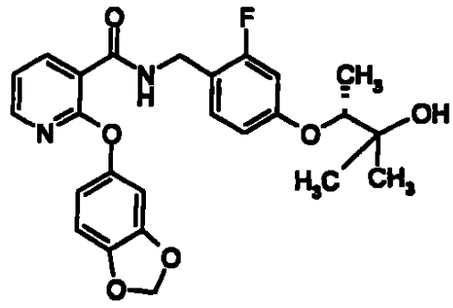
^{1}H NMR ($CDCl_3$) 8 58 (dd, 1H J=2 Hz 8 Hz) 8 43 (t 1H J= 6 Hz), 8 21 (dd, 1H J= 2 Hz, 5 Hz), 7 13 (m, 2H) 6 79 (d, 1H, J= 8 Hz), 6 61 (d, 1H, J= 2 Hz), 6 53 (m, 3H), 5 99 (s, 2H), 5 72 (q, 1H, J= 7 Hz), 4 57 (d, 2H, J= 5 Hz), 1 78 (d 3H, J= 6 Hz)

MS (m/z) 479 (M^++1, 40)

577

Ejemplo 23

(R)-2-(Benzo[1 3]dioxol-5-iloxi)-N-[2-fluoro-4-(2-hidroxi-1 2-dimetil-propoxi)-bencil]-nicotinamida de Fórmula (5 5 23)



(5 5 23)

A una solucion agitada del (R)-éster metílico de acido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico (0,10 g, 0,213 mmol) en tetrahidrofurano (5 ml) a -10°C, se le añadió cloruro de metil-magnesio (3,0 ml, 1,07 mmol) y se agitó a -10°C durante 15 min La solución se dejó calentar a la temperatura ambiente y se agito durante 16 h adicionales La mezcla de reaccion se sofocó en agua y se extrajo con acetato de etilo Los materiales orgánicos agrupados se secaron (sobre $MgSO_4$), se filtraron y se concentraron para dar un aceite opaco de color blanco El residuo se purificó por cromatografía en columna (con una mezcla 1 1 de acetato de etilo y hexano) proporcionando 40 mg de un polvo de color blanco (con un rendimiento de 40%)

^{1}H NMR ($CDCl_3$) 8 60 (d, 1H, J= 7 4 Hz), 8 25 (s, 1H), 8.21 (d, 1H, J= 4 8 Hz), 7 31 (t, 1H, J= 8.3 Hz), 7 12 (dd, 1H, J= 5 0, 7 9 Hz), 6.83 (d, 1H, J= 8 3 Hz), 6 67 (m, 4H), 6 00 (s, 2H), 4 64 (d 2H, J= 4 6 Hz) 4 12 (q, 1H, J= 6.2 Hz), 1 25 (s, 6H) 1.22 (d 3H, J= 6 2 Hz)

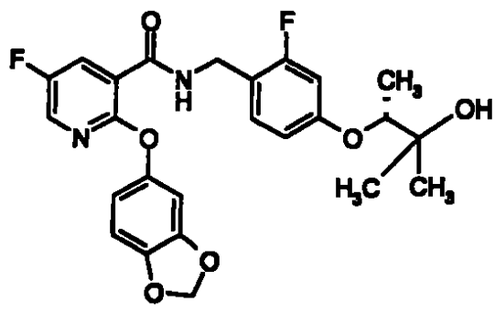
MS (m/z) 467 (M^-, 100)

578

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Ejemplo 24

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(2-hidroxi-1,2-dimetil-propoxi)-bencil]-nicotinamida de Fórmula (5 5 24)



(5.5.24)

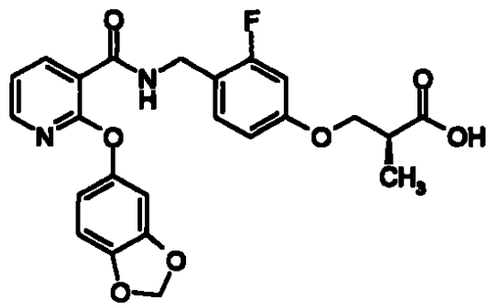
Preparada de una manera analoga a la del Ejemplo 23, reemplazando por el (R)-éster metílico de ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico

^{1}H NMR ($CDCl_3$) 8 33 (dd, 1H, J= 8 3, 3 3 Hz) 8 30 (s, 1H), 8 03 (d, 1H, J= 2 9 Hz), 7 30 (t, 1H, J= 8 7 Hz), 6 81 (d, 1H, J= 8 3 Hz), 6 62 (m, 4H), 6 01 (s, 2H), 4 63 (d, 2H, J= 5.8 Hz), 4 12 (q, 1H J= 6 2 Hz), 1 25 (s, 6H) 1 22 (d, 3H, J= 6 2 Hz)

MS (m/z) 487 (M^+ 100)

Ejemplo 25

(S)-ácido 3-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 25)



(5 5 25)

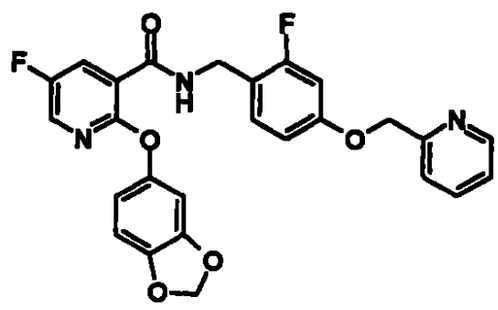
El ácido 2-(benzo[1,3]dioxol-5-iloxi)-nicotínico (0 168 g, 0 65 mmol) el (S)-hidrocloruro de ester metílico de ácido 3-(4-aminometil-3-fluoro-fenoxi)-2-metil-propiónico (0,18 g, 0,65 mmol) el hidrato de 1-hidroxi-benzotriazol (0,097 g, 0,72 mmol), el hidrocloruro de 1-[3-(dimetil-amino)propil]-3-etil-carbodiimida (0 138 g, 0,72 mmol) y la trietil-amina se disolvieron en *N,N*-dimetil-formamida (6 ml) y se agitaron a la temperatura ambiente durante una noche La mezcla de reacción se diluyó en acetato de etilo y se lavo sucesivamente con ácido clorhídrico acuoso diluido, con hidróxido de sodio acuoso diluido y con salmuera y se secó (sobre Na_2SO_4) El producto se purificó por cromatografía en columna de resolución rapida (con una mezcla de 20% de acetato de etilo y hexano) El residuo se recogió en tetrahidrofurano (10 ml) y en metanol (2 ml) y en una solución acuosa de hidróxido de litio (2 ml 1 M, 2 mmol) La mezcla de reacción se agitó a la temperatura ambiente durante 1 h Los disolventes se separaron por arrastre en vacio y el residuo se repartió entre una solución acuosa diluida de ácido clorhídrico y acetato de etilo La solución acuosa se extrajo con 2 partes alicuotas de acetato de etilo y los materiales orgánicos agrupados se lavaron con salmuera, se secaron sobre sulfato de sodio y se concentraron en vacio para proporcionar un material sólido de color blanco (0,12 g, con un rendimiento de 39%)

^{1}H NMR ($CDCl_3$) 8 60 (d, 1H, J= 8 Hz), 8 20 (m, 2H), 7 30 (t, 1H, J=8 Hz), 7 11 (m, 1H), 6 81 (d, 1H, J= 8 Hz), 6 82 (m, 3H), 6 00 (s, 2H), 4 63 (d, 2H, J= 6 Hz), 4 13 (dd, 1H, J= 7, 9 Hz), 3 93 (dd, 1H, J= 6, 9 Hz), 3 70 (s, 3H), 2 91 (m, 1H), 1.26 (d, 3H, J= 7 Hz)

MS (m/z) 469 (MH^+, 100)

Ejemplo 26

2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-2-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 26)



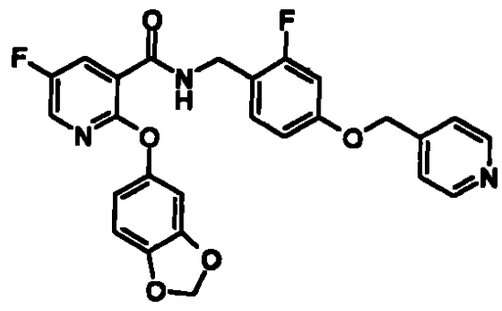
(5 5 26)

A una solucion agitada de 100 mg (0,25 mmol) de 2-(benzo[1 3]dioxol-5-iloxi)-5-fluoro-N-(2-fluoro-4-hidroxi-bencil)-nicotinamida, [preparada de un modo análogo a la Preparación 35 reemplazando por el ácido 2-cloro-5-fluoro-nicotinico (documento EP 0634413 A1)], de 10 ml de DMF y de 175 mg (1,25 mmol) de carbonato de potasio se le añadió una solución de DMF (5 ml) que contenia 82 mg (0,5 mmol) del hidrocloruro de 2-clorometil-pirıdina (de Aldrich) y 1 equivalente de trietil-amina La mezcla resultante se agitó durante 3 dias a la temperatura ambiente La mezcla de reaccion se vertió en una mezcla de agua y hielo (200 ml) y el material solido resultante se filtró, se lavó con agua fría y se secó en vacío para proporcionar el producto deseado

^{1}H-NMR ($CDCl_3$) 8 58 (d 1H, J= 5Hz), 8 32 (dd, 1 H, J=4,9Hz), 8 02 (d, 1H J= 3 Hz) 7 71 (dt, 1H J= 2,10Hz), 7 47 (d 1H J= 2 Hz), 7 26 (m, 1H), 6 80 (d, 1H, J=8Hz), 6 71 (m, 3H), 6 62 (d 1H, J=3Hz), 6 56 (dd, 1H J= 2 8Hz) 6 00 (s 2H), 5.2 (s 2H), 4 63 (d, 2H, J=6Hz)

Ejemplo 27

2-(Benzo[1 3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-2-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 27)



(5 5.27)

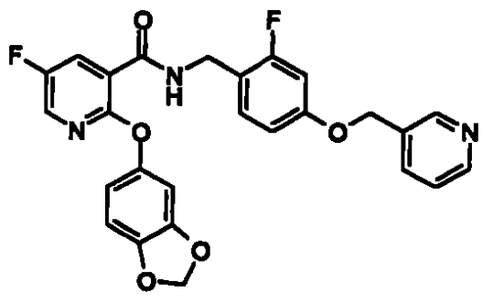
Preparada análogamente al Ejemplo 26, reemplazando por el hidrocloruro de 4-clorometil-pirıdina (de Aldrich)

MS (m/z) 492 (M^+, 100)

^{1}H-NMR ($CDCl_3$) 8 38 (m, 2 H), 8 02 (d, 1H, J= 3 Hz), 7 74 (m, 1H), 7 28 (m, 1H), 6 80 (d, 1H, J=8Hz), 6 71 (m, 3H) 6 62 (d, 1H, J=3Hz) 6 56 (dd, 1H, J= 2,8Hz), 6 00 (s, 2H), 5.2 (s, 2H), 4 63 (d, 2H, J=6Hz)

Ejemplo 28

2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-3-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 28)



(5 5 28)

Preparada análogamente al Ejemplo 26, reemplazando por el hidrocloruro de 4-clorometil-pirdina (de Aldrich)

MS (m/z) 492 (M^+, 100)

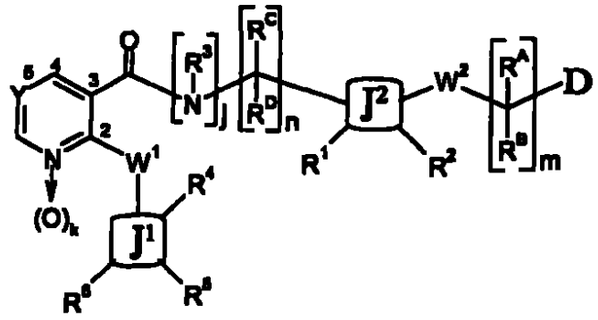
^{1}H-NMR ($CDCl_3$) 8 81 (s, 1H), 8 64 (d, 1H, J= 5Hz), 8 35 (m 2 H) 8 02 (d 1H, J= 3 Hz), 7 71 (dt, 1H, J= 2,10Hz), 7 47 (d, 1H, J= 2 Hz), 7 26 (m, 1H), 6 80 (d, 1H, J=8Hz), 6 71 (m, 3H), 6 62 (d, 1H, J=3Hz), 6 56 (dd, 1H, J= 2,8Hz) 6 00 (s, 2H), 5 2 (s, 2H), 4 63 (d, 2H, J=6Hz)

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REIVINDICACIONES

1 Un compuesto de Fórmula (1 0 0)



(1 0 0)

- en la que -

-j es 0 ó 1 con la condición de que cuando j es 0, n debe ser 2,

-k es 0 ó 1

-m es 1, 2 ó 3,

-n es 1 ó 2

-W^1 y W_2 son independientemente -O-, -$S(=O)_t$-, en que t es 0, 1 ó 2, o -$N(R^3)$- en que R^3 tiene el mismo significado que se define seguidamente,

-Y es $=C(R^1{}_a)$-, en que $R^1{}_a$ tiene los mismos significados que se definen seguidamente o -$[N\Rightarrow(O)_k]$- en que k es 0 ó 1,

- en que -

--$R^1{}_a$ es un miembro seleccionado entre el grupo que consta de -H, -F -Cl -CN -NO_2, alquilo C_1-C_4, alquinilo (C_2-C_4), alquilo (C_1-C_3) fluorado, alcoxi (C_1-C_3) fluorado -OR^{10}, y -$C(=O)NR^{22}{}_aR^{22}{}_b$,

- en que -

---$R^{22}{}_a$ y $R^{22}{}_b$ son cada uno de ellos independientemente -H, -CH_3, -CH_2CH_3, -CH_2CH_2 CH_3, -$CH_2(CH_3)_2$, -$CH_2CH_2CH_2CH_3$, -$CH(CH_3)CH_2CH_3$, -$CH_2CH(CH_3)_2$ -$C(CH_3)_3$, ciclopropilo, ciclobutilo o ciclopentilo,

-R^A y R^B son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -CF_3, alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, y bencilo en que dichos restos de cicloalquilo, fenilo y bencilo están sustituidos cada uno de ellos independientemente con 0 a 3 sustituyentes R^{10},

- en que -

--R^{10} es un miembro seleccionado entre el grupo que consta de fenilo, pirídilo,

-F, -Cl -CF_3, oxo (=O), -OR^{16} -NO_2 -CN, -$C(=O)OR^{16}$ -$C(=O)R^{16}$, -$C(=O)NR^{16}R^{17}$, -O-$C(=O)NR^{16}R^{17}$ -$NR^{16}R^{17}$, $NR^{16}C(=O)R^{17}$ -$NR^{16}C(=O)OR^{17}$ -$NR^{16}S(=O)_2R^{17}$ y -$S(=O)_2NR^{16}R^{17}$, en que dicho fenilo o piridilo está sustituido con 0 a 3 R^{11},

- en que -

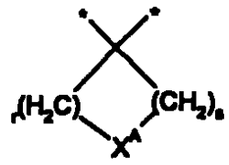
---R^{11} es -F, -Cl, -CF_3, -CN, -NO_2 -OH, alcoxi (C_1-C_3), alquilo (C_1-C_3), ó -$NR^{16}R^{17}$

- y -

----R^{16} y R^{17} son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H alquilo (C_1-C_4), alquenilo (C_2-C_4), cicloalquilo (C_3-C_6) fenilo, bencilo y piridilo, en que dicho alquilo, alquenilo, cicloalquilo, fenilo, bencilo o piridilo está sustituidos con 0 a 3 sustituyentes seleccionados entre el grupo que consta de -F, -Cl, -CF_3, -CN y alquilo (C_1-C_3),

- o -

-R^A y R^B se toman conjuntamente pero solamente en el caso en el que m sea 1, para formar un resto de tipo espiro de Fórmula (1 2 0)



(1.2 0)

- en que -

--r y s son independientemente de 0 a 4 con la condicion de que la suma de r + s ha de ser por lo menos 1 pero no mayor que 5,

- y -

--X^A se selecciona entre -CH_2- -$CH(R^{11})$- ó $C(R^{11})_2$-, en que cada R^{11} se selecciona de modo independiente de los otros y cada uno de ellos tiene el mismo significado que antes se define, -NR^{15}-, en que R^{15} tiene el mismo significado que se define seguidamente, -O-, y -$S(=O)_t$-, en que t es 0, 1 ó 2,

- y -

dicho resto de tipo espiro de la Fórmula parcial (1 2 0) está sustituido como en uno cualquiera o más átomos de carbono de este distinto del que define a X^A, por 0 a 3 sustituyentes R^{14}, en que R^{14} tiene el mismo significado que se define seguidamente, en lo referente a un átomo de nitrógeno de éste por 0 a 1 sustituyente R^{15}, en que R^{15} tiene el mismo significado que se define seguidamente, y en lo referente a un átomo de azufre de éste por 0 a 2 átomos de oxígeno

-R^C y R^D tienen los mismos significados que antes se definen para R^A y R^B excepto que uno de ellos debe ser -H, y que éstos se seleccionan independientemente uno de otro y de R^A y R^B

-R^1 y R^2 pueden aparecer individual o conjuntamente en cualquier anillo o en cualesquiera anillos que comprenden un significado del resto J^2 como se define seguidamente, y R^1 y R^2 son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -Cl, -CN, $-NO_2$, alquilo (C_1-C_4), alquinilo (C_2-C_4), alquilo (C_1-C_3) fluorado, $-OR^{16}$, y $-C(=O)NR^{22}_aR^{22}_b$, en que R^{16}, R^{22}_a y R^{22}_b tienen los mismos significados que antes se definen

-R^3 es -H, alquilo (C_1-C_3), fenilo, bencilo, ó $-OR^{16}$, en que R^{16} tiene los mismos significados que antes se definen,

-R^4, R^5 y R^6 pueden aparecer individual o conjuntamente en cualesquiera anillo o anillos que constituyan un significado del resto J^1 que se define seguidamente, y R^4, R^5 y R^6 son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

-(*a*) -H, -F -Cl alquinilo (C_2-C_4) $-R^{16}$, $-OR^{16}$, $-S(O)_pR^{16}$, $-C(=O)R^{16}$, $-C(=O)OR^{16}$, $-OC(=O)R^{16}$, -CN $-NO_2$, $-C(=O)NR^{16}R^{17}$, $-OC(=O)NR^{16}R^{17}$, $-NR^{22}_aC(=O)NR^{16}R^{17}$ $-NR^{22}_aC(=NR^{12})NR^{16}R^{17}$, $-NR^{22}_aC(=NCN)NR^{16}R^{17}$, $-NR^{22}_aC(=N\text{-}NO_2)NR^{16}R^{17}$, $-C(=NR^{22}_a)NR^{16}R^{17}$ $-CH_2C(=NR^{22}_a)NR^{16}R^{17}$, $-OC(=NR^{22}_a)NR^{16}R^{17}$ $-OC(=N\text{-}NO_2)NR^{16}R^{17}$, $-NR^{16}R^{17}$ $-CH_2NR^{16}R^{17}$, $-NR^{22}_aC(=O)R^{16}$, $-NR^{22}_aC(=O)OR^{16}$, $=NOR^{16}$, $-NR^{22}_aS(O)_pR^{17}$, $-S(=O)_pNR^{16}R^{17}$, y $-CH_2C(=NR^{22}_a)NR^{16}R^{17}$,

- en que -

–p es 0, 1 ó 2, y R^{22}_a, R^{16} y R^{17} tienen los mismos significados que se definen anteriormente

-(*b*) alquilo (C_1-C_4), y alcoxi (C_1-C_4) en el caso de que uno o más de los R^4, R^5 ó R^6 tenga el significado de $-OR^{16}$ en el párrafo (*a*) anterior y R^{16} sea definido como alquilo (C_1-C_4), en que dichos alquilo y alcoxi están sustituidos cada uno de ellos independientemente con 0 a 3 sustituyentes -F ó -Cl, o bien 0 ó 1 sustituyente alcoxi (C_1-C_2)-carbonilo-, alquil (C_1-C_2)-carbonilo-, o alquil (C_1-C_2)-carboniloxi-

- y -

-(*c*) un resto arilo o heterociclilo seleccionado entre el grupo que consta de fenilo, bencilo, furanilo, tetrahidrofuranilo, oxetanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolidinilo, oxazolilo, oxazolidinilo, isoxazolilo, isoxazolidinilo, tiazolilo, tiazolidinilo, isotiazolilo isotiazolidinilo pirazolilo, pirazolidinilo, oxadiazolilo, tiadiazolilo imidazolilo,

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imidazolidinilo, pirrolidinilo pirazinilo pirimidinilo, piridazinilo, piperidinilo, piperazinilo, triazolilo, triazinilo, tetrazolilo, piranilo, azetidinilo, morfolinilo, paratiazinilo, indolilo, indolinilo, benzo[*b*]furanilo, 2,3-dihidrobenzofuranilo, 2-*H*-cromenilo, cromanilo, benzotienilo, 1-*H*-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo, benzotiazolilo quinolinilo, isoquinolinilo ftalazinilo, quinazolinilo, quinoxalinilo y purinilo, en que dichos restos arilo y heterociclilo están sustituidos cada uno de ellos independientemente con 0 a 2 sustituyentes R^{14}

- en que -

--R^{14} es un miembro seleccionado entre el grupo que consta de alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, bencilo piridilo, y quinolinilo, en que dicho alquilo, cicloalquilo fenilo bencilo, piridilo o quinolinilo está sustituido con 0 1 ó 2 sustituyentes -F, -Cl, -CH_3, -OR^{16}, -NO_2, -CN, ó -$NR^{16}R^{17}$, y dicho grupo R^{14} consta adicionalmente de -F, -Cl, -CF_3, oxo (=O), -OR^{16}, -NO_2, -CN, -C(=O)OR^{16}, -O-C(=O)R^{16}, -C(=O)$NR^{16}R^{17}$, -O-C(=O)$NR^{16}R^{17}$, -$NR^{16}R^{17}$, -NR^{16}C(=O)R^{17}, -NR^{16}C(=O)OR^{17}, -NR^{16}S(=O_2)R^{17}, ó -S(=$O)_2NR^{16}R^{17}$, en que R^{16} y R^{17} tienen los mismos significados que antes se definen,

- y además en que -

--R^{15} es un miembro seleccionado independientemente entre el grupo que consta de -H, -$NR^{16}R^{17}$, -C(=O)R^{16}, -OR^{16}, alquil (C_1-C_4)-OR^{16}, -C(=O)OR^{16}, alquil (C_1-C_2)-C(=O)OR^{16}, -C(=O)$NR^{16}R^{17}$, alquilo (C_1-C_4), alquenilo (C_2-C_4) -$(CH_2)_u$-cicloalquilo (C_3-C_7) en que u es 0, 1 ó 2, fenilo, bencilo, piridilo, y quinolinilo, en que dicho alquilo, alquenilo, alcoxi, cicloalquilo, fenilo bencilo piridilo o quinolinilo está sustituido con 0 a 3 sustituyentes R^{12}, en que R^{16} y R^{17} tienen los mismos significados que antes se definen, y

- en que -

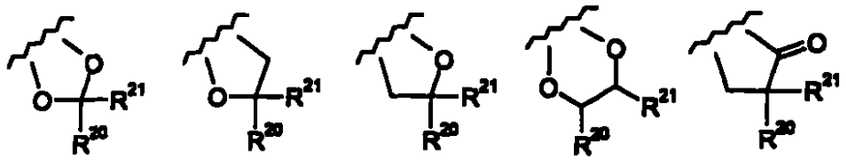
---R^{12} es un miembro seleccionado independientemente entre el grupo que consta de -F -Cl, -CO_2R^{16}, -OR^{16}, -CN -C(=O)$NR^{16}R^{18}$, -$NR^{16}R^{18}$, -NR^{16}C(=O)R^{18}, -NR^{16}C(=O)OR^{18} -NR^{16}S(=$O)_pR^{18}$, -S(=$O)_pNR^{16}R^{18}$, en que p es 1 ó 2, alquilo (C_1-C_4), y alcoxi (C_1-C_4) en el caso de que R^{12} tenga el significado de -OR^{16} anterior y R^{16} está definido como alquilo (C_1-C_4), en que dichos alquilo y alcoxi están sustituidos cada uno de ellos independientemente con 0 a 3 sustituyentes seleccionados independientemente entre -F, -Cl, alcoxi (C_1-C_2)-carbonilo, alquil (C_1-C_2)-carbonilo, y alquil (C_1-C_2)-carbonil-oxi, en que R^{16} tiene los mismos significados que antes se han definido, y

- en que -

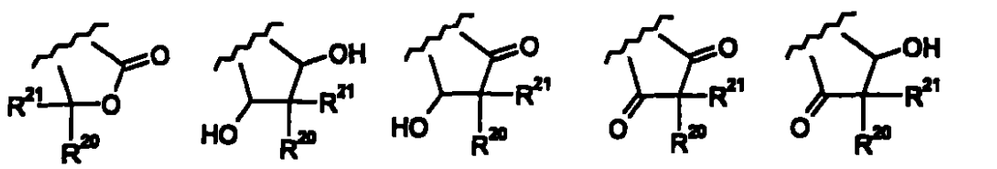
-----R^{18} y R^{19} se seleccionan independientemente entre el grupo que consta de -H, alquilo (C_1-C_4), y fenilo, en que dicho alquilo o fenilo está sustituido con 0-3 de -F, ó -Cl,

- o en el caso en el que J^1 es fenilo -

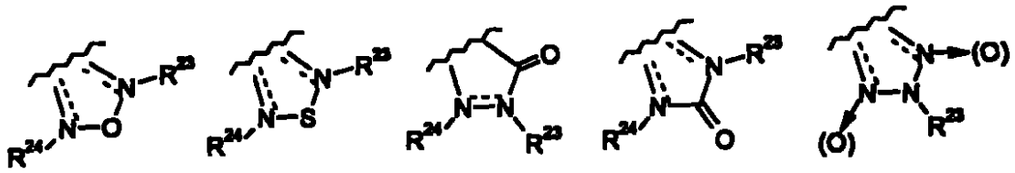
-(*d*) R^5 y R^6 se toman conjuntamente para formar un resto que es un miembro seleccionado entre el grupo que consta de las fórmulas parciales (1 3 1) hasta (1 3 15)



(1 3 1) (1 3 2) (1 3 3) (1.3.4) (1 3 5)



(1 3 6) (1 3 7) (1 3 8) (1 3 9) (1 3 10)



(1 3 11) (1 3 12) (1.3 13) (1 3 14) (1.3 15)

- en las que -

--R^{20} y R^{21} son cada uno de ellos un miembro seleccionado independientemente entre el grupo que consta de -H, -F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-OCH_3$, y $-OCF_3$,

--R^{23} y R^{24} son cada uno de ellos independientemente -H, $-CH_3$, $-OCH_3$, $-CH_2CH_3$ $-OCH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$ $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, o están ausentes, en cuyo caso la línea de trazos - - - - representa un doble enlace,

-J^1 es un resto que comprende un sistema anular de carbonos, saturado o insaturado, que es monocíclico de 3 a 7 miembros, o que es policíclico condensado de 7 a 12 miembros, con la condición de que J^1 no ha de ser un resto de bianlo discontinuo o restringido, y en el que opcionalmente un átomo de carbono de dicho sistema anular de carbonos puede estar reemplazado por un heteroátomo seleccionado entre N, O y S, en el que opcionalmente un segundo átomo de carbono del mismo y opcionalmente además un tercer átomo de carbono del mismo puede estar reemplazado por N,

- en el que -

dicho resto que define J^1 está sustituido en cualesquiera anillo o anillos del mismo con R^4 R^5 y R^6 que tienen los mismos significados que antes se definen,

-J^2 es un resto que comprende un sistema anular de carbonos, saturado o insaturado que es monocíclico de 3 a 7 miembros o que es policíclico condensado de 7 a 12 miembros con la condicion de que J^2 no ha de ser un resto de biarilo discontinuo o restringido, y en que opcionalmente un átomo de carbono de dicho sistema anular de carbonos puede estar reemplazado por un heteroátomo seleccionado entre N, O y S, en que opcionalmente un segundo átomo de carbono del mismo y además opcionalmente un tercer átomo de carbono del mismo puede estar reemplazado por N

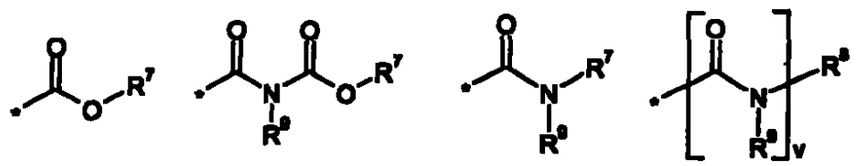
- en el que -

dicho resto que define J^2 está sustituido en cualesquiera anillo o anillos del mismo con R^1 y R^2, que tienen los mismos significados que antes se definen

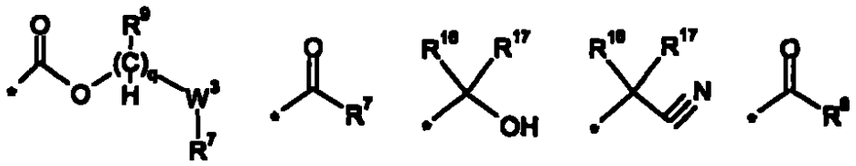
-D es un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

-(*a*) el grupo que consta de las Fórmulas parciales (1 1 1) hasta (1 1 9)



(1 1 1) (1 1 2) (1 1 3) (1 1.4)



(1 1 5) (1 1 6) (1 1 7) (1 1 8) (1 1 9)

- en las que -

--"a" indica el sitio de unión de cada Fórmula parcial (1 1 1) hasta (1 1 9) a la restante porción de la Fórmula (1 0 0),

--q es 1 2 ó 3, con la condición de que cuando q es 2 ó 3, R^9 ha de tener el significado de -H en por lo menos un caso, o en dos casos, respectivamente,

--v es 0 ó 1,

--W^3 es -O-, -N(R^9)-, en que R^9 tiene el mismo significado que se define

seguidamente o -OC(=O)-,

--R^7 es un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

--(*1*) -H,

--(*2*) alquilo (C_1-C_6), alquenilo (C_2-C_6), o alquinilo (C_2-C_6), en que dicho alquilo alquenilo o alquinilo está sustituido con 0 a 3 sustituyentes R^{10}, en que R^{10} tiene el mismo significado que se ha definido anteriormente,

--(*3*) -$(CH_2)_u$-cicloalquilo (C_3-C_7) en que u es 0, 1 ó 2, y además en que dicho cicloalquilo (C_3-C_7) está sustituido con 0 a 3 sustituyentes R^{10} en que R^{10} tiene los mismos significados que se han definido anteriormente,

- y -

--(*4*) fenilo o bencilo en que dicho fenilo o bencilo está sustituido independientemente con 0 a 3 sustituyentes R^{10} en que R^{10} tiene el mismo significado que se ha definido anteriormente,

--R^8 es un miembro seleccionado independientemente entre el grupo que consta de

- lo siguiente -

--(*1*) fenilo tetrazol-5-ilo 1,2 4-triazol-3-ilo, 1,2,4-triazol-3-on-5-ilo, 1 2 3-triazol-5-ilo imidazol-2-ilo, imidazol-4-ilo, imidazolidin-2-on-4-ilo 1,3 4-oxadiazolilo, 1,3 4-oxadiazol-2-on-5-ilo, 1,2,4-oxadiazol-3-ilo 1,2,4-oxadiazol-5-on-3-ilo, 1,2 4-oxadiazol-5-ilo 1 2 4-oxadiazol-3-on-5-ilo 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, morfolinilo, paratiazinilo oxazolilo isoxazolilo, tiazolilo, isotiazolilo, pirrolilo, pirazolilo, succinimidilo, glutarimidilo pirrolidinilo 2-piperidonilo, 2-piridonilo 4-piridonilo, piridazin-3-onilo, piridilo pirimidinilo, pirazinilo, piridazinilo,

- y -

--(*2*) indolilo, indolinilo, isoindolinilo, benzo[*b*]furanilo, 2,3-dihidrobenzofuranilo, 1,3-dihidroisobenzofuranilo, 2*H*-1-benzopiranilo 2-*H*-cromenilo, cromanilo, benzotienilo, *1H*-indazolilo, bencimidazolilo benzoxazolilo benzoisoxazolilo, benzotiazolilo, benzotriazolilo, benzotriazinilo, ftalazinilo, 1,8-naftiridinilo, quinolinilo, isoquinolinilo, quinazolinilo quinoxalinilo, pirazolo[3,4-*d*]pirimidinilo, pirimido[4,5-*d*]pirimidinilo, imidazo[1,2-*a*]piridinilo, piridopiridinilo, pteridinilo, y 1*H*-purinilo,

- en que -

cualquier resto citado en (*1*) o (*2*) anteriormente está sustituido opcionalmente con respecto a (*i*) uno cualquiera o más átomos de carbono del mismo, opcionalmente con un sustituyente R^{14} en que R^{14} tiene el mismo significado que antes se ha definido, con respecto a (*ii*) uno cualquiera o más átomos de nitrógeno del mismo que no sea un sitio de unión de dicho resto, opcionalmente con un sustituyente R^{15} en que R^{15} tiene el

mismo significado que antes se ha definido y todas las formas tautómeras del mismo, y con respecto a (iii) cualquier atomo de azufre del mismo que no sea un sitio de unión de dicho resto, con 0 1 ó 2 átomos de oxígeno,

–R^8 es un miembro seleccionado entre el grupo que consta de -H, alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, bencilo, pirídilo, -C(=O)OR^{16}, -C(=O)R^{16}, -OR^{16} alquil (C_1-C_2)-OR^{16} y alquil (C_1-C_2)-C(=O)OR^{16} en que R^{16} tiene los mismos significados que antes se han definido

- y D se selecciona adicionalmente entre -

-(*b*) un resto que comprende un miembro seleccionado entre el grupo que consta de -O-P(=O)$(OH)_2$ (fosfórico), -PH(=O)OH (fosfínico), -P(=O)$(OH)_2$ (fosfónico), -[P-(=O)(OH)-O-alquilo (C_1-C_4)] (alquil-fosfono), -P-(=O)(OH)-O-alquilo (C_1-C_4) (alquil-fosfinilo), -P-(=O)$(OH)NH_2$ (fosforamido), -P-(=O)(OH)NH-alquilo (C_1-C_4) y -P-(=O)(OH)NHR^{25} (fosforamido sustituido), -O-S(=O)$_2$OH (sulfurico), -S(=O)$_2$OH (sulfónico), -S(=O)$_2$$NHR^{26}$ ó -$NHS(=O)_2R^{26}$ (sulfonamido) en que R^{26} es -CH_3, -CF_3 ó o-toluilo y acil-sulfonamido seleccionado entre el grupo que consta de -C(=O)$NHS(=O)_2R^{25}$, -C(=O)$NHS(=O)_2NH_2$, -C(=O)NHS(=O)$_2$-alquilo (C_1-C_4), -C(=O)$NHS(=O)_2$NH-alquilo (C_1-C_4) -C(=O)$NHS(=O)_2$N[alquilo (C_1-C_4)]$_2$, -S(=O)$_2$NHC(=O)alquilo (C_1-C_4), -S(=O)$_2$$NHC(=O)NH_2$, -S(=O)$_2$NHC(=O)NH-alquilo ($C_1$-$C_4$), -S(=O)$_2$NHC(=O)N[alquilo ($C_1$-$C_4$)]$_2$, -S(=O)$_2$$NHC(=O)R^{25}$, -S(=O)$_2$NHCN, -S(=O)$_2$$NHC(=S)NH_2$ -S(=O)$_2$NHC(=S)NH-alquilo (C_1-C_4) -S(O)$_2$NHC(=S)N[alquilo (C_1-C_4)]$_2$, y -S(=O)$_2$$NHS(=O)_2R^{25}$

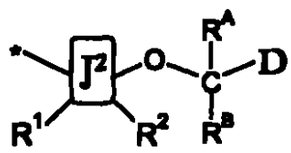
- en que -

–R^{25} es -H, alquilo (C_1-C_4), fenilo, ó -OR^{16}, en que R^{16} tiene los mismos significados que antes se han definido,

- o -

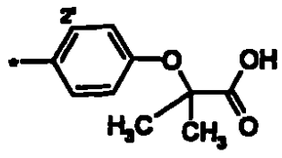
una sal farmacéuticamente aceptable del mismo

2 Un compuesto de acuerdo con la reivindicación 1 en el que el extremo derecho del mismo, en que m es 1 está representado por la Fórmula parcial (1 0 5)

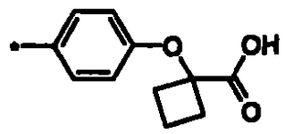


(1 0 5)

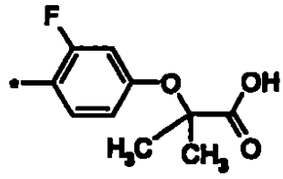
en la que "*" es un símbolo que representa el sitio de unión del grupo de Fórmula parcial (1 0 5) a la porción remanente de un compuesto de Fórmula (1 0 0), en que R^A y R^B son ambos -H o uno de ellos es -H y el otro es $-CH_3$ o ambos son $-CH_3$, o ambos se toman conjuntamente para formar espiro-ciclopropilo o espiro-ciclobutilo, R^1 es -H, $-OCH_3$, ó 2'–F, R^2 es -H, y los restos J^2 y D se seleccionan de manera tal que dicho grupo de Fórmula parcial (1 0 5) es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (1 5 1) hasta (1 5 54)



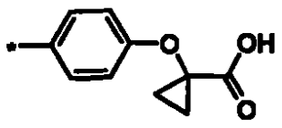
(1 5 1)



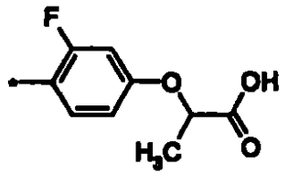
(1 5 2)



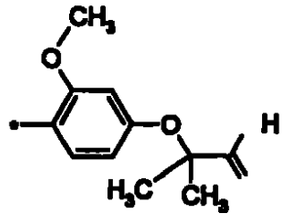
(1 5 3)



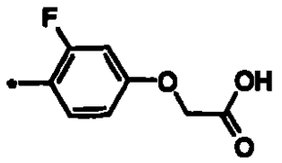
(1 5 4)



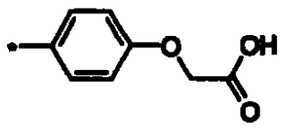
(1 5 5)



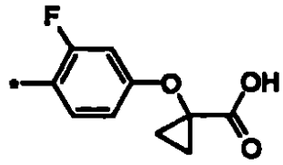
(1 5 6)



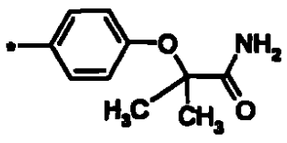
(1 5 7)



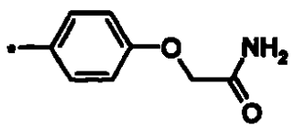
(1 5 8)



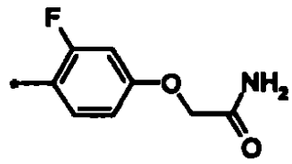
(1 5 9)



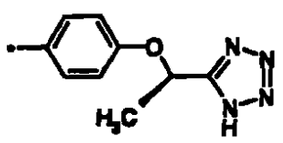
(1 5 10)



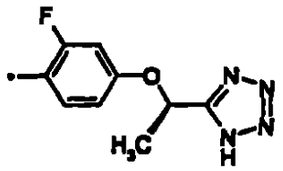
(1 5 11)



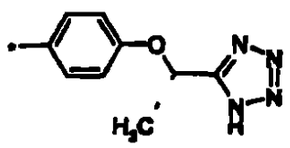
(1 5 12)



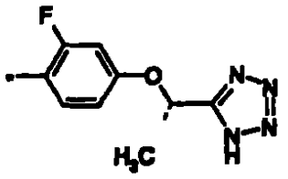
(1.5 13)



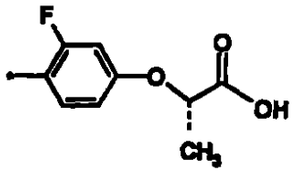
(1 5 14)



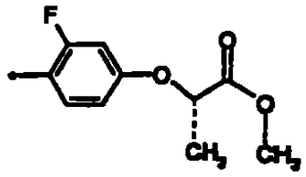
(1.5 15)



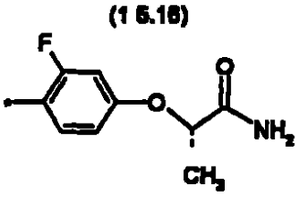
(1 5.16)



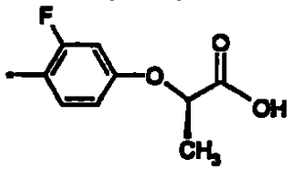
(1.5 17)



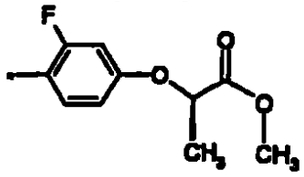
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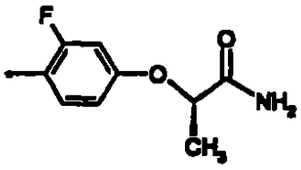
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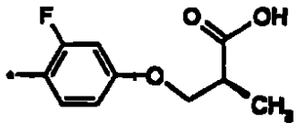
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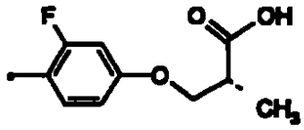
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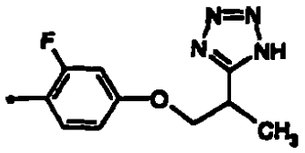
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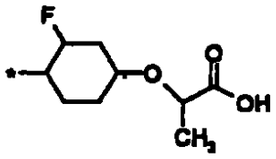
(1 5.23)



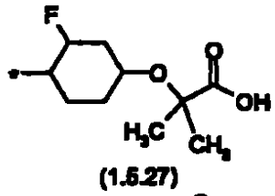
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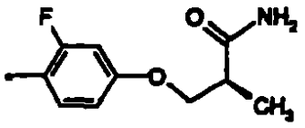
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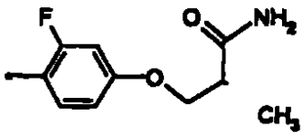
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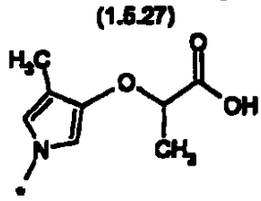
(1.5.27)



(1 5.28)

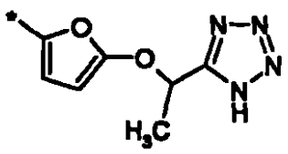


(1 5.29)

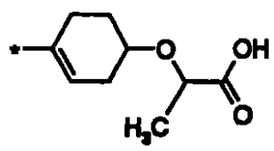


(1 5.30)

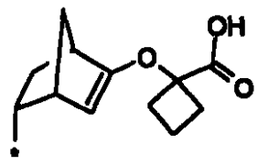
592



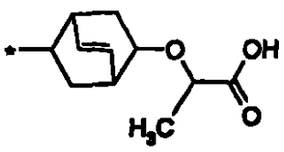
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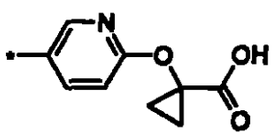
(1 5 32)



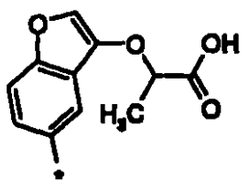
(1 5 33)



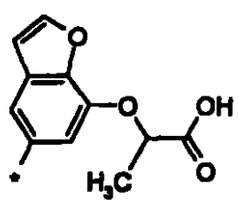
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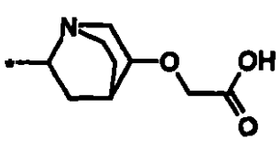
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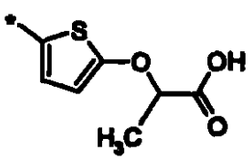
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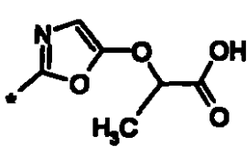
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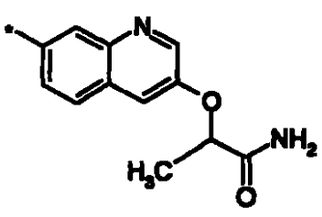
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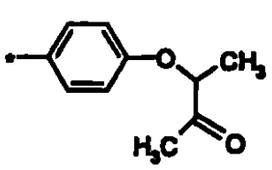
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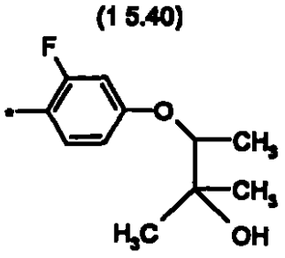
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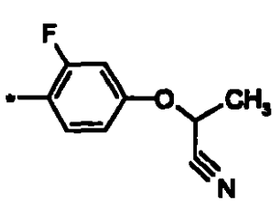
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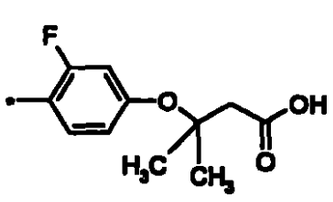
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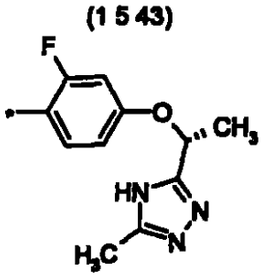
(1 5 43)



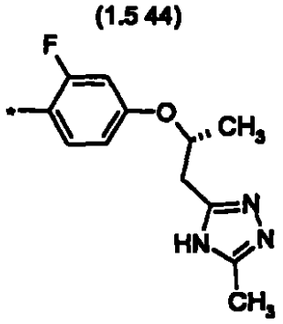
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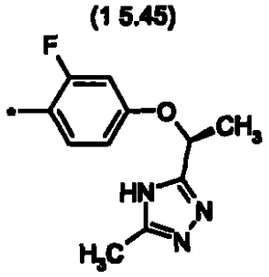
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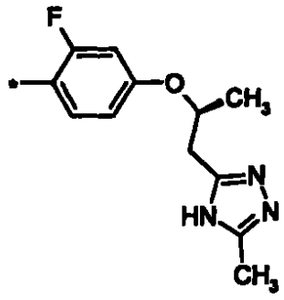
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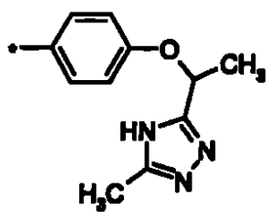
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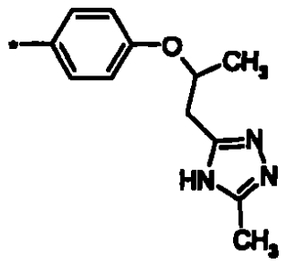
(1 5.48)



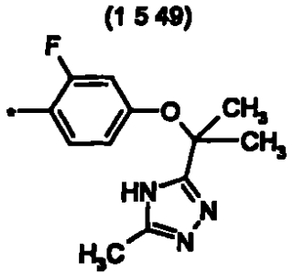
(1 5 49)



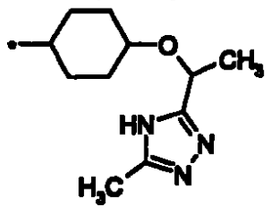
(1 5 50)



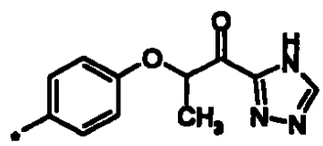
(1 5 51)



(1 5 52)



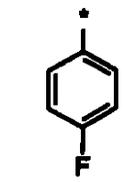
(1.5 53)

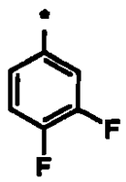


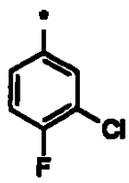
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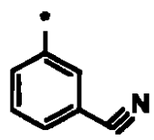
–"*" indica el sitio de unión de cada uno de dichos grupos de Fórmula parcial (1 0 5), representado por las Fórmulas parciales (1 5 1) hasta (1 5 54) con la porción remanente de la Fórmula (1 0 0)

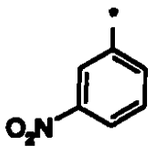
3 Un compuesto de acuerdo con la reivindicación 1 en el que J^1 y los sustituyentes R^4, R^5 y R^6 se seleccionan de una manera tal que una porción del extremo izquierdo de compuesto de la reivindicación 1 es un miembro seleccionado entre el grupo que consta de las siguientes Fórmulas parciales (2 0 1) hasta (2 0 72)

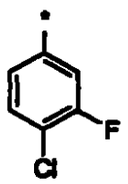

(2 0 1)

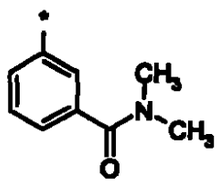

(2.0.2)

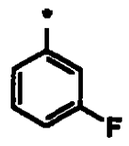

(2 0.3)

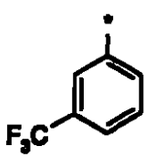

(2 0.4)

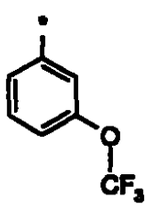

(2 0 5)

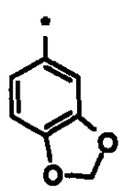

(2 0 6)

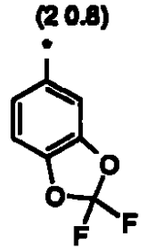

(2 0 7)

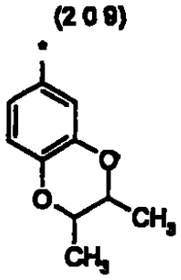

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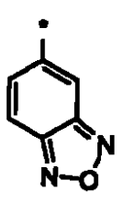

(2 0 9)

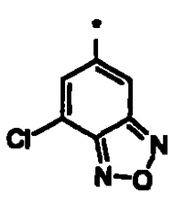

(2 0 10)

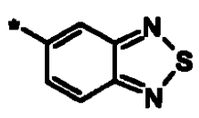

(2 0 11)

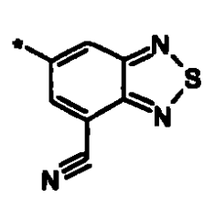

(2.0 12)


(2 0 13)

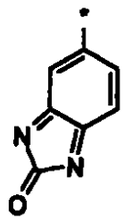

(2 0 14)


(2 0 15)

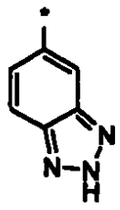

(2.0 16)



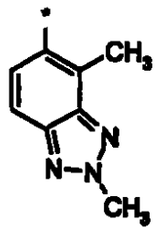
(2 0 17)



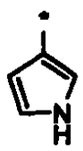
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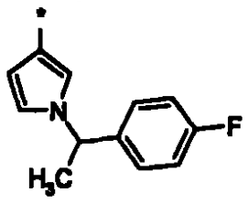
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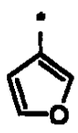
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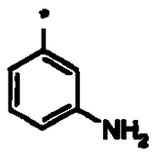
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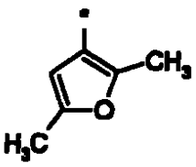
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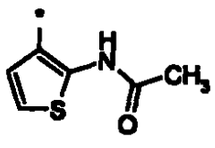
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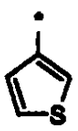
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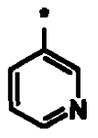
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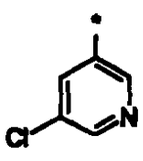
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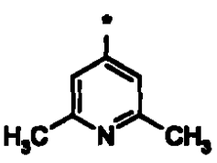
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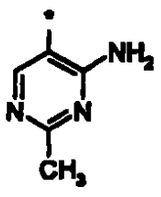
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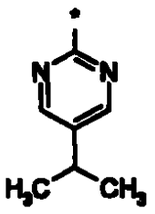
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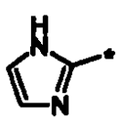
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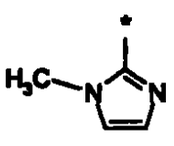
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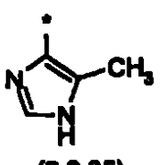
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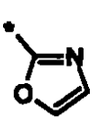
(2 0 33)



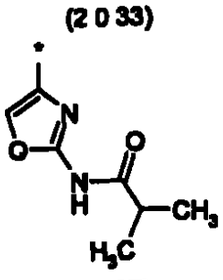
(2 0 34)



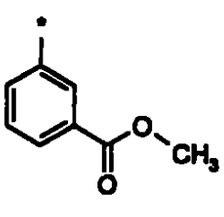
(2 0 35)



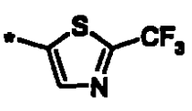
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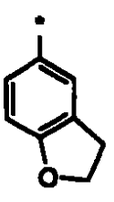
(2 0.37)



(2 0 38)



(2 0 39)



(2.0.40)

596
00800



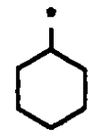
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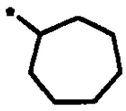
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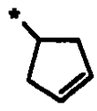
(2 0 43)



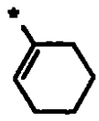
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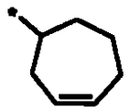
(2 0 45)



(2 0 46)



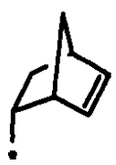
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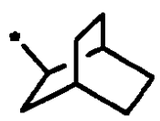
(2 0.48)



(2 0.49)



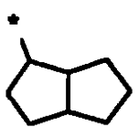
(2 0 50)



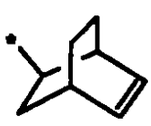
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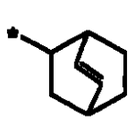
(2 0 52)



(2 0 53)



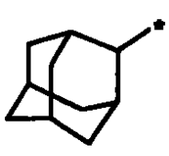
(2 0 54)



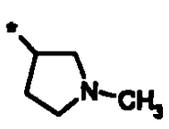
(2 0 55)



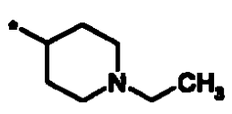
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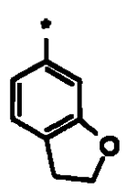
(2 0 57)



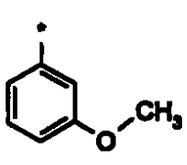
(2 0 58)



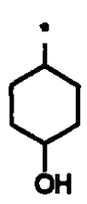
(2 0 59)



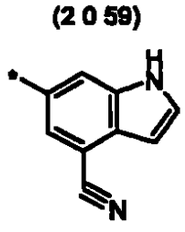
(2 0 60)



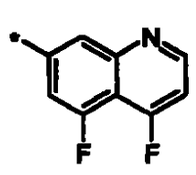
(2 0 61)



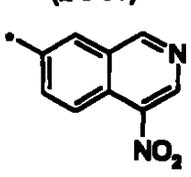
(2 0 62)



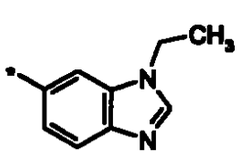
(2 0 63)



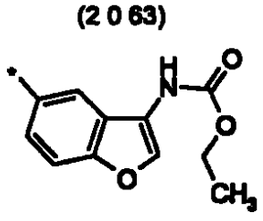
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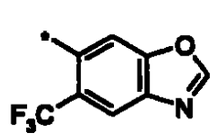
(2 0 65)



(2 0 66)



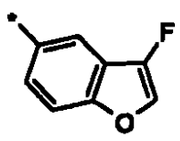
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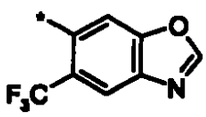
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597

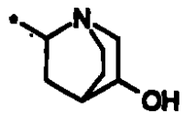
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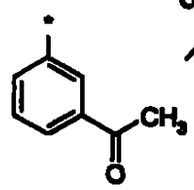
(2 0 69)



(2 0 70)

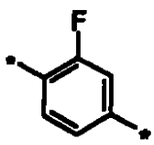


(2 0 71)

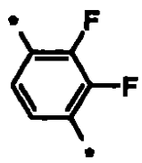


(2 0 72)

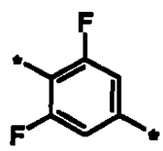
4 Un compuesto de acuerdo con la reivindicación 1 en el que J^2 y los sustituyentes R^1 y R^2 se seleccionan de una manera tal que una porción del extremo derecho de un compuesto de la reivindicación 1 es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (2 5 1) hasta (2 5 50)



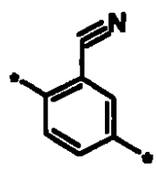
(2 5 1)



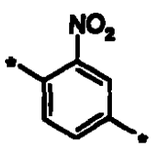
(2 5.2)



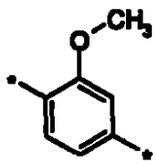
(2 5 3)



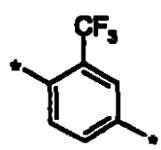
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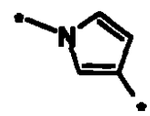
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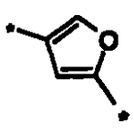
(2 5 6)



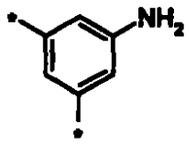
(2 5 7)



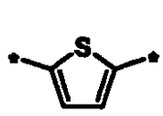
(2 5.8)



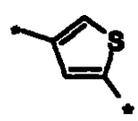
(2 5 9)



(2 5 10)



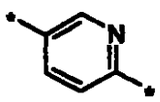
(2 5 11)



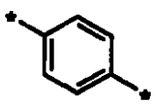
(2 5 12)

598

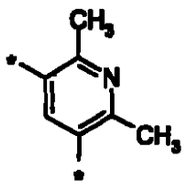
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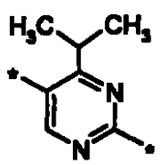
(2 5 13)



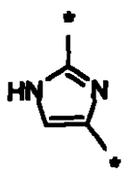
(2 5 14)



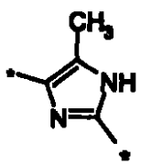
(2 5 15)



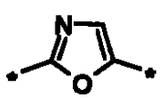
(2.5 16)



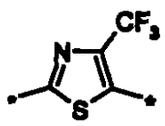
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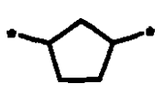
(2 5 18)



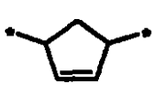
(2 5 19)



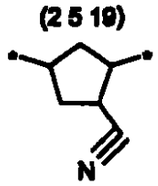
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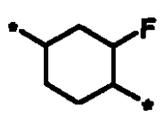
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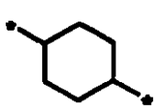
(2 5.22)



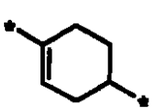
(2 5.23)



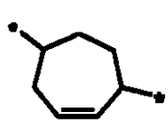
(2 5 24)



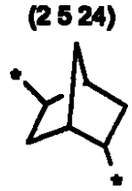
(2 5 25)



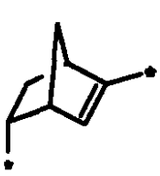
(2 5.26)



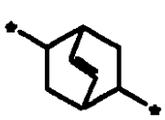
(2 5.27)



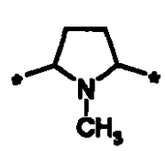
(2 5.28)



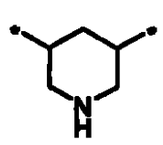
(2 5.29)



(2 5.30)



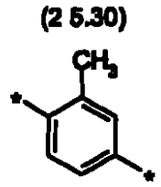
(2.5 31)



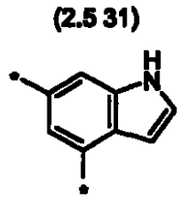
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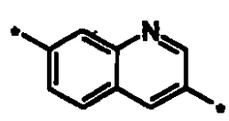
(2 5 33)



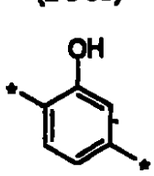
(2 5 34)



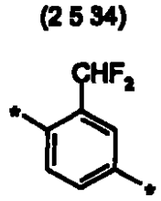
(2 5 35)



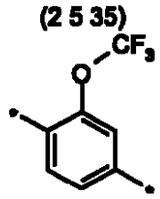
(2.5 36)



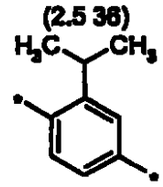
(2 5.37)



(2 5 38)



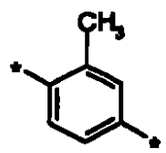
(2 5 39)



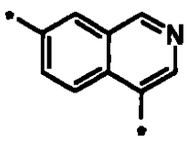
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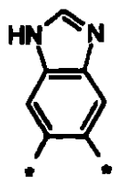
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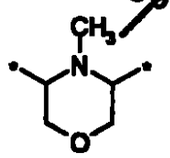
(2 5.41)



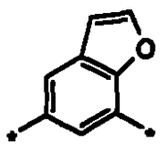
(2 5.42)



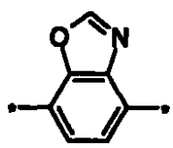
(2 5.43)



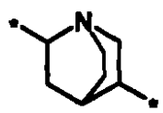
(2 5.44)



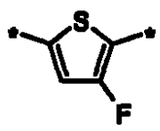
(2 5 45)



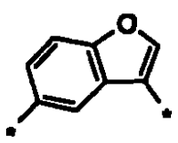
(2.5.46)



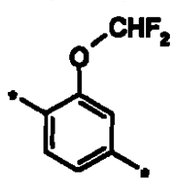
(2.5.47)



(2.5.48)

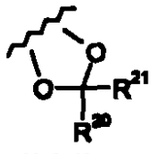


(2 5 49)

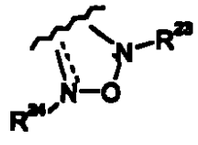


(2.5.50)

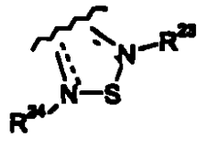
5 Un compuesto de acuerdo con la reivindicación 1, en el que R^5 y R^6 se toman conjuntamente para formar un resto que es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (1 3 1) (1 3 11), (1 3 12) y (1 3 15)



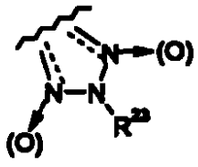
(1.3 1)



(1 3 11)



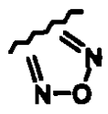
(1 3 12)



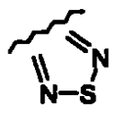
(1.3 15)

en las que R^{20}, R^{21}, R^{23} y R^{24} tienen los mismos significados que se definen en la reivindicacion 1

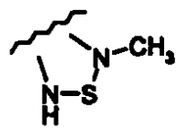
6 Un compuesto de acuerdo con la reivindicación 8 en que en que R^5 y R^6 se toman conjuntamente para formar un resto que es un miembro seleccionado entre el grupo que consta de las Fórmulas parciales (2 1 1), (2 1 4) hasta (2 1 6), (2 1 11) y (2 1 16) hasta (2 1 20)



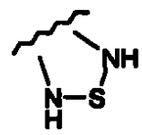
(2 1 1)



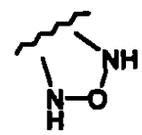
(2 1 4)



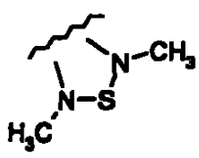
(2 1 5)



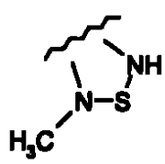
(2 1 6)



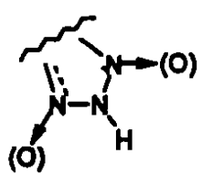
(2 1 11)



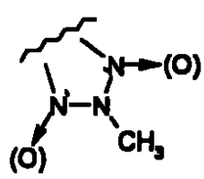
(2 1 16)



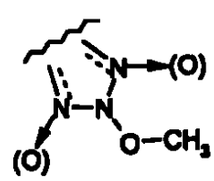
(2 1 17)



(2 1 18)



(2 1 19)



(2 1 20)

en que la linea de trazos - - - - en las Fórmulas parciales (2 1 18), (2 1 19) y (2 1 20) representa un doble enlace cuando ningun átomo de oxígeno está unido al correspondiente átomo de nitrogeno y representa un enlace simple cuando un átomo de oxígeno esta unido a dicho correspondiente átomo de nitrógeno

7 Un compuesto de acuerdo con la reivindicación 1 en el que dicho compuesto es un miembro seleccionado entre el grupo que consta de los siguientes

Ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-acético de Fórmula (5 5 1)

(±)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 2),

(±)-Ácido 2-[4-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 3),

(±)-Ácido 2-[3-fluoro-4-({[2-(4-fluoro-fenoxi)-pirıdina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Formula (5 5 4)

(±)-Ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 5),

(±)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 6),

(±)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 7),

(R)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 8),

(S)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-3-

fluoro-fenoxi]-propiónico de Fórmula (5 5 9),

(R)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 10),

(R)-Ácido 2-[3-fluoro-4-({[2-(3-ciano-fenoxi)-pirídina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 11),

(R)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 12),

(R)-Ácido 2-[4-({[2-(benzo[2 1,3]tiadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-propiónico de Fórmula (5 5 13),

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 14),

(R)-2-(Benzo[2,1,3]oxadiazol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 15),

(R)-2-(Benzo[2,1 3]tiadiazol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-nicotinamida de Fórmula (5 5 16),

(R)-N-[4-(1-Carbamoil-etoxi)-2-fluoro-bencil]-2-(3-ciano-fenoxi)-nicotinamida de Fórmula (5 5 17),

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(1-carbamoil-etoxi)-2-fluoro-bencil]-5-fluoro-nicotinamida de Fórmula (5 5 18),

(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(1*H*-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 19),

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(5-metil-4H-[1 2,4]triazol-3-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 20),

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-{2-fluoro-4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 21),

(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-{2-fluoro-4-[1-(1*H*-tetrazol-5-il)-etoxi]-bencil}-nicotinamida de Fórmula (5 5 22),

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-N-[2-fluoro-4-(2-hidroxi-1,2-dimetil-propoxi)-bencil]-nicotinamida de Fórmula (5 5 23),

(R)-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(2-hidroxi-1,2-dimetil-propoxi)-bencil]-nicotinamida de Fórmula (5 5 24)

(S)-Ácido 3-[4-({(2-(benzo[1,3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propionico de Fórmula (5 5 25),

2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-2-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 26),

2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-4-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 27),

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2-(Benzo[1 3]dioxol-5-iloxi)-5-fluoro-N-[2-fluoro-4-(piridin-3-ilmetoxi)-bencil]-nicotinamida de Fórmula (5 5 28),

Ácido [4-({[2-(3-ciano-fenoxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 29)

Ácido [4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 30)

(±)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 31),

(±)-Ácido 2-[4-({[2-(benzo[2,1 3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 32),

(±)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 33),

(±)-Ácido 2-[4-({[2-(4-fluoro-fenoxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 34),

(±)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 35),

(±)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 36),

(R)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohexil-3-eniloxi]-propiónico de Fórmula (5 5 37),

(R)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 38),

(R)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 39),

(R)-Ácido 2-[4-({[2-(4-fluoro-fenoxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 40)

(R)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 41),

(R)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-propiónico de Fórmula (5 5 42),

Ácido [4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohexiloxi]-acético de Fórmula (5 5 43),

Ácido [4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohexiloxi]-acético de Fórmula (5 5 44),

Ácido [4-({[2-(benzo[1 3]dioxol-5-iloxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohexil-oxi]-acético de Fórmula (5 5 45),

Ácido [4-({[2-(4-fluoro-fenoxi)-pirıdina-3-carbonil]-amino}-metil)-ciclohexiloxi]-

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acético de Fórmula (5 5 46),

Ácido [4-({[2-(3-ciano-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-acético de Formula (5 5 47)

Ácido [4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-acético de Fórmula (5 5 48),

(±)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 49),

(±)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Formula (5 5 50)

(±)-Ácido 2-[4-({[2-(4-fluoro-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 51),

(±)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 52)

(±)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 53)

(R)-Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 54)

(R)-Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 55),

(R)-Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 56)

(R)-Ácido 2-[4-({[2-(4-fluoro-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 57)

(R)-Ácido 2-[4-({[2-(3-ciano-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 58),

(R)-Ácido 2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-propiónico de Fórmula (5 5 59),

Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-2-metil-propiónico de Fórmula (5 5 60),

Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-2-metil-propiónico de Fórmula (5 5 61)

Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-2-metil-propiónico de Fórmula (5 5 62),

Ácido 2-[4-({[2-(4-fluoro-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-2-metil-propiónico de Fórmula (5 5 63)

Ácido 2-[4-({[2-(3-ciano-fenoxi)-pirıdına-3-carbonil]-amino}-metil)-cicloheхiloxi]-2-metil-propiónico de Fórmula (5 5 64),

Ácido 2-metil-2-[4-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-ciclohexiloxi]-propiónico de Fórmula (5 5 65)

Ácido [5-({[2-(benzo[2 1 3]tiadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-acetico de Fórmula (5 5 66)

(±)-Ácido 2-[5-({[2-(benzo[2 1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-propiónico de Fórmula (5 5 67)

(R)-Ácido 2-[5-({[2-(benzo[1 3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-propionico de Fórmula (5 5 68)

Ácido 2-[5-({[2-(4-fluoro-fenoxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-2-metil-propiónico de Fórmula (5 5 69),

Ácido 2-[5-({[2-(3-ciano-fenoxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-2-metil-propiónico de Fórmula (5 5 70)

(R)-Ácido 2-[5-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-propiónico de Fórmula (5 5 71),

Ácido [5-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-2-iloxi]-acético de Fórmula (5 5 72),

Ácido 2-[8-({[2-(benzo[2 1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[2 2 2]oct-5-en-2-iloxi]-2-metil-propiónico de Fórmula (5 5 73)

(R)-Ácido 2-[3-({[2-(benzo[2,1 3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[3 2 1]oct-8-iloxi]-propiónico de Fórmula (5 5 74),

Ácido 2-[3-({[2-(benzo[1,3]dioxol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclopent-3-eniloxi]-propionico de Fórmula (5 5 75),

Ácido [5-({[2-(2-metil-2H-benzotriazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-biciclo[2 2 1]hept-2-iloxi]-acético de Fórmula (5 5 76),

Ácido 2-[5-({[2-(benzo[2 1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-7-fluoro-biciclo[2 2 1]hept-5-en-2-iloxi]-2-metil-propiónico de Fórmula (5 5 77),

(R)-Ácido 2-[5-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-furan-2-iloxi]-propiónico de Fórmula (5 5 78),

(±)-Ácido 2-[6-({[2-(benzo[2,1 3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-pirídin-3-iloxi]-propiónico de Fórmula (5 5 79),

Ácido [2-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-oxazol-5-iloxi]-acético de Fórmula (5 5 80),

Ácido [2-({[2-(benzo[2 1 3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-tiazol-5-iloxi]-2-metil-propiónico de Fórmula (5 5 81)

(±)-Ácido 2-[5-(1-{[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-etil)-pirídin-2-iloxi]-propiónico de Fórmula (5 5 82),

Ácido 2-[4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-

fenoxi]-2-metil-propiónico de Fórmula (5 5 83)

Ácido 2-[4-({[2-(benzo[2,1 3]oxadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 84),

Ácido 2-[4-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 85),

Ácido 2-[4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 86),

Ácido 2-[3-fluoro-4-({[2-(4-fluoro-fenoxi)-piridina-3-carbonil]-amino}-metil)-fenoxi]-2-metil-propiónico de Fórmula (5 5 87),

Ácido 2-[4-({[3-ciano-fenoxi)-pirídina-3-carbonil]-amino}-metil)-3-fluoro-fenoxi]-2-metil-propiónico de Fórmula (5 5 88),

Ácido [4-({[2-benzo[2,1 3]tiadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 89)

(±)-2-(3-Ciano-fenoxi)-N-{4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-ciclohexilmetil}-nicotinamida de Fórmula (5 5 90),

(±)-2-(3-Ciano-fenoxi)-N-{4-[1-(1H-tetrazol-5-il)-etoxi]-ciclohexilmetil}-nicotinamida de Fórmula (5 5 91)

(±)-N-{2-Fluoro-4-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-bencil}-2-(3-metoxi-fenoxi)-nicotinamida de Fórmula (5 5 92),

N-[2-Fluoro-4-(piridin-2-ilmetoxi)-bencil]-2-(3-metoxi-fenoxi)-nicotinamida de Fórmula (5 5 93)

(±)-Ácido 2-[3-fluoro-4-({[2-(3-nitro-fenoxi)-pirídina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 94),

(±)-N-{2-Fluoro-4-[1-(1H-tetrazol-5-il)-etoxi]-bencil}-2-(3-nitro-fenoxi)-nicotinamida de Fórmula (5 5 95),

(±)-N-{2-Fluoro-4-[1-(5-metil-4H-[1 2,4]triazol-3-il)-etoxi]-bencil}-2-(3-nitro-fenoxi)-nicotinamida de Fórmula (5 5 96),

Ácido [4-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)-piridina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 97),

Ácido [4-({[2-(benzo[1,3]dioxol-5-iloxi)-pirídina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Fórmula (5 5 98),

Ácido [4-({[2-(4-fluoro-fenoxi)-pirídina-3-carbonil]-amino}-metil)-ciclohex-3-eniloxi]-acético de Formula (5 5 99),

(R)-Ácido 2-[4-({[2-(3-metoxi-fenoxi)-pirídina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 100),

(R)-Ácido 2-[3-fluoro-4-({[2-(3-metoxi-fenoxi)-pirídina-3-carbonil]-amino}-metil)-fenoxi]-propiónico de Fórmula (5 5 101),

(R)-Ácido 2-[3-fluoro-4-({[5-fluoro-2-(3-metoxi-fenoxi)-pirıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıonıco de Fórmula (5 5 102)

(R)-Ácido 2-[4-({[2-(3-nıtro-fenoxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıónico de Fórmula (5 5 103),

(R)-Ácido 2-[4-({[2-(3-cloro-4-fluoro-fenoxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıónico de Fórmula (5 5 104),

(R)-Ácido 2-[4-({[2-(3,4-difluoro-fenoxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıónico de Fórmula (5 5 105),

(R)-Ácido 2-[4-({[2-(2,3-dıhıdro-benzofuran-5-ıloxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıónico de Fórmula (5 5 106)

(R)-Ácido 2-[4-({[2-(2 3-dıhıdro-benzofuran-6-ıloxı)-pırıdına-3-carbonıl]-amıno}-metıl)-fenoxı]-propıonıco de Formula (5 5 107),

(S)-2-(Benzo[1,3]dıoxol-5-ıloxı)-N-{2-fluoro-4-[1-(1H-tetrazol-5-ıl)-etoxı]-bencıl}-nıcotınamıda de Fórmula (5 5 108),

(R)-2-(Benzo[1,3]dıoxol-5-ıloxı)-N-{2-fluoro-4-[1-(1H-tetrazol-5-ıl)-etoxı]-bencıl}-nıcotınamıda de Fórmula (5 5 109),

(R)-Ácido 3-[4-({[2-(benzo[1 3]dıoxol-5-ıloxı)-pırıdına-3-carbonıl]-amıno}-metıl)-3-fluoro-fenoxı]-2-metıl-propıónico de Fórmula (5 5 110),

(S)-2-(Benzo[1,3]dıoxol-5-ıloxı)-N-[4-(2-carbamoıl-propoxı)-2-fluoro-bencıl]-nıcotınamıda de Fórmula (5 5 111)

(R)-2-(Benzo[1,3]dıoxol-5-ıloxı)-5-fluoro-N-{2-fluoro-4-[1-(1H-tetrazol-5-ıl)-etoxı]-bencıl}-nıcotınamıda de Fórmula (5 5 112),

(±)-2-(3-Metoxı-fenoxı)-N-{4-[1-(1H-tetrazol-5-ıl)-etoxı]-bencıl}-nıcotınamıda de Fórmula (5 5 113),

Ácido 2-{5-({[2-(benzo[1,3]dıoxol-5-ıloxı)-pırıdına-3-carbonıl]-amıno}-metıl)-tıofen-2-ıloxı]-propıónico de Fórmula (5 5 114) y

(±)-2-(Benzo[1,3]dıoxol-5-ıloxı)-N-{2-fluoro-4-[1-metıl-2-oxo-2-(4H-[1,2,4]trıazol-3-ıl)-etoxı]-bencıl}-nıcotınamıda de Fórmula (5 5 115)

8 Un método para tratar a un ındıvıduo que padece de una enfermedad o condıcıón medıada por la ısozıma PDE4 en su cometıdo de regular la actıvacıón y desgranulacıón de eosınófılos humanos que comprende admınıstrar a dıcho ındıvıduo que necesıta de dıcho tratamıento una cantıdad terapéutıcamente eficaz de un compuesto de Fórmula (1 0 0) como se define en la reıvındıcacıón 1

9 Una composıcıón farmacéutıca destınada a su uso en el tratamıento de un ındıvıduo que padece de una enfermedad, un trastorno o una condıcıón medıada/o por la ısozıma PDE4, con lo que éste regula la actıvacıón y la desgranulacıón de eosınófılos, que comprende una cantıdad terapéutıcamente eficaz de un compuesto de Fórmula

(1 0 0) como se define en la reivindicación 1, conjuntamente con un vehículo farmacéuticamente aceptable para éste

10 Un método de tratamiento de acuerdo con la reivindicación 28 en el que dicha enfermedad trastorno o condición es un miembro seleccionado entre el grupo que consta de (1) enfermedades y condiciones inflamatorias que comprenden una inflamación de las articulaciones, artritis reumatoide espondilitis reumatoide, osteoartritis, enfermedad inflamatoria de los intestinos, colitis ulcerativa, glomerulonefritis crónica, dermatitis y enfermedad de Crohn, (2) enfermedades y condiciones respiratorias que comprenden asma, síndrome de ahogo respiratorio agudo enfermedad inflamatoria pulmonar crónica bronquitis enfermedad obstructiva crónica de las vías respiratorias, y silicosis, (3) enfermedades y condiciones infecciosas que comprenden septicemia, choque séptico choque endotóxico, septicemia gram negativa, síndrome del choque tóxico, fiebre y mialgias debidas a infecciones causadas por bacterias, virus u hongos, e influenza (4) enfermedades y condiciones inmunitarias que comprenden diabetes autoinmunitaria, lupus sistémico eritematoso, reacción de injerto frente a hospedante, rechazos de aloinjertos, esclerosis multiple psoriasis y rinitis alérgica, y (5) otras enfermedades y condiciones que comprenden enfermedades de resorción ósea, lesión por reperfusión, caquexia secundaria a una infección o malignidad, caquexia secundaria al síndrome de inmunodeficiencia adquirida humana (SIDA), infección causada por un virus de inmunodeficiencia humana (HIV) o un complejo relacionado con el SIDA (ARC), formación de queloides, formación de tejido cicatricial diabetes mellitus del tipo 1, y leucemia

11 La combinación de un compuesto de Fórmula (1 0 0) como se ha definido en la reivindicación 1 conjuntamente con uno o más miembros seleccionados entre el grupo que consta de los siguientes

(a) Agentes inhibidores de la biosíntesis de leucotrienos, inhibidores de 5-lipoxigenasa (5-LO) y agentes antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP) seleccionados entre el grupo que consta de zileuton, ABT-761, fenleuton tepoxalin, Abbott-79175, Abbott-85761, N-tiofeno (sustituido en 5)-2-alquil-sulfonamidas de Fórmula (5 2 8) 2,6-di-*terc* -butil-fenol-hidrazonas de Fórmula (5 2 10), Zeneca ZD-2138 de Formula (5 2 11), SB-210661 de Fórmula (5 2 12), un compuesto de 2-ciano-naftaleno sustituido con pindinilo L-739,010, el compuesto de 2-ciano-quinolina L-746,532, compuestos de indol y quinolina MK-591, MK-886 y BAY x 1005,

(b) Agentes antagonistas de receptores para los leucotrienos LTB_4, LTC_4, LTD_4 y LTE_4 seleccionados entre el grupo que consta del compuesto de fenotiazin-3-ona L-651 392, el compuesto de amidino CGS-25019c, el compuesto de benzoxazol-

amina ontazolast el compuesto de benceno-carboximido-amida BIIL 284/260, los compuestos zafirlukast ablukast, pranlukast, montelukast, verlukast (MK-679), RG-12525 Ro-245913 iralukast (CGP 45715A) y BAY x 7195,

(c) Agentes inhibidores de las PDE4 e inhibidores de la isoforma PDE4D de las PDE4,

(d) Agentes inhibidores de 5-lipoxigenasa (5-LO) y agentes antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP),

(e) Dobles agentes inhibidores de 5-lipoxigenasa (5-LO) y agentes antagonistas del factor de activacion de plaquetas (PAF)

(f) Agentes antagonistas de leucotrienos (LTRA's) de LTB_4, LTC_4, LTD_4 y LTE_4,

(g) Agentes antagonistas del receptor H_1 antihistaminico cetirizina, loratadina, desloratadina, fexofenadina, astemizol, azelastina y clorofeniramina,

(h) Agentes antagonistas de receptores H_2 protectores del estómago,

(i) Agentes simpatomimeticos vasoconstrictores agonistas de adrenoceptores α_1 y α_2 administrados por vía oral o tópica para uso descongestionante, seleccionados entre el grupo que consta de propilhexedrina, fenilefrina, fenilpropanolamina pseudoefredina hidrocloruro de nafazolina, hidrocloruro de oximetazolina, hidrocloruro de tetrahidrozolina, hidrocloruro de xilometazolina e hidrocloruro de etilnorepinefrina

(j) Uno o más agentes agonistas de adrenoceptores α_1 y α_2 como se han citado en (i) antes en combinación con uno o más inhibidores de 5-lipoxigenasa (5-LO) como se citan en (a) antes,

(k) Agentes anticolinérgicos bromuro de ipratropio, bromuro de tiotropio, bromuro de oxitropio pirenzepina y telenzepina

(l) Agentes agonistas de adrenoceptores desde β_1 hasta β_4 seleccionados entre el grupo que consta de metaproterenol, isoproterenol, isoprenalina, albuterol, salbutamol, formoterol salmeterol, terbutalina, orciprenalina, bitolterol y pirbuterol,

(m) Teofilina y aminofilina,

(n) Cromoglicato de sodio,

(o) Agentes antagonistas de receptores muscarinicos (M1, M2 y M3)

(p) Agentes inhibidores de COX-1 (NSAIDs), y NSAIDs con óxido nítrico,

(q) El agente inhibidor selectivo para COX-2 rofecoxib,

(r) Compuestos miméticos del factor de crecimiento similar a insulina del tipo I (IGF–1),

(s) Ciclesonida,

(t) Glucocorticoides inhalados con efectos colaterales sistémicos reducidos, seleccionados entre el grupo que consta de prednisona, prednisolona, flunisolida,

acetonuro de triamcinolona, dipropionato de beclometasona, budesonida, propionato de fluticasona y furoato de mometasona

(u) Inhibidores de triptasa,

(v) Agentes antagonistas del factor activador de plaquetas (PAF),

(w) Anticuerpos monoclonales activos contra entidades inflamatorias endógenas,

(x) IPL 576,

(y) Agentes contra el factor de necrosis de tumores (TNFα) seleccionados entre el grupo que consta de etanercept, infliximab y D2E7

(z) DMARS's seleccionados entre el grupo que consta de leflunomida,

(aa) Péptidos de TCR,

(bb) Agentes inhibidores de la enzima convertidora de interleucina (ICE),

(cc) Agentes inhibidores de IMPDH,

(dd) Agentes inhibidores de moléculas de adhesion que incluyen agentes antagonistas de VLA-4

(ee) Catepsinas,

(ff) Agentes inhibidores de cinasas de MAP,

(gg) Agentes inhibidores de deshidrogenasas de glucosa-6 fosfato,

(hh) Agentes antagonistas de receptores B_1 y B_2 de cinina

(ii) Oro en la forma de un grupo aurotio en combinación con grupos hidrófilos,

(jj) Agentes supresores de inmunidad seleccionados entre el grupo que consta de ciclosporina, azatioprina y metotrexato,

(kk) Agentes contra la gota seleccionados entre el grupo que consta de colquicina,

(ll) Agentes inhibidores de oxidasa de xantina seleccionados entre el grupo que consta de alopurinol,

(mm) Agentes uricosuncos, seleccionados entre el grupo que consta de probenecida, sulfinpirazona y benzobromarona,

(nn) Agentes antineoplásticos que son fármacos antimitóticos seleccionados entre el grupo que consta de vinblastina y vincristina,

(oo) Secretagogos de hormonas de crecimiento,

(pp) Inhibidores de metaloproteasas de matriz (MMP's) que se seleccionan entre el grupo que consta de las estromelisinas, las colagenasas, las gelatinasas, agrecanasa, colagenasa-1 (MMP-1), colagenasa-2 (MMP-8), colagenasa-3 (MMP-13), estromelisina-1 (MMP-3) estromelisina-2 (MMP-10) y estromelisina-3 (MMP-11),

(qq) Factor de crecimiento en transformación (TGFβ),

(rr) Factor de crecimiento derivado de plaquetas (PDGF),

(ss) Factor de crecimiento de fibroblastos, seleccionado entre el grupo que consta del

factor de crecimiento de fibroblastos de carácter básico (bFGF),

(tt) Factor estimulador de colonias de granulocitos-macrófagos (GM-CSF),

(uu) Capsaicina,

(vv) Agentes antagonistas de receptores NK_1 y NK_3 de taquicininas seleccionados entre el grupo que consta de NKP-608C SB-233412 (talnetant) y D-4418,

(ww) Agentes inhibidores de elastasas seleccionados entre el grupo que consta de UT-77 y ZD-0892, y

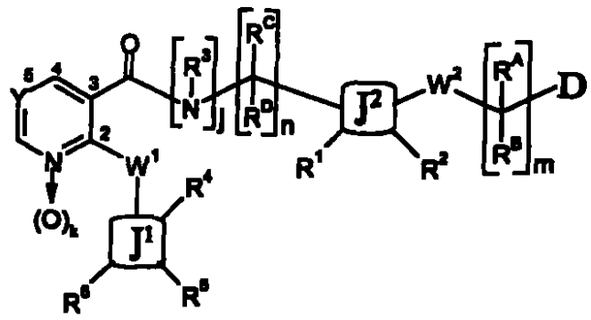
(xx) Agentes agonistas de receptores A2a de adenosina

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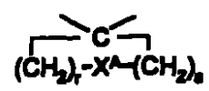
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RESUMEN

Compuestos utiles como inhibidores de las PDE4 en el tratamiento de enfermedades reguladas por la activación y desgranulacion de eosinófilos, especialmente asma, bronquitis crónica y enfermedad pulmonar obstructiva crónica, de la fórmula

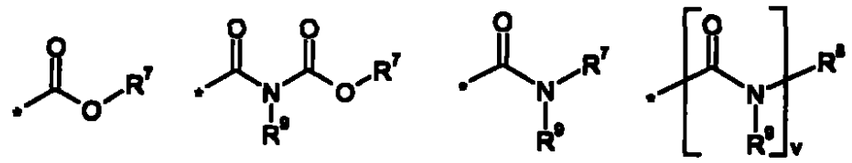


en la que j es 0 ó 1, con la condición de que cuando j es 0, n debe ser 2, k es 0 ó 1, m es 1, 2 ó 3 n es 1 ó 2 W^1 y W^2 son -O- $-S(=O)_t-$ en que t es 0, 1 ó 2 ó $-N(R^3)-$, Y es $=C(R^1{}_a)-$ ó $-[N\rightarrow O)_k-$ en que k es 0 ó 1, $R^1{}_a$ es -H -F, -Cl, -CN, $-NO_2$, alquilo (C_1-C_4), alquinilo (C_2-C_4), alquilo (C_1-C_3) fluorado, alcoxi (C_1-C_3) fluorado, $-OR^{16}$, ó $-C(=O)NR^{22}{}_aR^{22}{}_b$, R^A y R^B son -H, -F $-CF_3$ alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo o bencilo sustituido con 0-3 R^{10} o R^A y R^B se toman juntos para formar un resto espiro

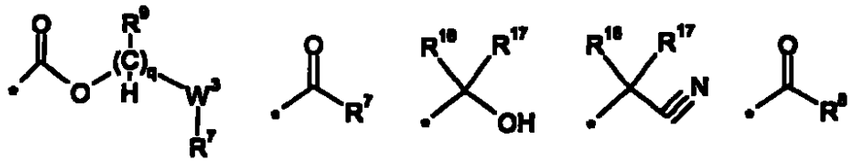


en que r y s son 0-4 con la condición de que r + s ha de ser ≥ 1 pero no > 5, y X^A es $-CH_2-$ -CHF, $-CF_2$, $-NR^{15}-$, -O-, ó $-S(=O)_t-$ en que t es 0, 1, R^C y R^D son los mismos que R^A y R^B excepto que uno de ellos debe ser -H, R^1 y R^2 son -H, -F, -Cl, -CN $-NO_2$, alquilo (C_1-C_4), alquinilo (C_2-C_4), alquilo (C_1-C_3) fluorado, $-OR^{16}$ ó $-C(=O)NR^{22}{}_aR^{22}{}_b$, R^3 es -H, alquilo (C_1-C_4), fenilo bencilo ó $-OR^{16}$, R^4, R^5 y R^6 son (a) -H, -F, -Cl, alquinilo (C_2-C_4), $-R^{16}$, $-OR^{16}$, $-S(=O)_pR^{16}$, $-S(=O)R^{16}$, $-C(=O)OR^{16}$, $-OC(=O)R^{16}$, -CN, $-NO_2$ $-C(=O)NR^{16}R^{17}$, $-OC(=O)NR^{16}R^{17}$, $-NR^{22}{}_aC(=O)NR^{16}R^{17}$, $-NR^{22}{}_aC(=NR^{12})NR^{16}R^{17}$, $-NR^{22}{}_aC(=NCN)NR^{16}R^{17}$ $-NR^{22}{}_aC(=N\text{-}NO_2)NR^{16}R^{17}$ $-C(=NR^{22}{}_a)NR^{16}R^{17}$, $-CH_2C(=NR^{22}{}_a)NR^{16}R^{17}$, $-OC(=NR^{22}{}_a)NR^{16}R^{17}$, $-OC(=N\text{-}NO_2)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-CH_2NR^{16}R^{17}$, $-NR^{22}{}_aC(=O)R^{16}$, $-NR^{22}{}_aC(=O)OR^{16}$, $=NOR^{16}$, $-NR^{22}{}_aS(=O)R^{17}$, $-S(=O)_pNR^{16}R^{17}$, ó $-CH_2C(=NR^{22}{}_a)NR^{16}R^{17}$, en que p es 0, 1 ó 2, (b) alquilo (C_1-C_4) o alcoxi (C_1-C_4) sustituido con 0-3 de -F ó -Cl, o 0 ó 1 de alcoxi (C_1-C_2)-carbonilo, alquil (C_1-C_2)-carbonilo o alquil (C_1-C_2)-carboniloxi, o (c) fenilo bencilo, furanilo, tetrahidrofuranilo,

oxetanilo tienilo tetrahidrotienilo pirrolilo pirrolidinilo oxazolilo oxazolidinilo, isoxazolilo, isoxazolidinilo, tiazolilo, tiazolidinilo isotiazolilo, isotiazolidinilo, pirazolilo, pirazolidinilo, oxadiazolilo, tiadiazolilo imidazolilo imidazolidinilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, piperidinilo piperazinilo, triazolilo, triazinilo, tetrazolilo, piranilo, azetidinilo, morfolinilo paratiazinilo indolilo indolinilo, benzo[*b*]furanilo, 2 3-dihidro-benzofuranilo, 2-*H*-cromenilo cromanilo benzotienilo, 1-*H*-indazolilo bencimidazolilo benzoxazolilo benzoisoxazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, ftalazinilo, quinazolinilo, quinoxalinilo o purinilo, todos ellos sustituidos con 0-2 de R^{14} o (d) R^8 y R^9 se toman conjuntamente para formar un resto de Fórmulas parciales (1 3 1) hasta (1 3 15), D es un grupo de Formulas parciales (1 1 1) hasta (1 1 9)



(1 1 1) (1 1.2) (1 1 3) (1 1.4)



(1 1.5) (1 1 6) (1 1 7) (1 1 8) (1 1 9)

en que q es 1-3, con la condición de que cuando q es 2 ó 3, R^9 ha de ser -H, v es 0-1, W^3 es -O-, -N(R^9)- ó -OC(=O)-, R^7 es (a) -H, (b) alquilo (C_1-C_6), alquenilo (C_2-C_6) o alquinilo (C_2-C_6), todos ellos sustituidos con 0-3 de R^{10} (c) -$(CH_2)_u$-cicloalquilo (C_3-C_7) en que u es 0-2, sustituido con 0-3 de R^{10}, o (d) fenilo o bencilo sustituido con 0-3 de R^{10} R^8 es (a) tetrazol-5-ilo, 1,2,4-triazol-3-ilo, 1,2,4-triazol-3-on-5-ilo, 1,2,3-triazol-5-ilo, imidazol-2-ilo, imidazol-4-ilo, imidazolidin-2-on-4-ilo, 1,2,4-oxadiazol-3-ilo, 1,2,4-oxadiazol-5-on-3-ilo, 1,2,4-oxadiazol-5-ilo, 1,2,4-oxadiazol-3-on-5-ilo, 1,3,4-oxadiazolilo, 1,3,4-oxadiazol-2-on-5-ilo, oxazolilo, isoxazolilo, pirrolilo, pirazolilo, succinimidilo, glutarimidilo, pirrolidonilo, 2-piperidonilo, 2-piridonilo, 4-piridonilo, piridazin-3-onilo, tiadiazolilo, paratiazinilo, (b) indolilo indolinilo, isoindolinilo benzo[*b*]furanilo, 2 3-dihidro-benzofuranilo, 2-*H*-cromenilo, cromanilo benzotienilo *1H*-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo benzotiazolilo, benzotriazolilo, benzotriazinilo, quinazolinilo quinoxalinilo, pirazolo[3,4-*d*]pirimidinilo, pirimido[4,5-*d*]pirimidinilo, imidazo[1 2-*a*]piridinilo pirido-piridinilo, pteridinilo o purinilo, todos ellos opcionalmente sustituidos en un átomo de carbono con R^{14}, en un átomo de nitrógeno con R^{15} y todas

sus formas tautómeras, o en un átomo de azufre con 0-2 átomos de oxígeno, R^9 es -H, alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo, bencilo, -(C=O)OR^{16}, -C(=O)R^{16}, -OR^{16}, alquil (C_1-C_2)-OR^{16} o alquil (C_1-C_2)-C(=O)OR^{16}, o (c) -O-P(=O)$(OH)_2$ (fosfónco), -PH(=O)OH (fosfínico), -P(=O)$(OH)_2$ (fosfónico), [P(=O)(OH)-O-alquilo (C_1-C_4)] (alquil-fosfono), -P(=O)(OH)-O-alquilo (C_1-C_4) (alquil-fosfinilo) -P(=O(OH)NH_2 (fosforamido), -P(=O)(OH)NH-alquilo (C_1-C_4) y -P(=O)(OH)NHR^{25} (fosforamido sustituido), -O-S(=O)$_2$OH (sulfurico) -S(=O)$_2$OH (sulfónico) -S(=O)$_2$$NHR^{26}$ ó -NHS(=O)$_2$$R^{26}$ (sulfonamido) en que R^{26} es -CH_3, -CF_3, u o-toluilo, y acil-sulfonamido seleccionado entre el grupo que consta de -C(=O)NHS(=O)$_2$$R^{25}$, -C(=O)NHS(=O)$_2$$NH_2$, -C(=O)NHS(=O)$_2$-alquilo ($C_1$-$C_4$), -C(=O)NHS(=O)$_2$NH-alquilo ($C_1$-$C_4$), -C(=O)NHS(=O)$_2$N[alquilo ($C_1$-$C_4$)]$_2$, -S(=O)$_2$NHC(=O)alquilo ($C_1$-$C_4$), -S(=O)$_2$NHC(=O)$NH_2$, -S(=O)$_2$NHC(=O)NH-alquilo ($C_1$-$C_4$), -S(O)$_2$NHC(=O)N[alquilo ($C_1$-$C_4$)]$_2$, -S(=O)$_2$NHC(=O)$R^{25}$, -S(=O)$_2$NHCN -S(=$O_2$)NHC(=S)$NH_2$, -S(=O)$_2$NHC(=S)NH-alquilo ($C_1$-$C_4$), -S(=O)$_2$NHC(=S)N[alquilo ($C_1$-$C_4$)]$_2$, ó -S(=O)$_2$NHS(=O)$_2$$R^{25}$ en que R^{25} es -H -alquilo (C_1-C_4), fenilo o -OR^{16}, J^1 y J^2 son un resto que comprende un sistema anular de carbonos saturado o insaturado que es monocíclico de 3 a 7 miembros, o que es policíclico condensado o discontinuo de 7 a 12 miembros, en que opcionalmente un átomo de carbono de dicho sistema anular de carbonos puede ser reemplazado por un heteroatomo seleccionado entre N, O y S, y cuando se selecciona N, opcionalmente un segundo átomo de carbono de éste puede ser reemplazado por un heteroátomo seleccionado entre N, O y S, o una sal farmacéuticamente aceptable de éste

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
LUMB, J Trevor
Pfizer Inc
201 Tabor Road
Morris Plains, New Jersey 07950
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71 1)

Date of mailing *(day/month/year)*	05/11/2002
Applicant s or agent s file reference: PC11896ARMS	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ IB 01/ 02726	24/12/2001	31/01/2001

Applicant

PFIZER PRODUCTS INC et al

1 The applicant is hereby notified that the International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any established on the international application

2 A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices

4 REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant s Guide

The applicant's attention is drawn to Article 33(5) which provides that the criteria of novelty inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State the claimed inventions is patentable or not (see also Article 27(5)) Such additional criteria may relate, for example, to exemptions from patentability requirements for enabling disclosure clarity and support for the claims.

Name and mailing address of the IPEA/	Authorized officer
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Form PCT/IPEA/416 (August 2002) P20473

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant s or agent s file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PC11896ARMS		
International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 01/ 02726	24/12/2001	31/01/2001
International Patent Classification (IPC) or national classification and IPC		
C07D405/12		
Applicant		
PFIZER PRODUCTS INC et al		

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 2 sheets, including this cover sheet.

☐ 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 consists of a total of _____ sheets.

3 This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty inventive step and 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
18/02/2002	30/10/2002
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel (+49-89) 2399-0, Tx. 523656 epmu d Fax. (+49-89) 2399-4465	BARTHL-WAGNER J C R Tel (+49-89) 2399 2828

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

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No PCT/ IB 01/ 02726

I Basis of the report

The basis of this international preliminary examination is the application as originally filed

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT), see also international search report)

V Reasoned statement under Rule 66 2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i e does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references)

INTERNATI NAL SEARCH REPORT

Inte al Application No
PCT/IB 01/02726

621
617
00823

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 A61K31/44 A61P11/06 A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 01 57036 A (MARFAT ANTHONY ,PFIZER PROD INC (US), CHAMBER ROBERT JAMES (US)) 9 August 2001 (2001-08-09) claim 1	1-10
P,Y	WO 01 57025 A (CHAMBERS ROBERT JAMES ,MAGEE THOMAS VICTOR (US), MARFAT ANTHONY (U) 9 August 2001 (2001-08-09) claim 1	1-10
Y	GB 2 327 675 A (EISAI CO LTD) 3 February 1999 (1999-02-03) claims 1,5	1-10
Y	WO 98 45628 A (NEVREKAR VENKATESH R) 15 October 1998 (1998-10-15) cited in the application claim 2	1-10

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2002	07/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATI NAL SEARCH REPORT

Int ni Application No
PCT/18 01/02726 618

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VINICK F J ET AL "NICOTINAMIDE ETHERS NOVEL INHIBITORS OF CALCIUM-INDEPENDENT PHOSPHODISTERASE AND U3HROLIPRAM BINDING" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY WASHINGTON, US, vol 34, no 1, 1991, pages 86-89, XP002066969 ISSN 0022-2623 table I	1-10
Y	EP 0 773 024 A (PFIZER) 14 May 1997 (1997-05-14) claim 1	1-10
A	US 4 270 946 A (GUTMAN ARNOLD D) 2 June 1981 (1981-06-02) claim 1	1
A	US 4 692 185 A (MICHAELY WILLIAM J) 8 September 1987 (1987-09-08) claim 1	1

International Application No. PCT/IB 01 /02726

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I 2

Present claims 1-6 relate to an extremely large number of possible compounds Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds where Y is C(R1) (i e pyridines), j is 1, n is 1, W1 is -O-, J1 is an optionally substituted phenyl or benzofused ring, J2 is an optionally substituted phenyl ring No limitation has been made as regards the remaining substituents in formula (1 0 0) The searched matter covers all of the examples

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66 1(e) PCT) The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure

INTERNATIONAL SEARCH REPORT

Ir nal Application No
PCT/IB 01/02726

627
620
08626

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0157036	A	09-08-2001	AU	2700201 A	14-08-2001
			WO	0157036 A1	09-08-2001
WO 0157025	A	09-08-2001	AU	2700301 A	14-08-2001
			WO	0157025 A1	09-08-2001
GB 2327675	A	03-02-1999	JP	11147874 A	02-06-1999
WO 9845628	A	15-10-1998	US	5618027 A	08-04-1997
			WO	9845628 A1	15-10-1998
			AU	2458297 A	30-10-1998
EP 0773024	A	14-05-1997	AU	722829 B2	10-08-2000
			AU	7042796 A	01-05-1997
			CA	2188901 A1	28-04-1997
			CN	1157136 A	20-08-1997
			EP	0773024 A2	14-05-1997
			JP	9291032 A	11-11-1997
			NZ	299645 A	28-07-2000
			ZA	9608990 A	28-04-1998
US 4270946	A	02-06-1981	US	4327218 A	27-04-1982
US 4692185	A	08-09-1987	NONE		

625
621
00827

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN X 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.	( )	( )
- Descripcion 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		
- Representacion grafica y fotografica del Diseño Industrial o muestra del		
Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicacion de que solicita el registro de un Esquema de trazado	( )	( )
- Datos de identificación del solicitante o de la persona que presenta		
La solicitud	( )	( )
Representacion gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03065410 00000000 Folios: 624

Fecha Fecha (AMD): 2003-07-31 16:52 59

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

622

Folio 628

2020
Bogotá DC

Doctor(a)
CARLOS R OLARTE
Apoderado(a)
PFIZER PRODUCTS INC

REFERENCIA.	Radicación No	03 65410
	Solicitud Internacional	PCT/IB2001/02726
	Fecha inicio fase nacional	31/08/2003
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No	1334
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial

Cúmplase
Dado en Bogotá DC, 04 NOV

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202057