Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. EXPEDIENTE No. 03-6545

54. TÍTULO DERIVADOS BICÍCLICOS DE SULFONAMIDA DE UTILIDAD COMO INHIBIDORES DE LIPOZIMA PLA

51. CLASIFICACIÓN INTERNACIONAL A61K 31/44

71. SOLICITANTE PFIZER PRODUCTS INC

DOMICILIO EASTERN POINT ROAD, ESTADO DE CONNECTICUT E.U.A

74. APODERADO CARLOS R. OLARTE

22. BOGOTÁ, D. C., Julio 31, 2003

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

03 068415 00

SUPERINTENDENCIA Y COMERCIO
Radicacion : 03068415 00000000 Folios: 585
Fecha (AMD): 2003-07-31 15:25:11 ción
Tramite : 911 PCT-PATENT 379 PAGE DOCI 411 PRESENTOR:
Dependencia: 0000 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

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

(2) SOLICITANTE (71)

Nombre: PFIZER PRODUCTS INC.
Dirección: Eastern Point Road, Groton, Connecticut 06340, Estados Unidos de América.
Nacionalidad o Domicilio: ESTADOUNIDENSE
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 74.205

(4) INVENTOR (ES) (72)

Nombre: Robert James Chambers, Thomas Victor Magee, Anthony Marfat
Dirección: Eastern Point Road, Groton, CT 06340, Estados Unidos de América.
Nacionalidad o Domicilio: ESTADOUNIDENSE

(5) PCT (86)

Solicitud Internacional No. PCT/IB01/02341 Fecha Diciembre 6, 2001
Publicación Internacional No. WO 02/060875 Fecha Agosto 8, 2002

(6) Título (54): DERIVADOS BIARILICOS DE NICOTINAMIDA DE UTILIDAD COMO INHIBIDORES DE ISOZIMA PDE4

(7) Clasificación Internacional (51) A61K 31/44

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Enero 31, 2001	60/265,492

(9) Comprobante de pago No. 52871 **Fecha** 28-07-03

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

(10) **ANEXOS**

2

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredite 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: Búsqueda 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. 74295

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

Tabla de Contenido

	COMPROBANTE DE PAGO
2	PODER
3	DOCUMENTO DE CESION
4	SOLICITUD INTERNACIONAL
5	TRADUCCION DE LA SOLICITUD INTERNACIONAL
6	COPIA DEL EXAMEN PRELIMINAR
7	BUSQUEDA INTERNACIONAL
8	
9	
10	
11	
12	

Guías clasificadoras a Color
MyM

8

4

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03065415 00000000
Fecha (AMD): 2003-07-31 16:36:11 Folios: 585
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 52,671
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	50003-01-01 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

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 Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

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.

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

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

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
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

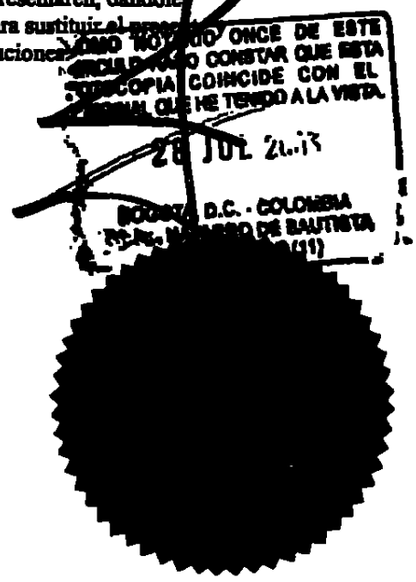
Eastern Point Road, Groton, Connecticut 06340 USA

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, dándole asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
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):

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 FREEMAN

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):

DESPACHO NOTARIO ONCE DE ESTE CIRCUITO HACE CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
28 JUL
BOGOTA, D.C. - COLOMBIA
DRA. NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

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.

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

12
9

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

APOSTILLA EN CESION A PFIZER PRODUCTS INC.

APOSTILLA

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

1. Distrito de Columbia. Estados Unidos de América
   Este documento Público
2. ha sido firmado por Kevin Woodward
3. Quien ejerce funciones de Notario Público en y para el Distrito de Columbia
4. Lleva el sello del Distrito de Columbia

CERTIFICADO

5. En Washington, D.C.
6. El 9 de mayo de 2003
7. Por el Secretario de Estado de Columbia
8. No. 61514
9. Gran Sello del Distrito de Columbia
10. Firma legible de Sherryl H. Newman

PC11897ARMS

CESION 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 América, por el presente yo (nosotros) vendemos y cedemos a la mencionada PFIZER PRODUCTS INC., todos mis (nuestros) derechos, título e interés en y referente a mi (nuestra) invención para una mejora nueva y útil en DERIVADOS DE NICOTINAMIDA BIARYL UTILES COMO INHIBIDORES DE ISOZIMAS PDE4 en cuanto a la República 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:

Marlen Neira C

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

Firma	Lugar y fecha
Robert James Chambers	Groton, Connecticut, mayo 2, 2003
Thomas Victor Magee	Groton, Connecticut, mayo 2, 2003
Anthony Marfat	Groton, Connecticut, mayo 2, 2003

Sello al reverso:

Por el presente se certifica que este documento es original

- Sami Swadek - 5 - 09- 2003 -

Suscrito y legalizado ante notario el 9 de mayo de 2003

Firma y sello de Kevin Woodward- Notario público, Distrito de Columbia, sus funciones vencen el 4- 14- 2007. Sello en altó relieve de Notario.

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

101. 19
11

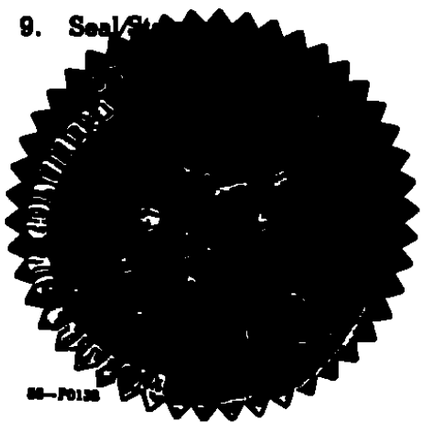
APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. *District of Columbia*
   United States of America
2. This public document has been signed by KEVIN WOODWARD
3. acting in the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA
4. bears the seal/stamp of KEVIN WOODWARD , NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA

CERTIFIED

5. at Washington, D. C.
6. the 9 day of MAY 2003
7. by *Secretary of the District of Columbia*
8. No. 61514
9. Seal/Stamp



10. Signature

SHERRYL H. NEWMAN

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 **NICOTINAMIDE BIARYL 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

Groton, Connecticut 02 May 2003

Place, date and signature - Robert James CHAMBERS

Groton, Connecticut 02 May 2003

Place, date and signature - Thomas Victor MAGEE

Groton, Connecticut 02 May 2003

Place, date and signature - Anthony MARFAT

I HEREBY CERTIFY THAT THIS
IS THE ORIGINAL DOCUMENT
JAMI SWADEK
5.9.03

District of Columbia: SS
Subscribed and Sworn to before me
this 9th day of MAY 2003
Kevin Woodward
Notary Public, D.C.
My commission expires 04-14-2007

Kevin Woodward
Notary Public, District of Columbia
My Commission Expires 04-14-2007

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 August 2002 (08.08.2002)

PCT

(10) International Publication Number
WO 02/060875 A1

(51) International Patent Classification[7]: C07D 213/82, 405/12, A61K 31/44, A61P 11/06, 29/00

(21) International Application Number: PCT/IB01/02341

(22) International Filing Date: 6 December 2001 (06.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/265,492 31 January 2001 (31.01.2001) US

(71) Applicant *(for all designated States except US)*: PFIZER PRODUCTORS 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 & 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).

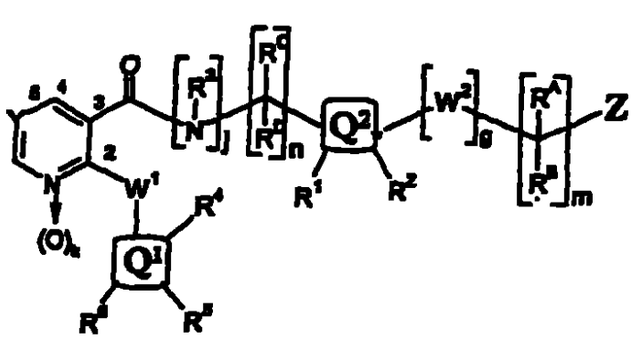
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, 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.

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



(I)



(II)

(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): where j is 0 or 1 provided that when j is 0, n must be 2; k is 0 or 1; m is 0, 1, or 2; n is 1 or 2; W^1 is -O-; or -S(=O)t-, where t is 0, 1, or 2; or -N(R^3)-; W^2 is -O-CR^AR^B- or is absent; Y is =C(R^1)- or -[N=>(O)k]- where k is 0 or 1; R^A and R^B are -H; -F; $-CF_3$; -(C_1-C_4)alkyl; -(C_3-C_7)cycloalkyl; phenyl; or benzyl substituted with 0 to 3 substituents R^{16}; or R^A and R^B are taken together, but only in the case where m is 1, to form a spiro moiety; R^C and R^D have the same meaning 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_3)alkyl; -(C_2-C_4)alkynal; fluorinated-(C_1-C_3)alkyl; -OR^{16}; and -C(=O)$NR^{22}R^{22}$; R^3 is -H; -(C_1-C_3)alkyl; phenyl; benzyl; or -OR^{16}; R^4, R^5 and R^6 in addition to other meanings may be taken together to form, e.g., form (II): Q', Q* and Z are as defined in the application.

WO 02/060875 A1

NICOTINAMIDE BIARYL DERIVATIVES USEFUL AS INHIBITORS OF PDE4 ISOZYMES

1.0 REFERENCE TO COPENDING APPLICATIONS

Reference is made to copending 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 selective inhibitors of the PDE4D isozyme, and thus 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 the unexpectedly high level of inhibitory selectivity for the PDE4D isozyme which said novel compounds possess.

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 PC11896, 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.

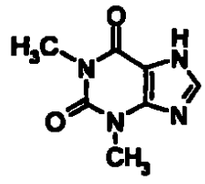
2.0 BACKGROUND OF THE INVENTION

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 is primarily concerned with the four gene products of the fourth family of PDEs, *i.e.*, PDE4A, PDE4B, PDE4C, and 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

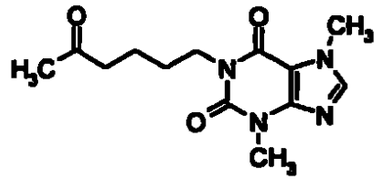
organization, molecular structure and enzymatic activity, differential splicing, transcriptional regulation and phosphorylation, distribution and expression, and selective inhibition of the PDE4 isozyme subtypes.

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.

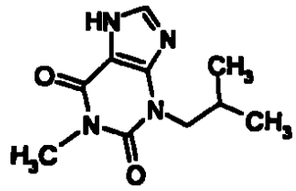
The present invention is also concerned with the use of selective PDE4 inhibitors for the improved therapeutic treatment of a number of inflammatory, respiratory and allergic diseases and conditions, but especially for the treatment of asthma; chronic obstructive pulmonary disease (COPD) including chronic 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)

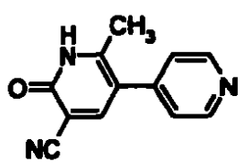


IBMX

(0.0.3)

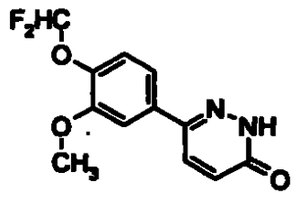
Theophylline, which has the PDEs as one of its biochemical targets, in addition to its well characterized bronchodilatory activity, affects the vasculature of patients with increased pulmonary artery pressure, suppresses inflammatory cell responses, and induces apoptosis of eosinophils. Theophylline's 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:



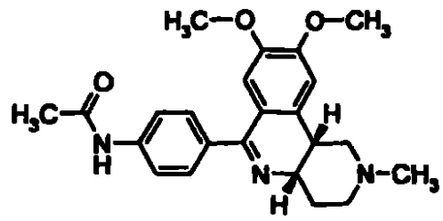
Milrinone

(0.0.4)



Zardaverine

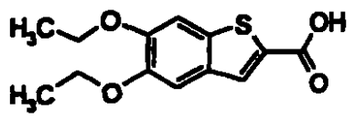
(0.0.5)



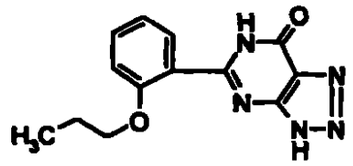
Benafentrine

(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)



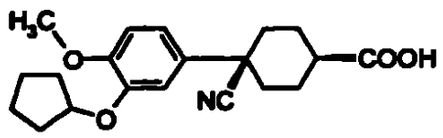
Zaprinast
(0.0.8)

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

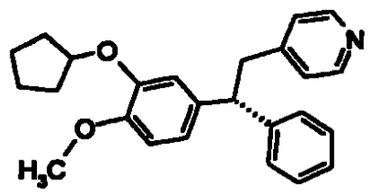
chronic inflammation, and are further implicated in the pathology of conditions such as emphysema.

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)

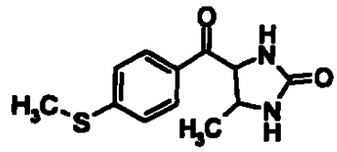
SB-207,499, administered orally at dosages of 5, 10, and 15 mg *b.i.d.*, has produced significant increases in trough FEV_1 (forced expiratory volume in 1 second) from placebo at week 2 of a study involving a large number of patients. Another potent, selective PDE4 inhibitor, CDP840, has shown suppression 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):



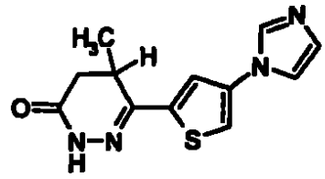
CDP840 (0.0.9)

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:

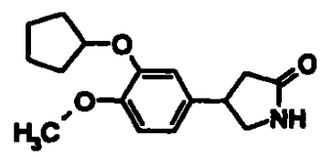


Enoximone
(0.0.10)

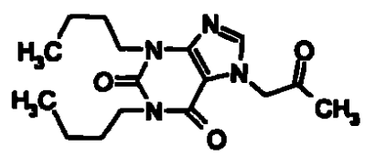


Motapizone
(0.0.11)

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:

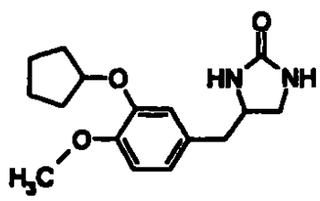


Rolipram
(0.0.12)



Denbufylline
(0.0.13)

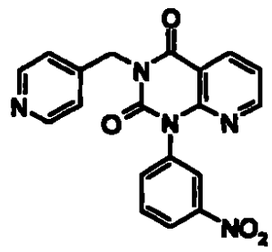
The mechanism(s) by which PDE4 inhibitors may potentially induce emesis is/are uncertain, but a study of the PDE4 inhibitor Ro-20-1724 suggests that nausea and vomiting are at least partially mediated by the emesis centers in the brain. Gastrointestinal adverse events may be caused by local effects, *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)

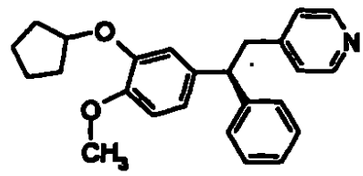
Efforts to minimize or eliminate the above-mentioned adverse events sometimes associated with PDE4 inhibitors have included creating inhibitors which do not penetrate the central nervous system, and administering PDE4 inhibitors by inhalation rather than orally.

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):

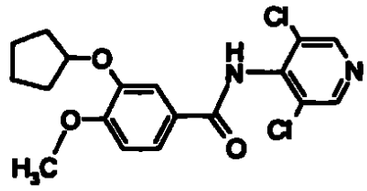


CT-1731 (0.0.16)

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.

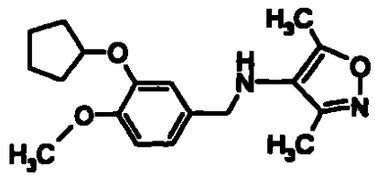
The impact of residues on inhibitor binding is also significant. A single amino acid substitution (alanine for aspartate) in the catalytic region of PDE4B has been shown to be critical for inhibition by rolipram, and this appears to be a class effect because related inhibitors RP-73,401 and Ro-20-1724 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)

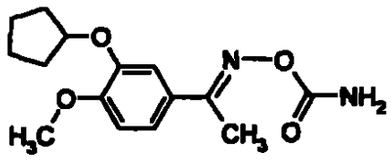
A related series of compounds is represented by RPR-132294 and RPR-132703, which have been demonstrated in rat studies to have activity in the inhibition of antigen-induced bronchospasm; Escott *et al.*, "Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic ratio in rats and dogs," *Br. J. Pharmacol.* 123(Proc. Suppl.) 40P, 1998; and Thurairatnam *et al.*, "Biological activity and side effect profile of RPR-132294 and RPR-132703 -- novel PDE4 inhibitors," *XV*th *EFMC Int. Symp. Med. Chem.*, 1998. The structure of RPR-132294 may be represented by Formula (0.0.18):



RPR-132294

(0.0.18)

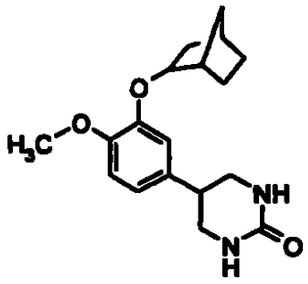
Another compound whose development has been discontinued is WAY-PDA-641, filaminast, which in studies in the dog, has been found to be active in the inhibition of serotonin-induced bronchoconstriction. Filaminast may be represented by Formula (0.0.19):



Filaminast (WAY-PDA-641)

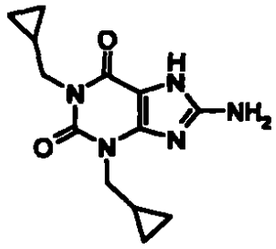
(0.0.19)

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_c 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)

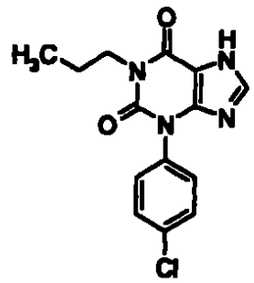
(0.0.20)



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; Beleta, 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) 362s, 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 A611, 1999.

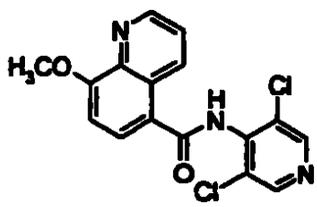
The compound D4418 has been administered to healthy volunteers in a single escalating dose, randomized, placebo-controlled Phase I study; Montana *et al.*, "Activity of D4418, a novel phosphodiesterase 4 (PDE4) inhibitor, effects in cellular and animal models of asthma and early clinical studies," *Am. J. Respir. Crit. Care Med.* 159 A108, 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

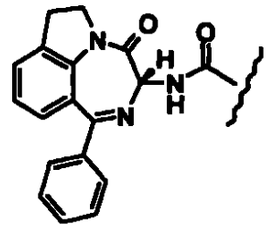
(0.0.22)



D4418

(0.0.23)

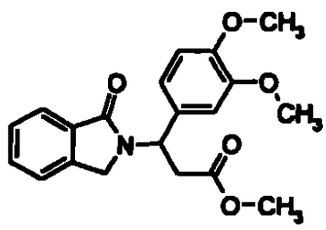
Another compound, CI-1018, has been evaluated in 54 subjects and no adverse events were reported at doses up to 400 mg; Pruniaux *et al.*, "The novel phosphodiesterase inhibitor CI-1018 inhibits antigen-induced lung eosinophilia in sensitized brown-norway rats - comparison with rolipram," *Inflammation* 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 diazepinone class whose nucleus may be represented by Formula (0.0.24):



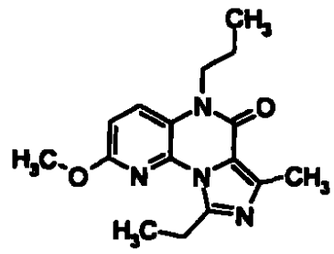
(0.0.24)

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.

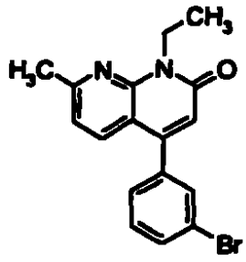
Other compounds which have been advanced in development include CDC-3052, D-22888, YM-58997, and roflumilast, which may be represented by Formulas (0.0.27), (0.0.28), (0.0.29), and (0.0.30), respectively:



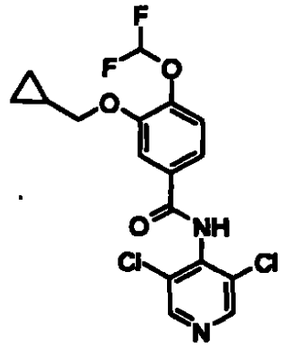
CDC-3052
(0.0.27)



D-22888
(0.0.28)

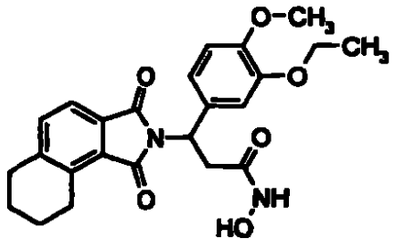


YM-58977
(0.0.29)

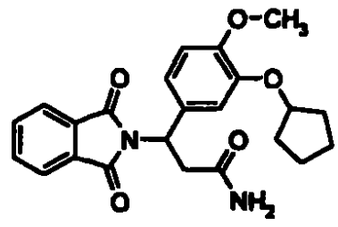


Roflumilast
(0.0.30)

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:



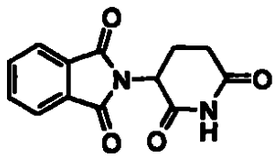
CDC-801
(0.0.31)



(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

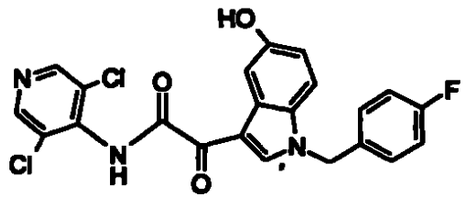
(0.0.33)

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.

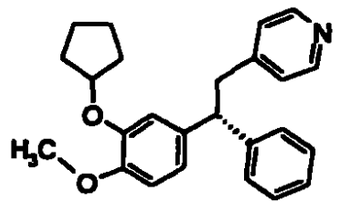
AWD-12,281, which is now designated as loteprednol, has been shown to be active in a rat model of allergic rhinitis, as described further below in a section which deals with allergic rhinitis and the use of PDE4 inhibitors to treat it. AWD-12,281 may be represented by Formula (0.0.34):



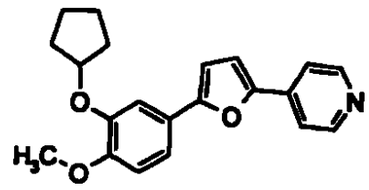
Loteprednol (AWD-12,281)

(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.* 9 323-326, 1999, and is represented by Formula (0.0.35):

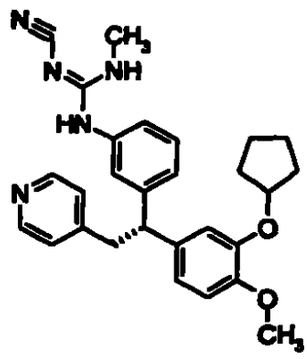


CDP840
(0.0.9)



(0.0.35)

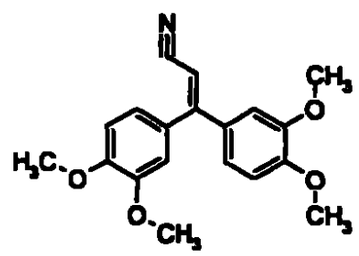
Other compounds which been found to be very potent PDE4 inhibitors are those represented by Formulas (0.0.36), (0.0.37), and (0.0.38):



(0.0.36)

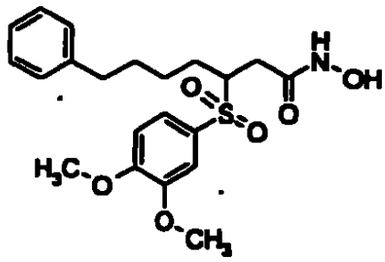


(0.0.37)

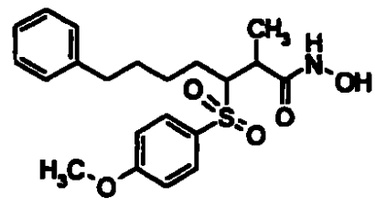


(0.0.38)

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)

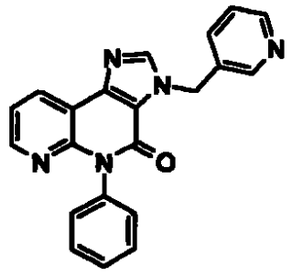


(0.0.40)

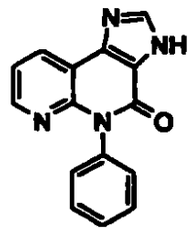
The respective IC_{50} values for the compounds of Formulas (0.1.36) and (0.1.37) using a guinea-pig macrophage PDE4 assay were 1 nM and 30 nM.

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 4868-4874, 1992; Matsuura *et al.*, "Substituted 1,8-naphthyridin-2(1H)-ones as selective phosphodiesterase IV inhibitors," *Biol. Pharm. Bull.* 17(4) 498-503, 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):

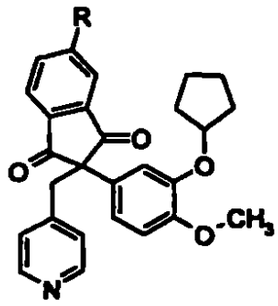


KF19514
(0.0.41)



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):

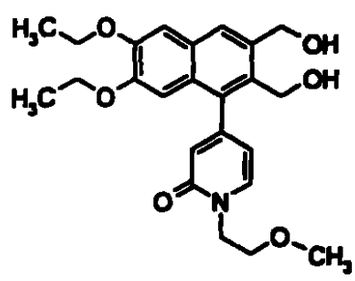


R = benzyloxy (0.0.43)

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

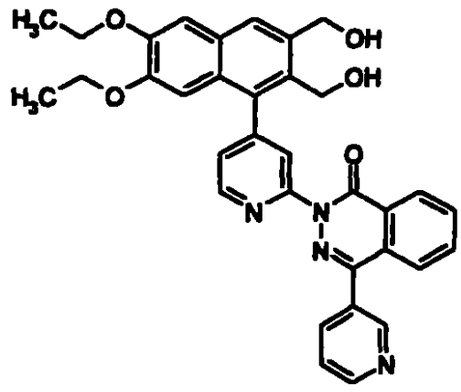
The PDE4 inhibitors that have been created heretofore fall into a significant number of different classes in terms of their chemical structures. Such classes have been as diverse as phenanthridines and naphthyridines. One class of PDE4 inhibitors are lignans such as T-440, which has been demonstrated 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

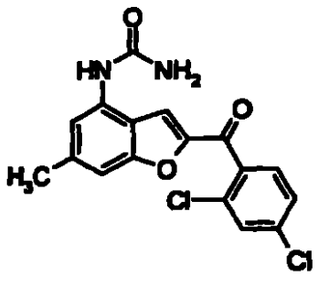
(0.0.45)



T-2585

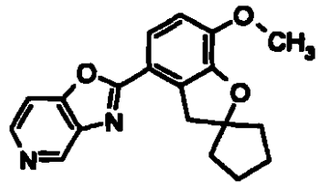
(0.0.46)

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):



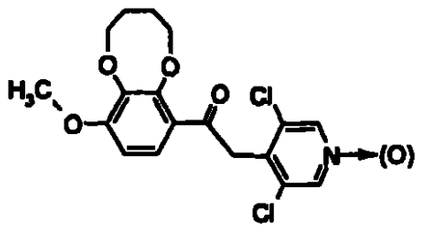
(0.0.47)

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):



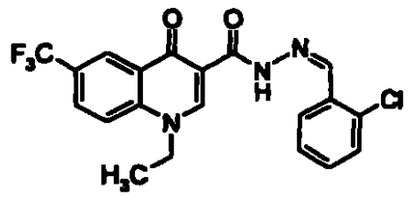
(0.0.48)

A compound with a related structure, which is not, however, a benzofuran, is characterized by a fused dioxicin 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):

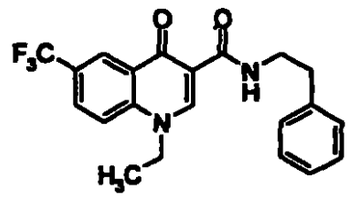


(0.0.49)

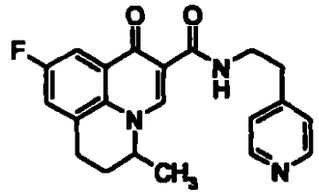
Quinolines and quinolones are a further class of PDE4 inhibitor structures, and they serve as surrogates for the catechol moiety of rolipram. This compound and two compounds of similar structure may be represented by Formulas (0.0.50), (0.0.51), and (0.0.52):



(0.0.50)

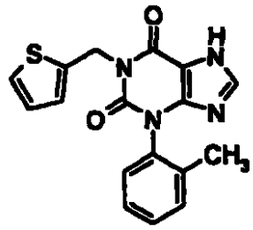


(0.0.51)



(0.0.52)

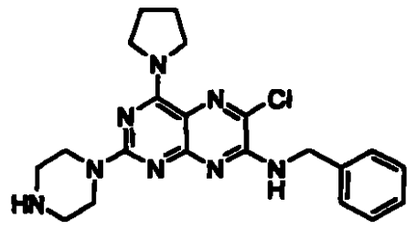
Purines, xanthines, and pteridines represent yet further classes of chemical compounds to which PDE4 inhibitors described heretofore in the art belong. The compound V-11294A described further above and represented by Formula (0.0.22), is a purine. A PDE4 inhibitor which is a xanthine compound, the class 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)

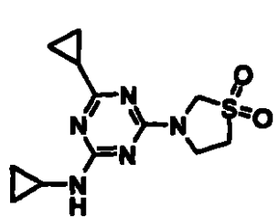
A potent PDE4 inhibitor belonging to the pteridine class of compounds has been demonstrated to have an IC_{50} value of 16 nM against a PDE4 derived from tumor cells and to inhibit the growth of tumor cells at micromolar concentrations; Merz *et al.*, "Synthesis of 7-

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):

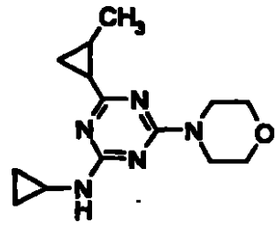


(0.0.55)

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)

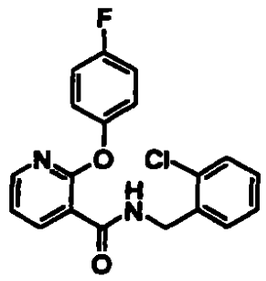


(0.0.57)

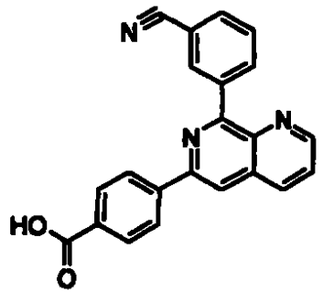
A triazine having a structure assumed to be closely related to that of the compounds of Formulas (0.0.56) and (0.0.57) is UCB-29936, which has been demonstrated to have activity in a murine model of septic shock; Danhaive *et al.*, "UCB29936, a selective phosphodiesterase Type IV inhibitor: therapeutic potential in endotoxic shock," *Am. J. Respir. Crit. Care. Med.* 159 A611, 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:

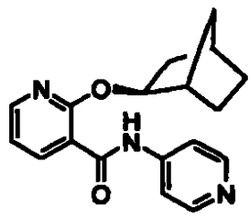


(0.0.58)

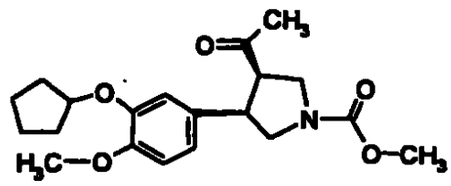


(0.0.59)

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)

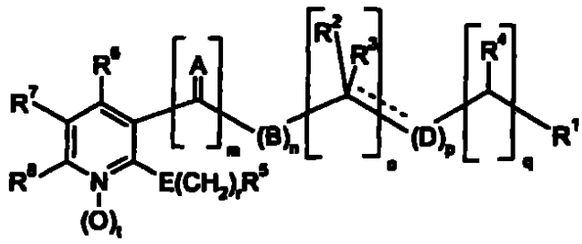


(0.0.61)

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.).

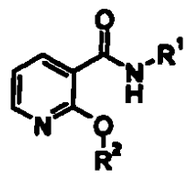
3.0 DESCRIPTION OF THE STATE OF THE ART

WO 98/45268 (Marfat *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):



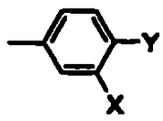
(0.1.1)

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):



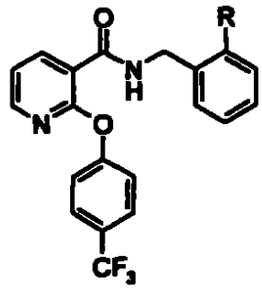
(0.1.2)

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).

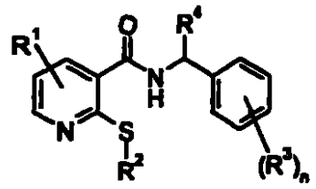
US 4,692,185 (Michaely *et al.*) discloses herbicides such as those of Formula (0.1.3):



(0.1.3)

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

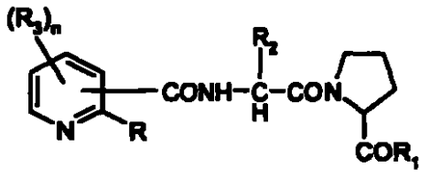
EP 550 900 (Jeschke *et al.*) discloses herbicides and plant nematicides of Formula (0.1.4):



(0.1.4)

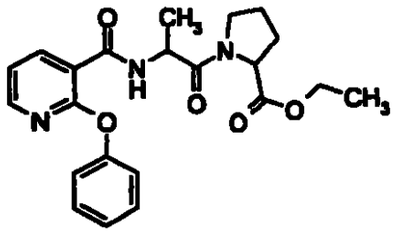
where n is 0-3; R^1 is selected from numerous groups, but is usually H, 6-CH_3, or 5-Cl; R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl; R1 and R2 is halo, CN, NO_2, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfonyl, haloalkylsulfonyl, aryl, aryloxy, or arylthio;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

EP 500 989 (Mollner *et al.*) discloses ACE inhibitors of Formula (0.1.5):



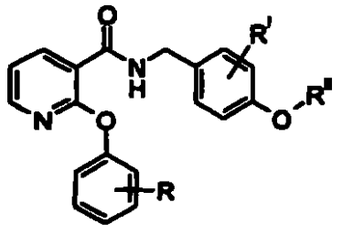
(0.1.5)

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)

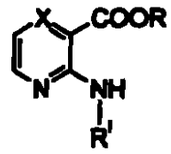
FR 2.140.772 (Aries) discloses compounds asserted to have utility as analgesics, tranquilizers, antipyretics, anti-inflammatories, and antirheumatics, of Formula (0.1.7):



(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):

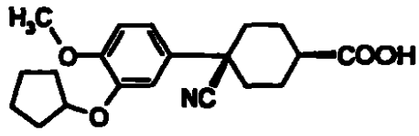


(0.1.8)

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

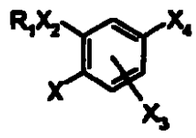
With regard to the disclosures of the above-identified patents and published patent applications, it will be appreciated that only the disclosure of WO 98/45268 (Marfat *et al.*) concerns the inhibition of PDE4 isozymes. The state of the art also contains information regarding compounds wholly dissimilar 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 5,614,540 (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:



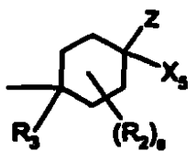
ARIFLO®
cis-[4-cyano-4-(3-cyclopentyl-oxy-4-methoxyphenyl)cyclo-hexane-1-carboxylic acid (0.1.9)

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)

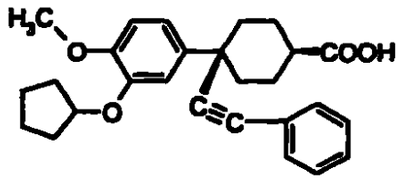
where R_1 = -$(CR_4R_5)_rR_6$ where r = 0 and R_6 = C_{3-6} cycloalkyl; X = YR_2 where Y = O and R_2 = $-CH_3$; X_2 = O; X_3 = H; and X_4 = a moiety of partial Formula (0.1.10.1)



(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.

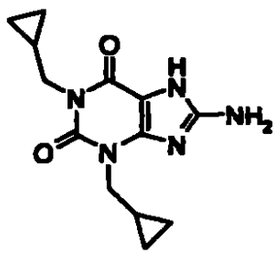
US 5,863,926 (Christensen *et al.*) discloses analogs of the ARIFLO® compound, *e.g.*, that of Formula (0.1.11):



(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.

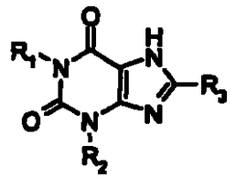
WO 99/20625 (Eggleston) discloses crystalline polymorphic forms of cipamfylline for treatment of PDE_4 and TNF mediated diseases, of Formula (0.1.12):



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):



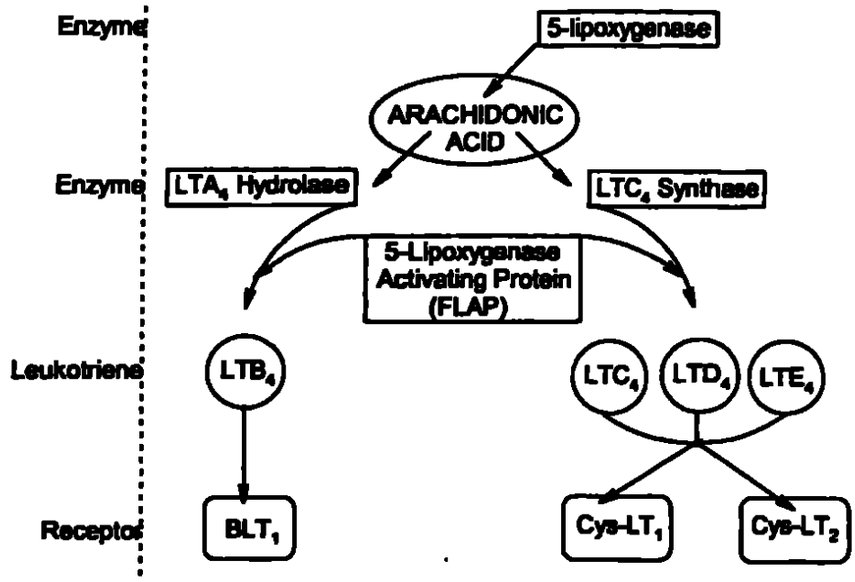
(0.1.13)

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.

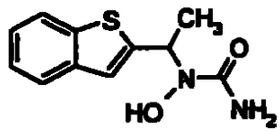
With regard to the disclosures of the above-identified patents and published patent applications, it will be appreciated that the compounds involved possess the same biological activity as the compounds of Formula (1.0.0). At the same time, however, the artisan will observe that the chemical structures 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:



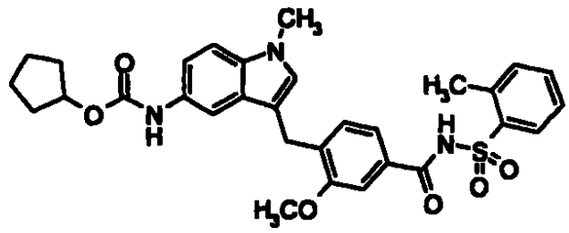
Accordingly, agents which are able to intervene in any of the steps of the 5-lipoxygenase pathway afford an opportunity for therapeutic treatment. An example of one such agent is the 5-lipoxygenase inhibitor, zileuton, a therapeutic agent identified as ZYFLO® which may be represented by Formula (0.1.14):



ZYFLO®

Zileuton (0.1.14)

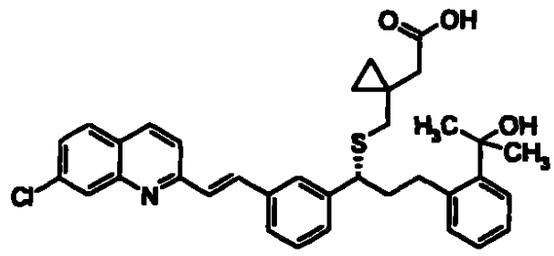
Another such agent is the LTD_4 receptor antagonist zafirlukast, a therapeutic agent identified as ACCOLATE® which may be represented by Formula (0.1.15):



ACCOLATE®

Zafirlukast (0.1.15)

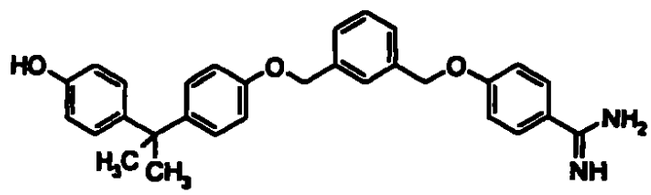
A further such LTD_4 receptor antagonist is montelukast, a therapeutic agent identified as SINGULAIR® which may be represented by Formula (0.1.16):



SINGULAIR®

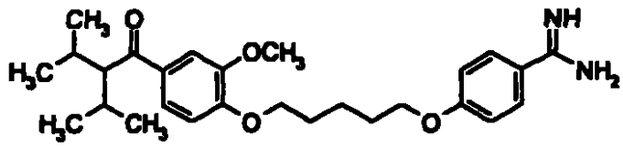
Montelukast (0.1.16)

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):



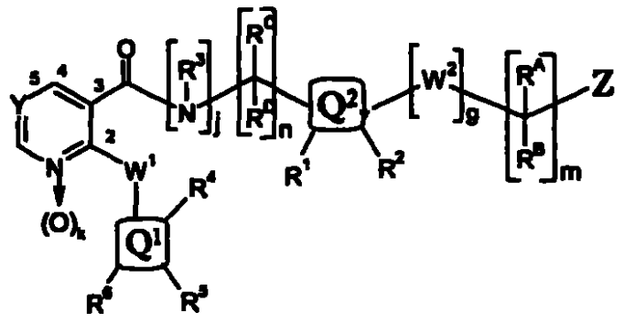
CGS-25019c (0.1.18)

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 —

-g is 0 or 1;

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

-k is 0 or 1

-m is 0, 1, or 2;

-n is 1 or 2;

-W^1 is –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;

-W^2 is –O–; –S(=O)$_t$–, where t is 0, 1, or 2; –N(R^3)– where R^3 has the same meaning as defined below, or –C$R^{29}R^{30}$–;

— where —

–R^{29} and R^{30} are each a member independently selected from the group consisting of –H; –F; –CF_3; –(C_1-C_8) alkyl; –(C_3-C_8) cycloalkyl; phenyl; benzyl; and pyridyl; wherein said alkyl, cycloalkyl, phenyl, benzyl, and pyridyl moieties are each independently substituted with 0 to 3 substituents R^{10}, where R^{10} 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_3) alkyl; fluorinated-(C_1-C_3) alkoxy; -OR^{18}; and –C(=O)N$R^{22}{}_a R^{22}{}_b$;

— 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 alkyl, 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)N$R^{16}R^{17}$; -O-C(=O)N$R^{16}R^{17}$; –N$R^{16}R^{17}$; –NR^{16}C(=O)R^{17}; -NR^{16}C(=O)OR^{17}; –NR^{16}S(=O)$_2R^{17}$; and -S(=O)$_2$N$R^{16}R^{17}$; where said phenyl or pyridyl is substituted by 0 to 3 R^{11};

— where —

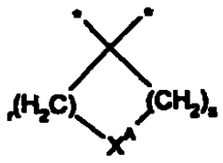
—R^{11} is –F; –Cl; –CF_3; –CN; –NO_2; –OH; –(C_1-C_3) alkoxy; –(C_1-C_3) alkyl; or –$NR^{16}R^{17}$;

— 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 Q^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 Q^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; $-NO_2$; $-C(=O)NR^{16}R^{17}$; $–OC(=O)NR^{16}R^{17}$; $-NR^{22}{}_aC(=O)NR^{16}R^{17}$; $-NR^{22}{}_aC(=NR^{22}{}_a)NR^{16}R^{17}$; $-NR^{22}{}_aC(=NCN)NR^{16}R^{17}$; $-NR^{22}{}_aC(=N-NO_2)NR^{16}R^{17}$; $-C(=NR^{22}{}_a)NR^{16}R^{17}$; $-CH_2C(=NR^{22}{}_a)NR^{16}R^{17}$; $-OC(=NR^{22}{}_a)NR^{16}R^{17}$; $–OC(=N–NO_2)NR^{16}R^{17}$; $-NR^{16}R^{17}$; $-CH_2NR^{16}R^{17}$; $-NR^{22}{}_aC(=O)R^{16}$; $-NR^{22}{}_aC(=O)OR^{16}$; $=NOR^{16}$; $–NR^{22}{}_aS(=O)_pR^{17}$ $-S(=O)_pNR^{16}R^{17}$; 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 —

$-R^{15}$ 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 —

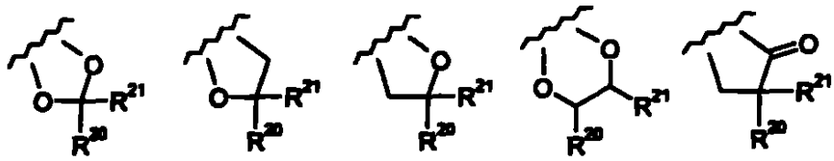
$-R^{12}$ is a member independently selected from the group consisting of –F; –Cl; $-CO_2R^{16}$; $-OR^{16}$; –CN; $-C(=O)NR^{16}R^{16}$; $-NR^{16}R^{16}$; $-NR^{16}C(=O)R^{16}$; $-NR^{16}C(=O)OR^{16}$; $-NR^{16}S(=O)_pR^{16}$; $-S(=O)_pNR^{16}R^{16}$, where p is 1 or 2; $-(C_1-C_4)$ alkyl; and $-(C_1-C_4)$ alkoxy in the case where R^{12} has the meaning of $-OR^{15}$ above and R^{15} 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 —

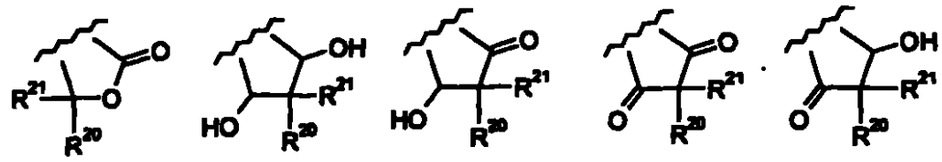
$-R^{16}$ and R^{19} are independently selected from the group consisting of –H; $-(C_1-C_4)$ alkyl; and phenyl; where said alkyl or phenyl is substituted by 0-3 of –F; or –Cl;

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

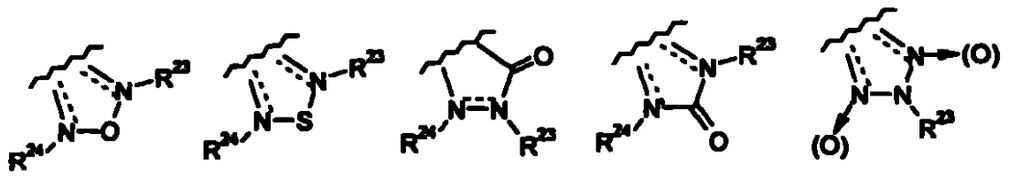
-(d) R^5 and R^6 are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3.1) through (1.3.15):



(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;

-Q^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 Q^1 is not a discontinuous or restricted biaryl moiety as defined under Q^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 —

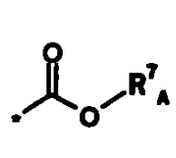
said moiety defining Q^1 is substituted on any ring or rings thereof by R^4, R^5 and R^6, which have the same meaning as defined above;

$-Q^2$ is a discontinuous or restricted biaryl moiety consisting of 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; 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;

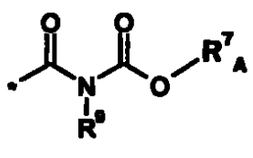
$-Z$ is a member independently selected from the group consisting of

— the following —

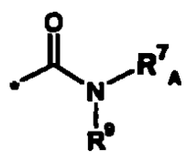
-(a) the group consisting of partial Formulas (1.1.1) through (1.1.15):



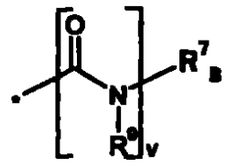
(1.1.1)



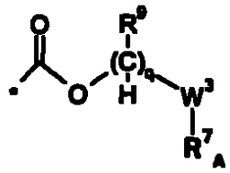
(1.1.2)



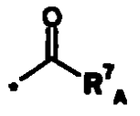
(1.1.3)



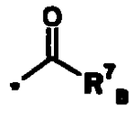
(1.1.4)



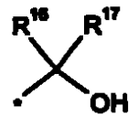
(1.1.5)



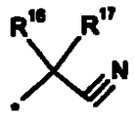
(1.1.6)



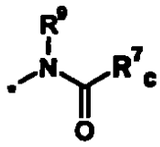
(1.1.7)



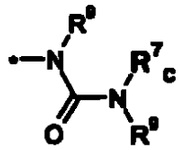
(1.1.8)



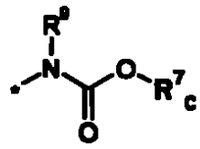
(1.1.9)



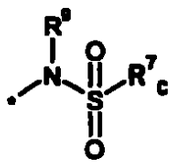
(1.1.10)



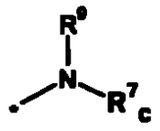
(1.1.11)



(1.1.12)



(1.1.13)



(1.1.14)



(1.1.15)

— wherein —

where R^{16} and R^{17} have the same meanings as defined above; and R^9 has the same meaning as defined below;

"~" indicates the point of attachment of each partial Formula (1.1.1) through (1.1.15) 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_A 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^7_B is a member independently selected from the group consisting of

— the following: —

—*(1)* 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; parathiazinyl; 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^{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;

–$R^7{}_C$ is a member independently selected from the group consisting of the meanings of $R^7{}_A$ and the meanings of $R^7{}_B$ defined above;

— and further wherein —



(1.1.15)

–comprises a saturated or unsaturated, 4– to 8–membered monocyclic, or 5– to 10–membered fused or open bicyclic, carbocyclic ring system containing a nitrogen heteroatom as shown in partial Formula (1.1.15); wherein optionally from 1 to 3 carbon atoms of said carbocyclic ring system may be individually replaced by a nitrogen heteroatom; or optionally 1 carbon atom thereof may be replaced by an oxygen heteroatom or by a sulfur heteroatom; or optionally 2 carbon atoms thereof may be individually replaced by a nitrogen heteroatom and an oxygen heteroatom, or by a nitrogen heteroatom and a sulfur heteroatom;

— where —

any moiety of partial Formula (1.1.15) recited above is optionally substituted with respect to *(1)* any one or more carbon atoms thereof, by a substituent R^{14} where R^{14} has the same meaning as defined above; *(2)* any one or more nitrogen atoms thereof by a substituent R^{15} where R^{15} has the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms thereof; or *(3)* any sulfur atom thereof by 0, 1, or 2 oxygen atoms;

— and Z 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^{18}, where R^{18} has the same meaning as defined above;

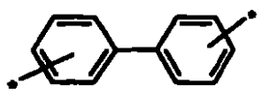
— or —

a pharmaceutically acceptable salt thereof.

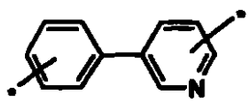
The present invention is concerned in particular with a compound of Formula (1.0.0) as above-recited wherein the group Q^2 comprises a member selected from the group consisting of

– the following –

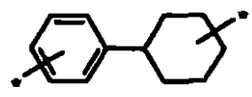
-moieties represented by partial Formulas (1.2.1) through (1.2.32):



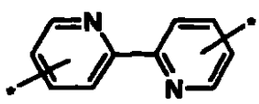
(1.2.1)



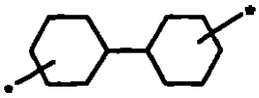
(1.2.2)



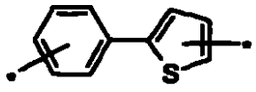
(1.2.3)



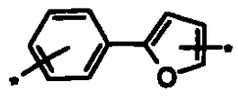
(1.2.4)



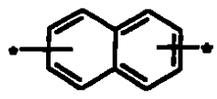
(1.2.5)



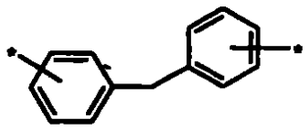
(1.2.6)



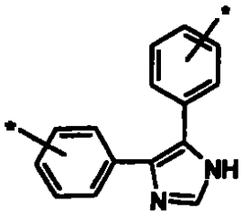
(1.2.7)



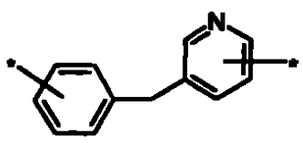
(1.2.8)



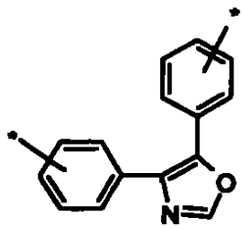
(1.2.9)



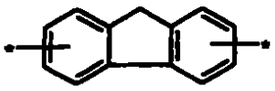
(1.2.10)



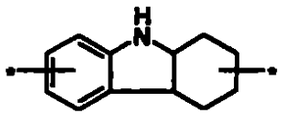
(1.2.11)



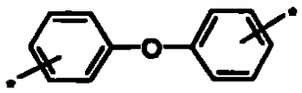
(1.2.12)



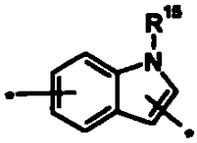
(1.2.13)



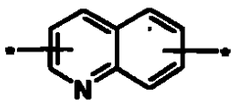
(1.2.14)



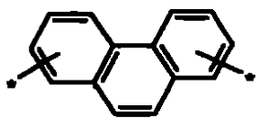
(1.2.15)



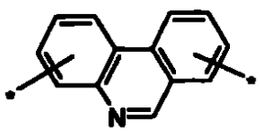
(1.2.16)



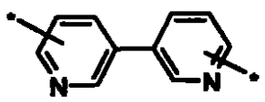
(1.2.17)



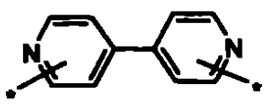
(1.2.18)



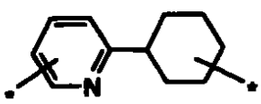
(1.2.19)



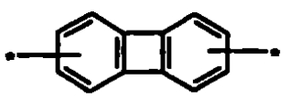
(1.2.20)



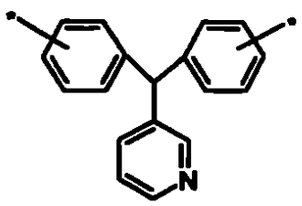
(1.2.21)



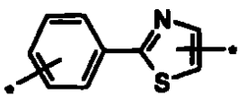
(1.2.22)



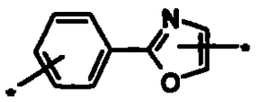
(1.2.23)



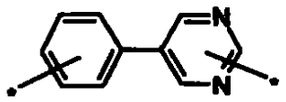
(1.2.24)



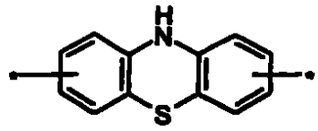
(1.2.25)



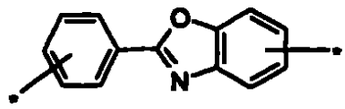
(1.2.26)



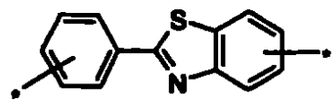
(1.2.27)



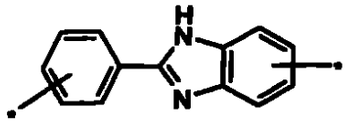
(1.2.28)



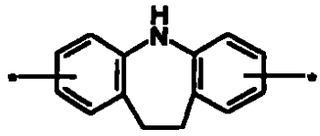
(1.2.29)



(1.2.30)



(1.2.31)

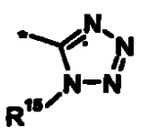


(1.2.32)

wherein " * " is a symbol indicating the two points of attachment of said group Q^2 to the remaining components of Formula (1.0.0).

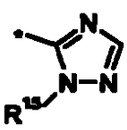
The present invention is concerned in particular with a compound of Formula (1.0.0) as above-recited wherein the terminal group Z comprises a member selected from the group consisting of partial Formulas (1.1.1) through (1.1.3), (1.1.5), (1.1.6), and (1.1.10) through (1.1.14), in which a preferred meaning of R^7_A or R^7_C is the meaning hydrogen, methyl, trifluoromethyl, *iso*-propyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl illustrated in partial Formulas (1.4.24) through (1.4.28) below.

The present invention is also concerned with a compound of Formula (1.0.0) in which Z comprises partial Formulas (1.1.4) and (1.1.10) through (1.1.14). A preferred meaning of R^7_B of partial Formula (1.1.4) where v is 0 or 1, or R^7_C of partial Formulas (1.1.10) through (1.1.14) is the meaning of a member selected from the group consisting of partial Formulas (1.4.1) through (1.4.28) illustrated below:



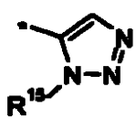
tetrazol-5-yl

(1.4.1)



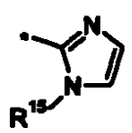
1,2,4-triazol-3-yl

(1.4.2)



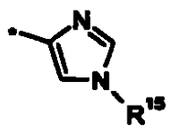
1,2,3-triazol-5-yl

(1.4.3)



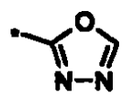
imidazol-2-yl

(1.4.4)



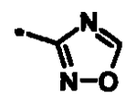
imidazol-4-yl

(1.4.5)



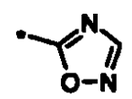
1,3,4-oxadiazolyl

(1.4.6)



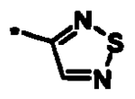
1,2,4-oxadiazol-3-yl

(1.4.7)

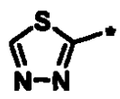


1,2,4-oxadiazol-5-yl

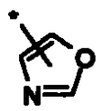
(1.4.8)



1,2,5-thiadiazol-2-yl
(1.4.9)



1,3,4-thiadiazolyl
(1.4.10)



oxazolyl
(1.4.11)



isoxazolyl
(1.4.12)



thiazolyl
(1.4.13)



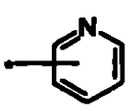
isothiazolyl
(1.4.14)



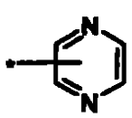
pyrrolyl
(1.4.15)



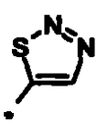
pyrazolyl
(1.4.16)



pyridyl
(1.4.17)



pyrazinyl
(1.4.18)



1,2,3-thiadiazol-5-yl
(1.4.19)



pyrrolidinyl
(1.4.20)



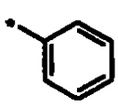
furanyl
(1.4.21)



tetrahydrofuranyl
(1.4.22)



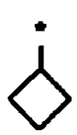
thienyl
(1.4.23)



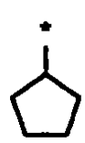
phenyl
(1.4.24)



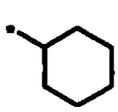
cyclopropyl
(1.4.25)



cyclobutyl
(1.4.26)



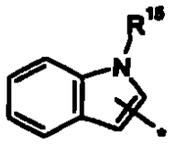
cyclopentyl
(1.4.27)



cyclohexyl
(1.4.28)

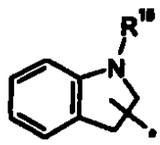
where "*" indicates the point of attachment to the remaining portion of Formula (1.0.0); and where each carbon atom is optionally substituted by a substituent R^{14}; and where R^{14} and R^{15} have the same meaning as defined above; and all tautomer forms, and optionally N-oxide forms, thereof.

The present invention is further concerned in particular with a compound of Formula (1.0.0) as above-recited wherein the terminal group Z comprises partial Formulas (1.1.4) and (1.1.10) through (1.1.14), and wherein preferred meanings of R^7_B and R^7_C in said partial Formulas (1.1.4) and (1.1.10) through (1.1.14) are each independently a member selected from the group consisting of partial Formulas (1.5.1) through (1.5.29):



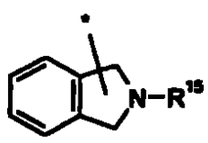
indolyl

(1.5.1)



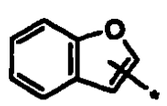
indolinyl

(1.5.2)



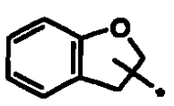
isoindolinyl

(1.5.3)



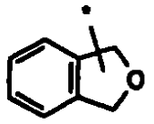
benzo[*b*]furanyl

(1.5.4)



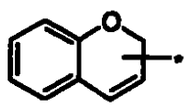
2,3-dihydrobenzo-furanyl

(1.5.5)



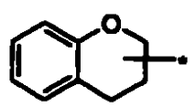
1,3-dihydroisobenzo-furanyl; phthalanyl

(1.5.6)



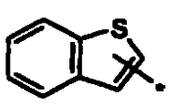
2*H*-1-benzopyranyl

(1.5.7)



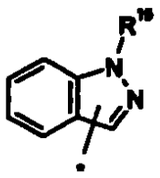
chromanyl

(1.5.8)



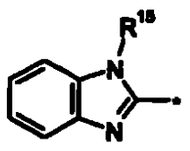
benzothienyl

(1.5.9)



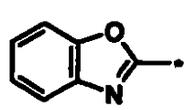
1*H*-indazolyl

(1.5.10)



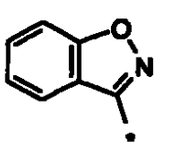
benzimidazolyl

(1.5.11)



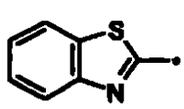
benzoxazolyl

(1.5.12)



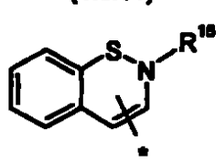
benzisoxazolyl

(1.5.13)



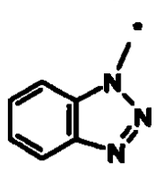
benzothiazolyl

(1.5.14)



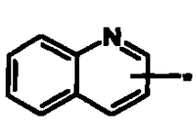
2H-1,2-benzothiazinyl

(1.5.15)



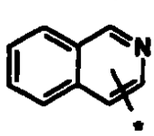
benzotriazolyl

(1.5.16)



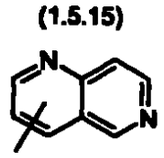
quinolinyl

(1.5.17)



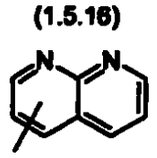
isoquinolinyl

(1.5.18)



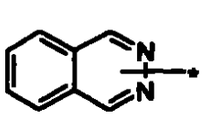
1,6-naphthyridinyl

(1.5.19)



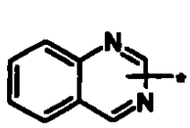
1,8-naphthyridinyl

(1.5.20)



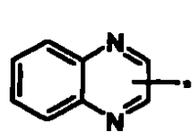
phthalazinyl

(1.5.21)



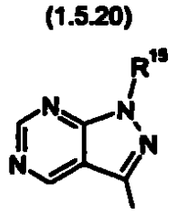
quinazolinyl

(1.5.22)



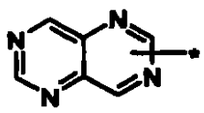
quinoxalinyl

(1.5.23)



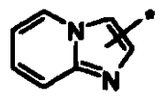
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(1.5.24)



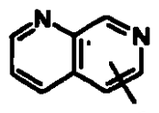
pyrimido[5,4-*d*]-pyrimidinyl

(1.5.25)



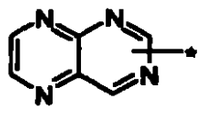
imidazo-[1,2-*a*]-pyridinyl

(1.5.26)



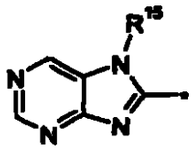
1,7-naphthyridinyl

(1.5.27)



pteridinyl

(1.5.28)

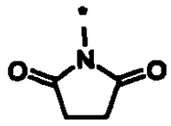


1*H*-purinyl

(1.5.29)

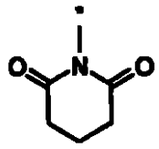
where "*" indicates the point of attachment to the remaining portion of Formula (1.0.0); and where each carbon atom is optionally substituted by a substituent R^{14}; and where R^{14} and R^{15} have the same meaning as defined above; and all tautomer forms, and optionally N-oxide forms, thereof.

The present invention is also concerned with a compound of Formula (1.0.0) wherein the terminal group Z has the meaning of a moiety of partial Formula (1.1.15) where the number and position of carbon atoms and replacement thereof by one or more heteroatoms, as well as the substitution of one or more said carbon atoms thereof by R^{14} where R^{14} is oxo (=O), are selected in such a way that Z comprises a member selected from the group consisting of partial Formulas (1.7.1) through (1.7.46):



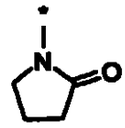
succinimid-1-yl

(1.7.1)



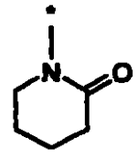
glutarimid-1-yl

(1.7.2)



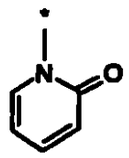
pyrrolidin-2-on-1-yl

(1.7.3)



piperid-2-on-1-yl

(1.7.4)



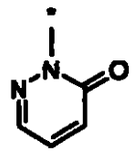
pyrid-2-on-1-yl

(1.7.5)



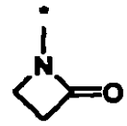
pyrid-4-on-1-yl

(1.7.6)



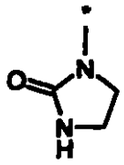
pyridazin-3-on-2-yl

(1.7.7)



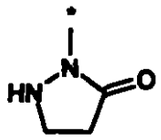
azetidin-2-on-1-yl

(1.7.8)



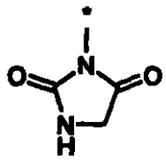
imidazolidin-2-on-1-yl

(1.7.9)



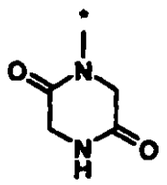
pyrazol-5-on-1-yl

(1.7.10)



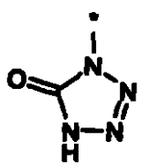
imidazolidin-2,4-dion-1-yl

(1.7.11)



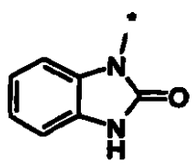
piperazin-2,5-dion-1-yl

(1.7.12)



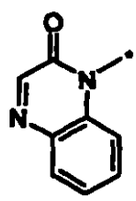
4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl

(1.7.13)



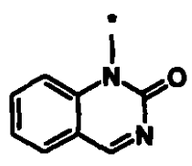
benzimidazolin-2-on-1-yl

(1.7.14)



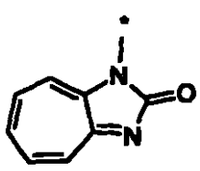
1*H*-quinoxalin-2-on-1-yl

(1.7.15)



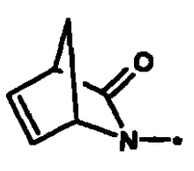
1*H*-quinazolin-2-on-1-yl

(1.7.16)



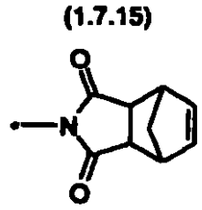
1H-cycloheptimid-azol-2-on-1-yl

(1.7.17)



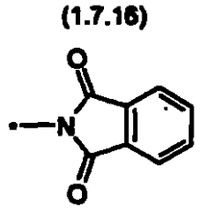
2-azabicyclo[2.2.1]-hept-5-en-3-on-1-yl

(1.7.18)



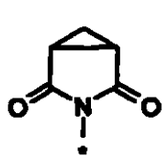
norborn-5-en-2,3-dicarboximid-1-yl

(1.7.19)



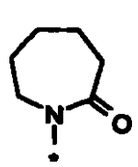
phthalimid-1-yl; 1*H*-isoindole-1,3(2*H*)-dion-1-yl

(1.7.20)



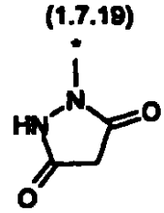
3-azabicyclo[3.1.0]-hexane-2,4-dion-3-yl

(1.7.21)



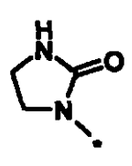
2*H*-azepin-2-on-1-yl

(1.7.22)



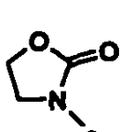
pyrazolidin-3,5-dion-1-yl

(1.7.23)



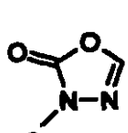
imidazolidin-2-on-1-yl

(1.7.24)



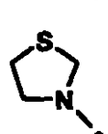
oxazolidin-2-on-1-yl

(1.7.25)



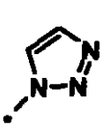
1,3,4-oxadiazol-2(3*H*)-on-3-yl

(1.7.26)



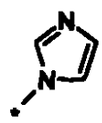
thiazolidin-3-yl

(1.7.27)



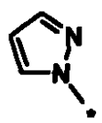
1*H*-1,2,3-triazol-1-yl

(1.7.28)



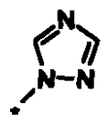
imidazol-1-yl

(1.7.29)



pyrazol-1-yl

(1.7.30)



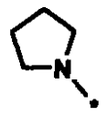
1*H*-1,2,4-triazol-1-yl

(1.7.31)



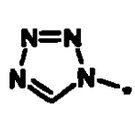
azetidin-1-yl

(1.7.32)



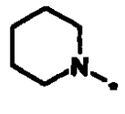
pyrrolidin-1-yl

(1.7.33)



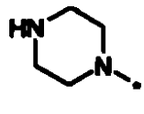
tetrazol-1-yl

(1.7.34)



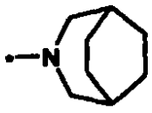
piperidin-1-yl

(1.7.35)



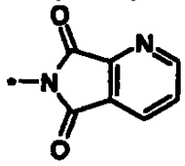
piperazin-1-yl

(1.7.36)



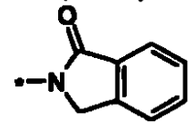
3-azabicyclo[3.2.2]-non-3-yl

(1.7.37)



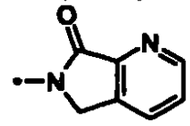
pyrrolo[3,4-*b*]pyridin-5,7-dion-6-yl

(1.7.38)



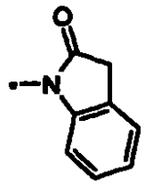
2,3-dihydro-*iso*-indol-1-on-2-yl

(1.7.39)



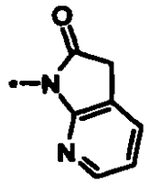
pyrrolo[3,4-*b*]pyridin-7-on-6-yl

(1.7.40)



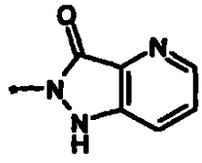
1,3-dihydro-indol-2-on-1-yl

(1.7.41)



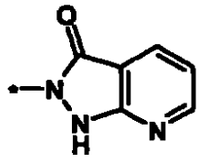
pyrrolo[4,5-*b*]pyridin-3-on-2-yl

(1.7.42)



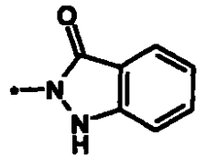
1*H*-pyrazolo[4,5-*e*]pyridin-7-on-2-yl

(1.7.43)



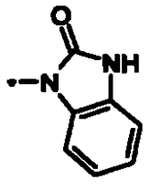
1*H*-pyrazolo[4,5-*b*]pyridin-4-on-2-yl

(1.7.44)



1*H*-indazol-3-on-2-yl

(1.7.45)



1*H*-benzimidazol-2-on-3-yl

(1.7.46)

Any moiety that is a member selected from the group consisting of partial Formulas (1.7.1) through (1.7.46) depicted above, includes optional substitution thereof with respect to *(1)* any one or more carbon atoms thereof, by a substituent R^{14} where R^{14} has the same meaning as defined above; *(2)* any one or more nitrogen atoms thereof by a substituent R^{15} where R^{15} has the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms thereof; or *(3)* any sulfur atom thereof by 0, 1, or 2 oxygen atoms.

The present invention is further concerned with a method of treating a subject suffering from a disease or condition mediated by the PDE4 isozyme, especially the D subtype thereof, 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, especially D subtype, 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 apparent 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.

– 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.

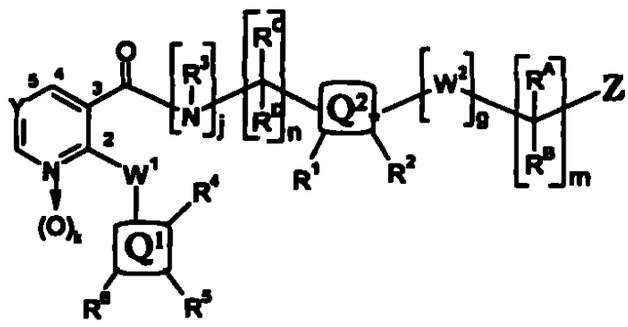
In particular, the compounds of Formula (1.0.0) are useful int the treatment of (1) inflammatory diseases and conditions comprising: joint inflammation, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, inflammatory bowel disease, ulcerative colitis, chronic glomerulonephritis, dermatitis, 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.

DETAILED DESCRIPTION OF THE INVENTION

5.0 Compounds

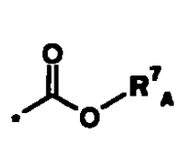
The present invention is concerned with novel compounds which may be represented by Formula (1.0.0) as follows:



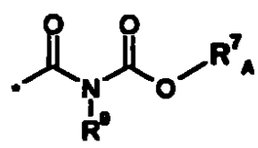
(1.0.0)

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 preferences is in no way intended to, and does not limit the scope of the present invention with regard to said compounds.

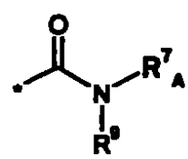
The meaning of the terminal moiety **Z** set forth in detail above is that of a member independently selected from the group consisting of partial Formulas (1.1.1) through (1.1.15):



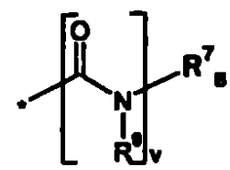
(1.1.1)



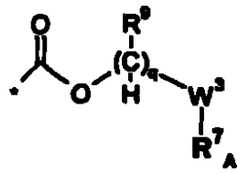
(1.1.2)



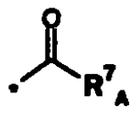
(1.1.3)



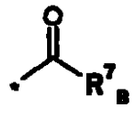
(1.1.4)



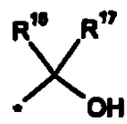
(1.1.5)



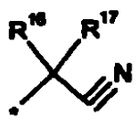
(1.1.6)



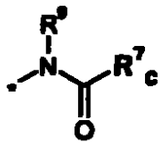
(1.1.7)



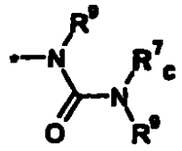
(1.1.8)



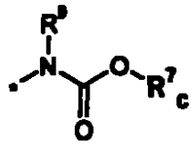
(1.1.9)



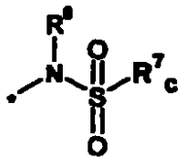
(1.1.10)



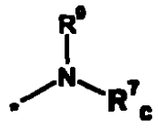
(1.1.11)



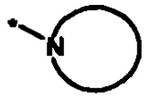
(1.1.12)



(1.1.13)



(1.1.14)



(1.1.15)

The substituents R^{7}_{A}, R^{7}_{B}, and R^{7}_{C}, as well as R^{9}, R^{16}, and R^{17} of the above enumerated partial Formulas, as well as their sub-substituents R^{10}, R^{11}, R^{12}, R^{14}, R^{15}, R^{18}, and R^{19}, are defined above and provide a clear delineation of the intended scope of the compounds of the present invention. Particular embodiments within said scope comprise particular meanings of the substituents R^{7}_{A}, R^{7}_{B}, R^{7}_{C}, and R^{9}, as well as of the other substituents that form a part of Formula (1.0.0). Said embodiments include, but are not limited to those set forth in paragraphs (i) through (vi) further below.

In order to assist the person of ordinary skill in considering the scope and extent of the description of the present invention set forth hereafter, certain terms and expressions used herein are defined in the paragraphs immediately below.

As used herein, the expressions "–(C_1-C_3) alkyl", "–(C_1-C_4) alkyl", and "-(C_1-C_6) alkyl", 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.

Both Q^1 and Q^2 are defined herein as 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; 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. These definitions 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 definition is also 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.

Respecting the situation where a carbon ring system has been selected that is discontinuous, as opposed to one that is fused, it should be noted that the moiety Q^1 is not permitted to be such a discontinuous carbon ring system. The moiety Q^2 on the other hand, is required to be discontinuous in this situation. It is further provided herein that the moiety Q^2 must either have the meaning of a carbon ring system that is discontinuous, or it must have the meaning of a "restricted biaryl" carbon ring system. Accordingly, these two essential requirements have been brought together under the expression "discontinuous or restricted biaryl", which as used herein is intended to mean a discontinuous ring system or 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.

Consequently, the types of restricted biaryl and discontinuous ring systems that may comprise a meaning of Q^2, but that may not comprise a meaning of Q^1 include, *inter alia*, the following, where the numbers after the names refer to the partial Formulas therefor recited elsewhere herein: biphenyl (1.2.1); 3-phenyl-pyridine (1.2.2); cyclohexyl-benzene (1.2.3); [2,2']bipyridinyl (1.2.4); bicyclohexyl (1.2.5); 2-phenyl-thiophene (1.2.6); 2-phenyl-furan (1.2.7); naphthalene (1.2.8); diphenylmethane (1.2.9); 4,5-diphenyl-1H-imidazole (1.2.10); 3-benzyl-pyridine (1.2.11); 4,5-diphenyl-oxazole (1.2.12); fluorene (1.2.13); 9*H*-carbazole (1.2.14); phenyl ether (1.2.15); 1*H*-indole (1.2.16); quinoline (1.2.17); phenanthrene (1.2.18); phenanthridine (1.2.19); [3,3']bipyridinyl (1.2.20); [4,4']bipyridinyl (1.2.21); 2-cyclohexyl-pyridine (1.2.22); biphenylene (1.2.23); 3-benzhydryl-pyridine (1.2.24); 2-phenyl-thiazole (1.2.25); 2-phenyl-oxazole (1.2.26); 5-phenyl-pyrimidine (1.2.27); 10*H*-phenothiazine (1.2.28); 2-phenyl-benzooxazole (1.2.29); 2-phenyl-benzothiazole (1.2.30); 2-phenyl-1*H*-benzolmidazole (1.2.31); and 10,11-dihydro-5*H*-dibenzo[b,f]azepine (1.2.32).

As a further illustration, it will be understood that, *e.g.*, a naphthyl moiety is a restricted biaryl moiety 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 a restricted biaryl moiety as defined herein, since a nitrogen heteroatom is also present, and the definition of restricted biaryl as used herein requires that the fused ring system be tricyclic or higher polycyclic where a heteroatom is present. The biphenyl moiety is an example of a discontinuous ring system that, accordingly, may be a meaning of Q^2 but may not be a meaning of Q^1.

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 discontinuous 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*.

(i) Embodiments of the present invention include those that are a compound of Formula (1.0.0) wherein Q^1 is phenyl or pyridyl; ∘∘ Q^2 is biphenyl, 3-phenyl-pyridine,

cyclohexyl-benzene, [2,2']bipyridinyl, bicyclohexyl, naphthalene, or biphenylene; ◇◇ j is 1; ◇◇ m is 0 or 1; ◇◇ n is 1; ◇◇ Z is a moiety selected from partial Formulas (1.1.1) through (1.1.3), (1.1.5), (1.1.6), and (1.1.10) through (1.1.14) where R^{7}_{A} is (a) –H, or $–CH_3$ substituted by 0-3 R^{10} where R^{10} is –F; or is $–CH_3$ substituted by 0 or 1 R^{10} where R^{10} is –CN, $–OR^{16}$ where R^{16} is $–CH_3$ or $–CH_2CH_3$, or $–NR^{16}R^{17}$ or $–NR^{16}C(=O)R^{17}$ where R^{16} and R^{17} are –H or $–CH_3$; (b) cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; or (c) phenyl or benzyl substituted by 0-2 R^{10} where R^{10} is –F, -Cl, $–CF_3$, $–CH_3$, $–CH_2OH$, $-SCH_3$, –CN, $-NO_2$, $–OR^{16}$, or $-NR^{16}R^{17}$ where R^{16} and R^{17} are -H, $–CH_3$, or $–CH_2CH_3$; ◇◇ R^9 is –H or $–CH_3$; ◇◇ W^1 is -O–; ◇◇ g is 1 and W^2 is –O– or $–CR^{29}R^{30}–$ where R^{29} and R^{30} are both –H, or g is 0 and W^2 is thus absent; ◇◇ Y is $=C(R^1_a)–$; ◇◇ R^1_a is –H, or –F; ◇◇ R^A and R^B are independently –H or $-CH_3$; or R^A and R^B are taken together to form a $-(C_3–C_7)$ cycloalkyl-apiro moiety; ◇◇ one of R^C and R^D is –H and the other is –H or $-CH_3$; ◇◇ R^1 and R^2 are –H, –F, or $-OCH_3$; ◇◇ R^3 is -H or $-CH_3$; and ◇◇ R^4, R^5 and R^6 are –H provided that R^5 and R^6 are not both –H at the same time, –F, –Cl, $-OCH_3$, –CN; $-NO_2$, or $-C(=O)R^3$ or $-C(=O)OR^3$ where R^3 is $–CH_3$; or R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1), (1.3.2), (1.3.3), (1.3.4), (1.3.11), (1.3.12), or (1.3.15).

(ii) Preferred embodiments of the type described in the paragraph immediately above are those wherein Z is a moiety of partial Formulas (1.1.1), (1.1.3), (1.1.6) or (1.1.10); R^9 is –H; R^A and R^B are both –H; R^C and R^D are both –H; R^3 is –H; R^4 is –H; R^5 is –H, –F, -Cl, –CN, $–OCH_3$, $–C(=O)CH_3$, or $–NO_2$; R^6 is –H, provided that R^5 and R^6 are not both –H at the same time, or –F; or R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1) or partial Formula (1.3.11) where R^{23} and R^{24} are both absent.

(iii) Further embodiments of the present invention comprise a compound of Formula (1.0.0) wherein Q^1 is phenyl or pyridyl; ◇◇ Q^2 is biphenyl, 3-phenyl-pyridine, cyclohexyl-benzene, [2,2']bipyridinyl, bicyclohexyl, naphthalene, or biphenylene; j is 1; ◇◇ m is 0 or 1; ◇◇ n is 1; ◇◇ Z is a moiety selected from partial Formulas (1.1.4) and (1.1.7) where R^{7}_{B} is tetrazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-3-on-5-yl, imidazol-2-yl, imidazol-4-yl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, oxazolyl, isoxazolyl, pyrrolyl, pyrazolyl, succinimidyl, pyrrolidonyl, thiazolyl, isothiazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, pyridyl, pyrazinyl, furanyl, tetrahydrofuranyl, thienyl, indolyl, 2,3-dihydrobenzofuranyl, benzothienyl, *1H*-indazolyl, benzimidazolyl, benzoxazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, 1,6-naphthyridinyl, or 1,8-

naphthyridinyl, all of which are independently substituted by 0 or 1 R^{14} where R^{14} is $-CH_3$, $-OR^{16}$ where R^{16} is –H or $-CH_3$, oxo (=O), $-C(=O)OR^{16}$ where R^{16} is —H or $-CH_3$, ◇◇ R^9 is -H or $-CH_3$; ◇◇ W^1 is -O–; ◇◇ g is 1 and W^2 is –O– or $-CR^{29}R^{30}-$ where R^{29} and R^{30} are both –H, or g is 0 and W^2 is thus absent; ◇◇ Y is $=C(R^1{}_a)-$; ◇◇ $R^1{}_a$ is –H; or –F; ◇◇ R^A and R^B are independently –H or $-CH_3$; or R^A and R^B are taken together to form a $-(C_3-C_7)$ cycloalkyl-spiro moiety; ◇◇ one of R^C and R^D is –H and the other is –H or $-CH_3$; ◇◇ R^1 and R^2 are –H, –F, or $-OCH_3$; ◇◇ R^3 is -H or $-CH_3$; and ◇◇ R^4, R^5 and R^6 are -H provided that R^5 and R^6 are not both –H at the same time, –F, –Cl, $-OCH_3$, –CN; $-NO_2$, or $-C(=O)R^3$ or $-C(=O)OR^3$ where R^3 is $-CH_3$; or R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1), (1.3.2), (1.3.3), (1.3.4), (1.3.11), (1.3.12), or (1.3.15).

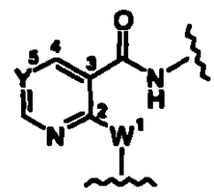
(iv) Preferred embodiments of the type described in the paragraph immediately above are those wherein R^9 is –H; R^A and R^B are both –H; R^C and R^D are both -H; R^3 is –H; R^4 is –H; R^5 is –H, –F, –Cl, –CN, $-OCH_3$, $-C(=O)CH_3$, or $-NO_2$; R^6 is –H, provided that R^5 and R^6 are not both –H at the same time, or –F; or R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1) or partial Formula (1.3.11) where R^{23} and R^{24} are both absent.

(v) Further embodiments of the present invention include a compound of Formula (1.0.0) wherein Q^1 is phenyl or pyridyl; ◇◇ Q^2 is biphenyl, 3-phenyl-pyridine, cyclohexyl-benzene, [2,2']bipyridinyl, bicyclohexyl, naphthalene, or biphenylene; ◇◇ j is 1; ◇◇ m is 0 or 1; ◇◇ n is 1; ◇◇ Z is a moiety of partial Formula (1.1.15) comprising phthalimid-1-yl, succinimid-1-yl, pyrrolid-2-on-1-yl, glutarimid-1-yl, piperid-2-on-1-yl, pyrid-2-on-1-yl, imidazolidin-2,4-dion-1-yl, 4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl, benzimidazolin-2-on-1-yl, norborn-5-en-2,3-dicarboximid-1-yl, imidazolidin-2-on-1-yl, thiazolidin-3-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,4-triazol-1-yl, pyrrolidin-1-yl, tetrazol-1-yl, piperidin-1-yl, piperazin-1-yl, 1*H*-pyrazolo[4,5-*e*]pyridin-7-on-2-yl, 1*H*-indazol-3-on-2-yl, 1*H*-benzimidazol-2-on-3-yl, or pyrrolo[3,4-*b*]pyridin-5,7-dion-6-yl; ◇◇ W^1 is -O–; ◇◇ g is 1 and W^2 is –O– or $-CR^{29}R^{30}-$ where R^{29} and R^{30} are both –H, or g is 0 and W^2 is thus absent; ◇◇ Y is $=C(R^1{}_a)-$; ◇◇ $R^1{}_a$ is –H; or –F; ◇◇ R^A and R^B are independently –H or $-CH_3$; or R^A and R^B are taken together to form a $-(C_3-C_7)$ cycloalkyl-spiro moiety; ◇◇ one of R^C and R^D is –H and the other is –H or $-CH_3$; ◇◇ R^1 and R^2 are –H, –F, or $-OCH_3$; ◇◇ R^3 is –H or $-CH_3$; and ◇◇ R^4, R^5 and R^6 are -H provided that R^5 and R^6 are not both –H at the same time, –F, –Cl, $-OCH_3$, –CN; $-NO_2$, or $-C(=O)R^3$ or $-C(=O)OR^3$ where R^3 is $-CH_3$; or R^5 and R^6 are taken together to form a

moiety of partial Formula (1.3.1), (1.3.2), (1.3.3), (1.3.4), (1.3.11), (1.3.12), or (1.3.15), where for partial Formulas (1.3.11) and (1.3.12) R^{23} and R^{24} are both absent.

(vi) Preferred embodiments of the type described in the paragraph immediately above are those wherein R^9 is –H; R^A and R^B are both –H; R^C and R^D are both –H; R^3 is –H; R^4 and R^5 are both –H, and R^6 is –F; or R^5 and R^6 are taken together to form a moiety of partial Formula (1.3.1) or (1.3.11).

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 $-[N\Rightarrow(O)_k]-$ where k is 0 or 1, and where the symbol $\Rightarrow(O)$ indicates a nitrogen heteroatom in the form of its N-oxide when k is 1. The N-containing heterocyclyl moieties which define $R^7{}_B$ and $R^7{}_C$, 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 $R^7{}_B$ and $R^7{}_C$.

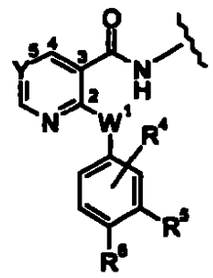
Where Y has the meaning of $-[N\Rightarrow(O)_k]-$ the compounds of the present invention are pyrimidines. The pyrimidine group of compounds of Formula (1.0.0) is a significant part of the scope of the present invention. It is preferred, nevertheless, that the compounds of Formula (1.0.0) have the Y 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; $-NO_2$; $-(C_1\text{-}C_4)$ alkyl; $-(C_2\text{-}C_4)$ alkynyl; fluorinated-$(C_1\text{-}C_3)$ alkyl; fluorinated-$(C_1\text{-}C_3)$ alkoxy; $-OR^{16}$; 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.

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.

5.1 Linkage (W^1) and the R^4–, R^5–, and R^6–Substituted Moiety Q^1

The nicotinamide core nucleus of the compounds of Formula (1.0.0) is characterized by the formation at the 2-position carbon atom of the pyridyl or pyrimidinyl ring of a linkage to a ring comprising the moiety Q^1. In preferred embodiments, the moiety Q^1 has the meaning of a phenyl ring which is *para*-substituted by a moiety R^6, *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 $-OR^{16}$, where R^{16} has the same meaning as defined above.

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 provided that they are not both –H at the same time. Accordingly, where the moiety Q^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 Q^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 provided that both are not –H at the same time; accordingly, a substituent will always be present at one or both of the positions occupied by R^5 and R^6. 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.

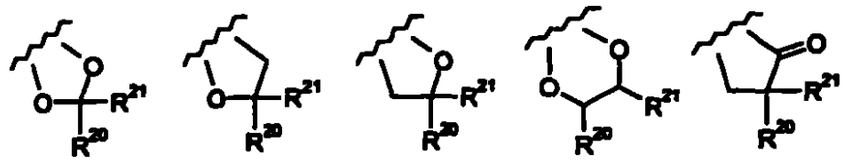
The medicinal chemist will appreciate that the choice of substituents from those described above will be influenced by the effect which such substituents have in turn on the physico-chemical properties of the overall molecules which result. The present state of the art provides the capability of quickly 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^6 is –H and R^5 is –F; $-OR^{16}$, *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 $-NO_2$, –CN, $-OCH_3$, or $-C(=O)CH_3$, and R^6 is –H.

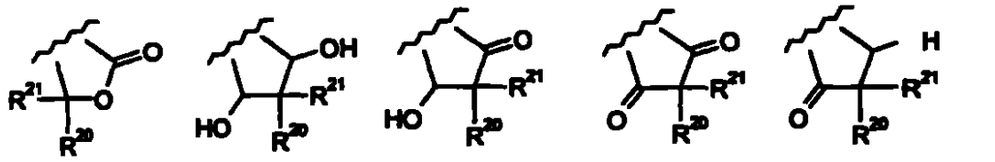
R^5 and R^6 may also be selected from substituents comprising $-(C_1-C_4)$ alkyl and $-(C_1-C_4)$ alkoxy wherein said alkyl and alkoxy are substituted with 0 to 3 substituents –F or -Cl; or 0 or 1 substituent (C_1-C_2) alkoxycarbonyl–; (C_1-C_2) alkylcarbonyl–; or (C_1-C_2) alkylcarbonyloxy–.

5.2.0 Q^1 is Phenyl and R^5 and R^6 Are Taken Together

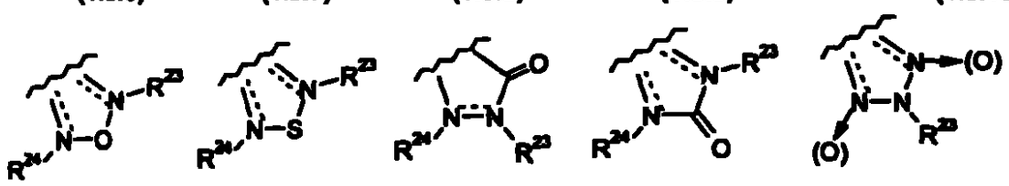
Where the moiety Q^1 has the preferred meaning of a phenyl ring, R^5 and R^6 may also be taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3.1) through (1.3.15):



(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)

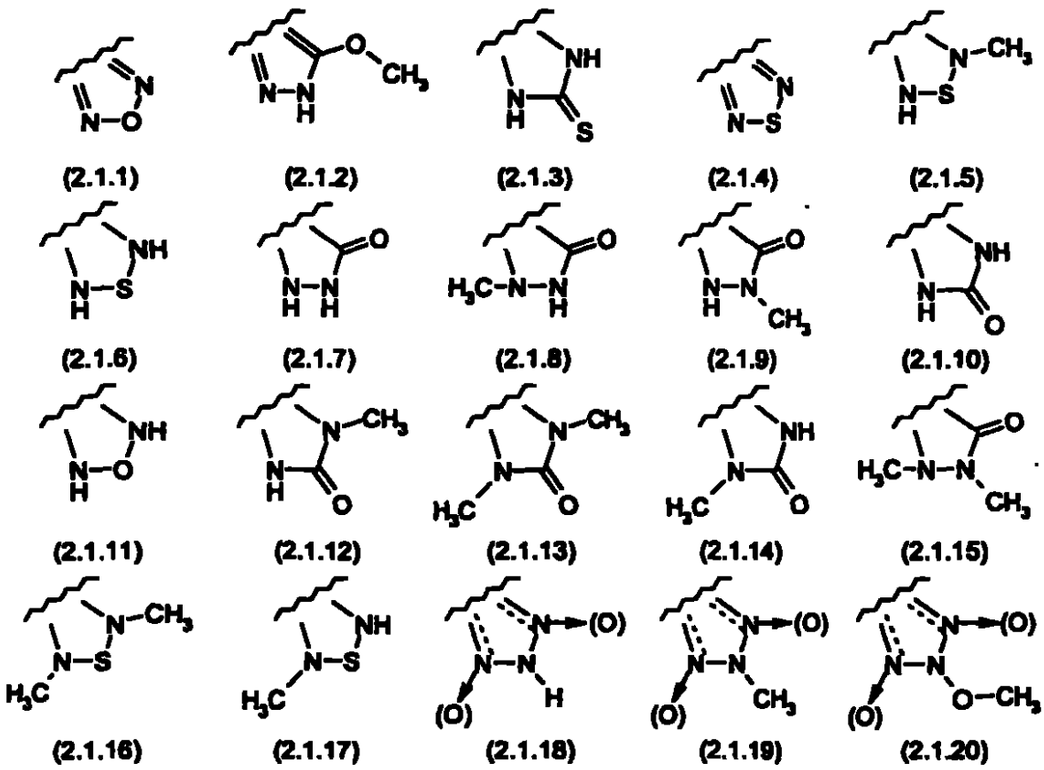


(1.3.11) (1.3.12) (1.3.13) (1.3.14) (1.3.15)

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 $-N(\Rightarrow O)_j-$ where j is 0 or 1, as in Formula (1.0.0).

Where the moiety Q^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 (1.3.2) forms a 1,4-benzodioxan group.

Where the moiety Q^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 (1.3.9) through (1.3.13) and R^{23} and R^{24} are as defined, benzofurazan, benzothiofurazan, 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)

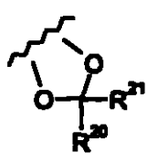
(2.1.11) (2.1.12) (2.1.13) (2.1.14) (2.1.15)

(2.1.16) (2.1.17) (2.1.18) (2.1.19) (2.1.20)

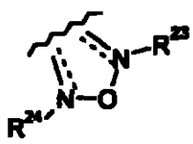
wherein the dashed line ---- in partial Formulas (2.1.18), (2.1.19), and (2.1.20) represents a double bond where no oxygen atom is attached to the corresponding nitrogen atom, and represents a single bond where an oxygen atom is attached to said corresponding nitrogen atom.

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.

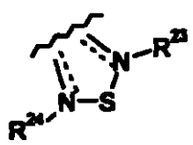
Preferred embodiments of the present invention result directly from the definition of R^5 and R^6 as taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3.1), (1.3.11), (1.3.12), and (1.3.15):



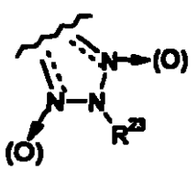
(1.3.1)



(1.3.11)

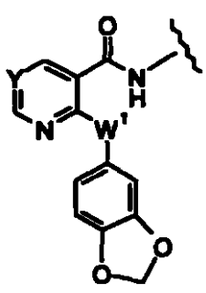


(1.3.12)

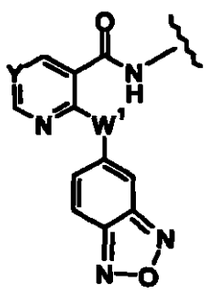


(1.3.15)

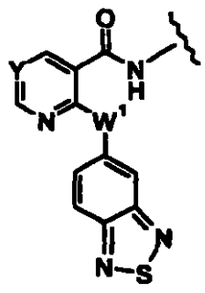
Accordingly, there further results moieties of partial Formulas (1.0.15) through (1.0.18):



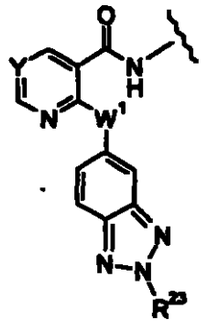
(1.0.15)



(1.0.16)



(1.0.17)



(1.0.18)

where R^{23} is –H or $–CH_3$; and W^1 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 (1.0.15) through (1.0.18) above.

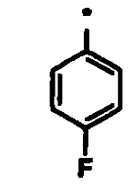
5.2.1 Q^1 Is Other Than Phenyl

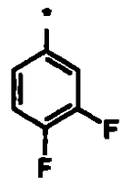
In addition to those embodiments of the present invention where Q^1 has the preferred meaning of phenyl, the present invention has also been defined above as being concerned with a compound of Formula (1.0.0) wherein Q^1 has the meaning defined above as a moiety comprising a saturated or unsaturated carbon ring system that is a 3- to 7-membered monocyclic, or that is a 7- to 12-membered, fused polycyclic; 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. The present invention is further concerned with a compound of Formula (1.0.0) wherein Q^1 comprises especially a member selected from the group consisting of 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 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 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.

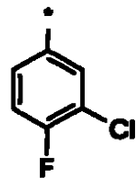
5.2.2 Representative Subgeneric Q^1 Moieties

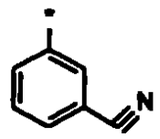
The present invention is still further concerned especially with a compound of Formula (1.0.0) wherein particularly Q^1 and the substituents R^4, R^5, and R^6 are selected in

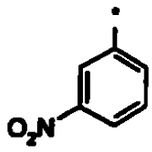
such a way that the left-hand terminus of said compound of Formula (1.0.0) is represented by the following partial Formulas (2.0.1) through (2.0.72):

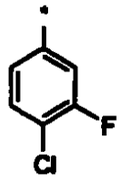

(2.0.1)

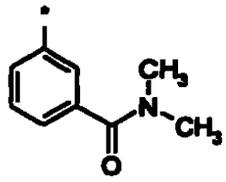

(2.0.2)

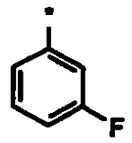

(2.0.3)

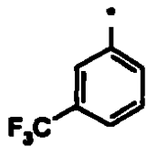

(2.0.4)

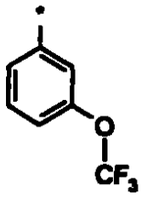

(2.0.5)

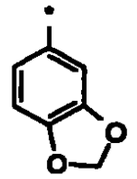

(2.0.6)

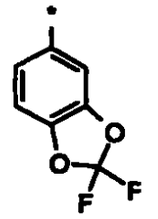

(2.0.7)

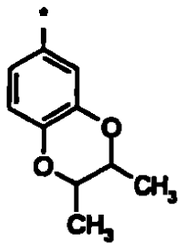

(2.0.8)

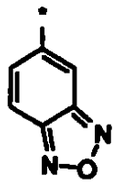

(2.0.9)

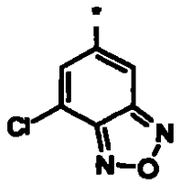

(2.0.10)

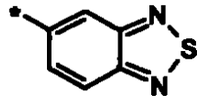

(2.0.11)

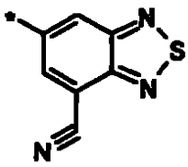

(2.0.12)

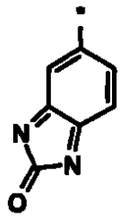

(2.0.13)

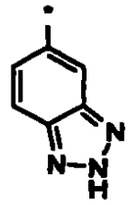

(2.0.14)

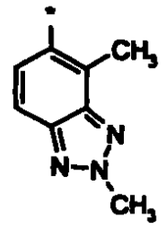

(2.0.15)

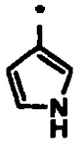

(2.0.16)

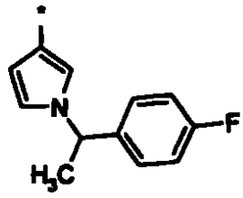

(2.0.17)

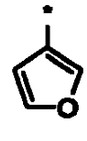

(2.0.18)

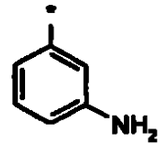

(2.0.19)

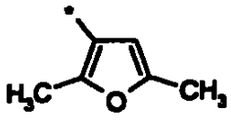

(2.0.20)


(2.0.21)

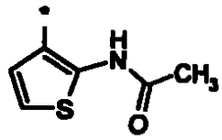

(2.0.22)


(2.0.23)

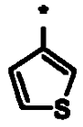

(2.0.24)



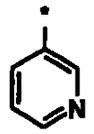
(2.0.25)



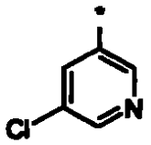
(2.0.26)



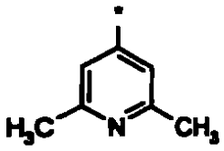
(2.0.27)



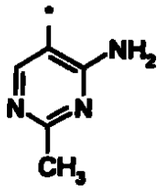
(2.0.28)



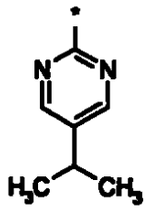
(2.0.29)



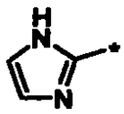
(2.0.30)



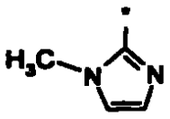
(2.0.31)



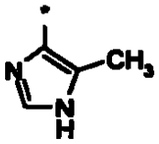
(2.0.32)



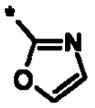
(2.0.33)



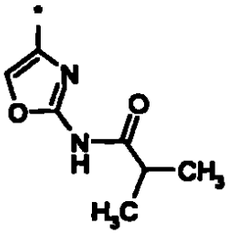
(2.0.34)



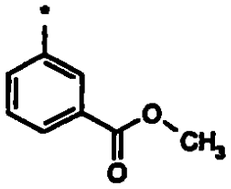
(2.0.35)



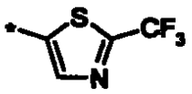
(2.0.36)



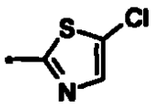
(2.0.37)



(2.0.38)



(2.0.39)



(2.0.40)



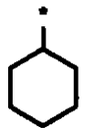
(2.0.41)



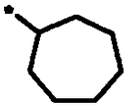
(2.0.42)



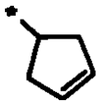
(2.0.43)



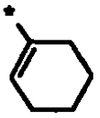
(2.0.44)



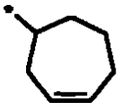
(2.0.45)



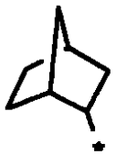
(2.0.46)



(2.0.47)



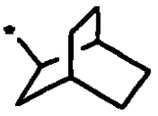
(2.0.48)



(2.0.49)



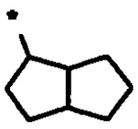
(2.0.50)



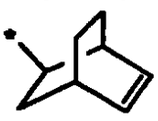
(2.0.51)



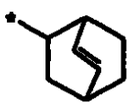
(2.0.52)



(2.0.53)



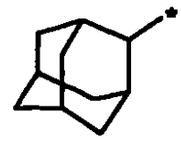
(2.0.54)

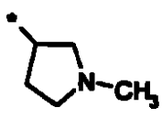


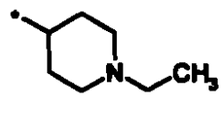
(2.0.55)

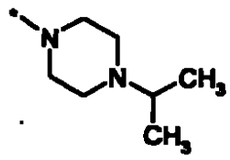


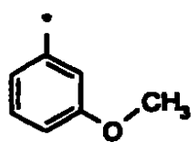
(2.0.56)

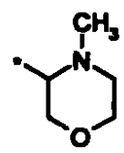

(2.0.57)

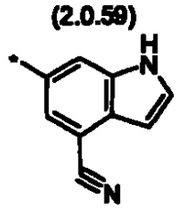

(2.0.58)

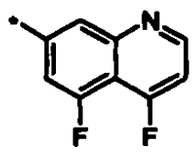

(2.0.59)

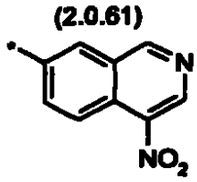

(2.0.60)

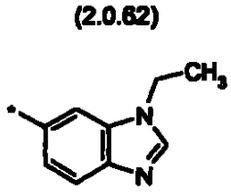

(2.0.61)

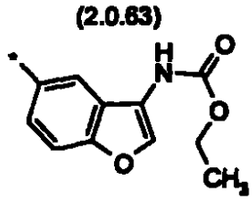

(2.0.62)

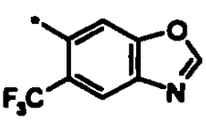

(2.0.63)

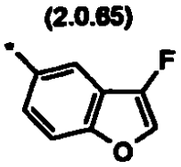

(2.0.64)

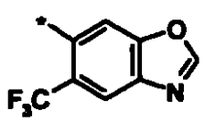

(2.0.65)

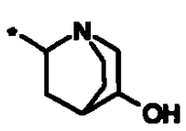

(2.0.66)

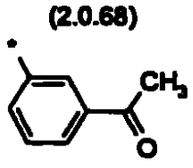

(2.0.67)


(2.0.68)


(2.0.69)


(2.0.70)

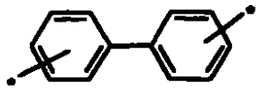

(2.0.71)


(2.0.72)

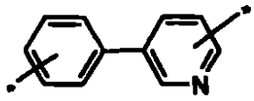
5.3.0 The Q^2 Moiety

The moiety Q^2 is one of the key features of the compounds of Formula (1.0.0) and is referred to herein as a biaryl moiety. As used herein the term "biaryl" includes not only such traditional biaryl groups as biphenyl, but fused variants thereof, naphthyl-containing and heteroatom-containing variants thereof, and benzhydryl variants thereof. The biaryl groups that define the moiety Q^2 thus comprise, *inter alia*, biphenyl (1.2.1); 3-phenyl-pyridine (1.2.2); cyclohexyl-benzene (1.2.3); [2,2']bipyridinyl (1.2.4); bicyclohexyl (1.2.5); 2-phenyl-thiophene (1.2.6); 2-phenyl-furan (1.2.7); naphthalene (1.2.8); diphenylmethane (1.2.9); 4,5-diphenyl-1H-imidazole (1.2.10); 3-benzyl-pyridine (1.2.11); 4,5-diphenyl-oxazole (1.2.12); fluorene (1.2.13); 9*H*-carbazole (1.2.14); phenyl ether (1.2.15); 1*H*-indole (1.2.16); quinoline (1.2.17); phenanthrene (1.2.18); phenanthridine (1.2.19); [3,3']bipyridinyl (1.2.20); [4,4']bipyridinyl (1.2.21); 2-cyclohexyl-pyridine (1.2.22); biphenylene (1.2.23); 3-benzhydryl-pyridine (1.2.24); 2-phenyl-thiazole (1.2.25); 2-phenyl-oxazole (1.2.26); 5-phenyl-pyrimidine (1.2.27); 10*H*-phenothiazine (1.2.28); 2-phenyl-benzooxazole (1.2.29); 2-phenyl-benzothiazole (1.2.30); 2-phenyl-1*H*-benzoimidazole (1.2.31); and 10,11-dihydro-5*H*-dibenzo[b,f]azepine (1.2.32). The parenthetical numerical references with the above-recited meanings of the moiety Q^2 correspond to structural formulas, which may be represented by partial Formulas (1.2.1)

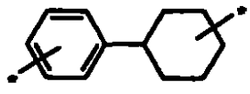
through (1.2.32) below. It should be noted that the points of attachment on either side of the biaryl moiety have been illustrated as being non-specific so that said partial Formulas may embrace variations within each moiety that are considered to be inside the scope of the present invention:



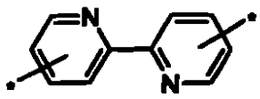
(1.2.1)



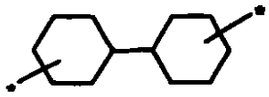
(1.2.2)



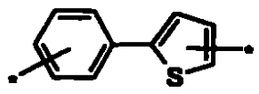
(1.2.3)



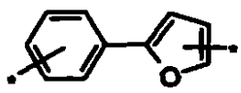
(1.2.4)



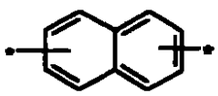
(1.2.5)



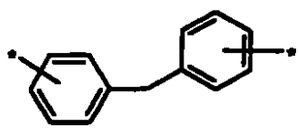
(1.2.6)



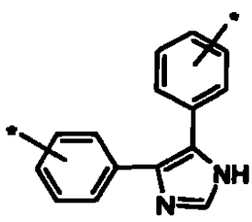
(1.2.7)



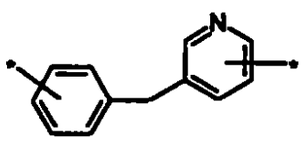
(1.2.8)



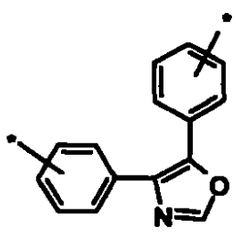
(1.2.9)



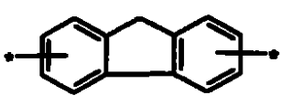
(1.2.10)



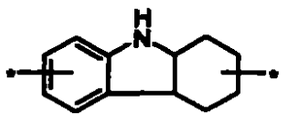
(1.2.11)



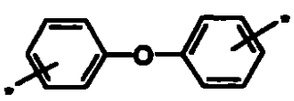
(1.2.12)



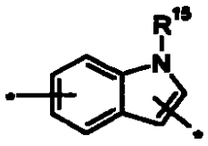
(1.2.13)



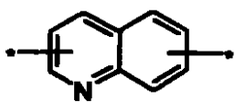
(1.2.14)



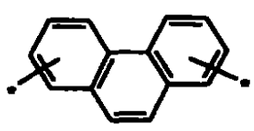
(1.2.15)



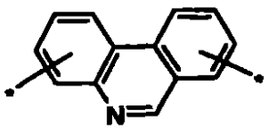
(1.2.16)



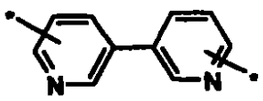
(1.2.17)



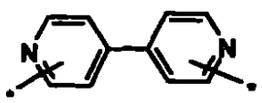
(1.2.18)



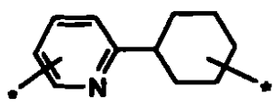
(1.2.19)



(1.2.20)



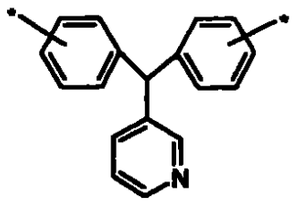
(1.2.21)



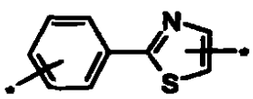
(1.2.22)



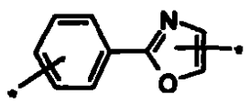
(1.2.23)



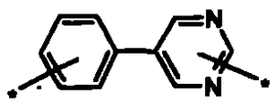
(1.2.24)



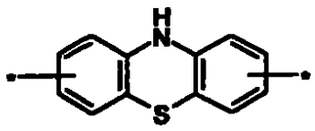
(1.2.25)



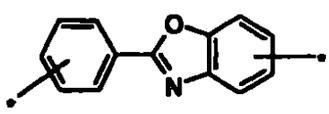
(1.2.26)



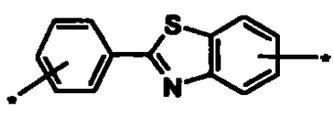
(1.2.27)



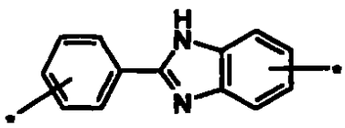
(1.2.28)



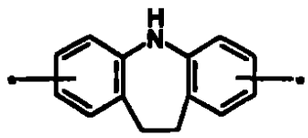
(1.2.29)



(1.2.30)



(1.2.31)



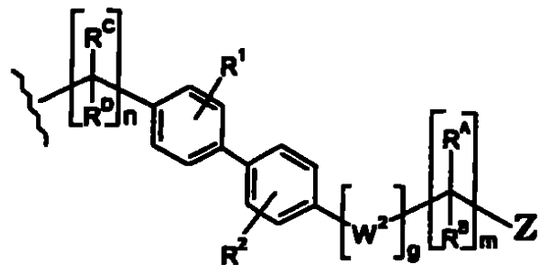
(1.2.32)

The above-illustrated groups of partial Formulas (1.2.1) through (1.2.32) which define the moiety Q^2 are optionally substituted by R^1 and R^2, where R^1 and R^2 may individually or together appear on any ring or rings comprising a moiety or component part of partial Formulas (1.2.1) through (1.2.32) which define Q^2. R^1 and R^2 are each a member independently selected from the group consisting of –H; –F; –Cl; $-R^{12}$; $-OR^{12}$; $-S(=O)_pR^{12}$; $-C(=O)OR^{12}$; $-OC(=O)R^{12}$; =O (oxo); –CN; $-NO_2$; $-C(=O)NR^{12}R^{13}$; $-OC(=O)NR^{15}R^{12}$; $-NR^{14}C(=O)NR^{15}R^{12}$; $-NR^{14}C(=NR^{14})NR^{15}R^{12}$; $-NR^{14}C(=NCN)NR^{15}R^{12}$; $-NR^{14}C(=N-NO_2)NR^{15}R^{12}$; $-C(=NR^{14})NR^{15}R^{12}$; $-OC(=NR^{14})NR^{15}R^{12}$; $-OC(=N-NO_2)NR^{15}R^{12}$; $-NR^{15}R^{12}$; $-CH_2NR^{15}R^{12}$; $-NR^{14}C(=O)R^{12}$; $-NR^{14}C(=O)OR^{12}$; $=NOR^{12}$; $-NR^{14}S(=O)_pR^{13}$; and $-S(=O)_pNR^{12}R^{13}$; where R^{12}, R^{13}, R^{14}, and R^{15} have the same meanings as defined above.

5.3.1 Q^2 Is Biphenyl Substituted by R^1 and R^2

The left-hand-side of a compound of Formula (1.0.0) has a nicotinamide nucleus with an ether, thioether or sulfonyl linkage to a substituted phenyl group; whereas, the right-hand-side of a compound of Formula (1.0.0) comprises preferred embodiments where Q^2 has the preferred meaning of biphenyl that is substituted by substituents R^1 and R^2. Preferably, only a single substituent, R^1 or R^2 is present on each ring, and the biphenyl group is substituted in

the 4-position by the moiety containing the substituents R^A, R^B, and Z. This preferred right-hand-side of the compound of Formula (1.0.0) may be represented by Formula (1.0.4):

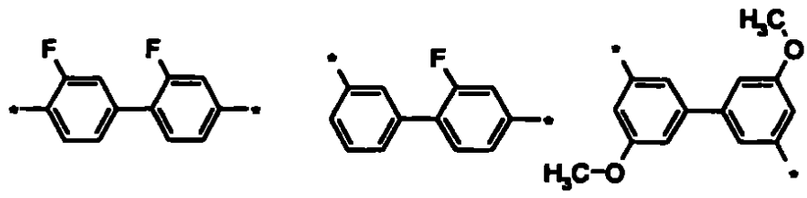


(1.0.4)

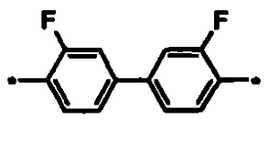
Where R^1 and/or R^2 is –H, preferably there will be no substituent at any position attached to the remainder of the left-hand side of the molecule of Formula (1.0.0). Other embodiments which are preferred are those compounds of the present invention which have a substituent, especially a substituent at the 2-position of either one or both of the phenyl groups that comprise the biphenyl moiety. 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.

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 inhibitory activity. 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.

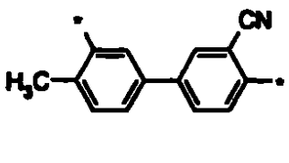
Accordingly, embodiments of the present invention in which the moiety Q^2 is substituted by R^1 and optionally R^2 include those represented by partial Formulas (2.6.1) through (2.6.12):



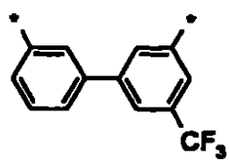
(2.6.1) (2.6.2) (2.6.3)



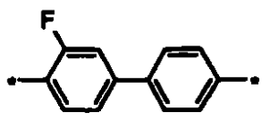
(2.6.4)



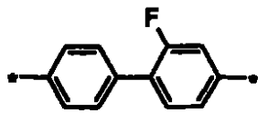
(2.6.5)



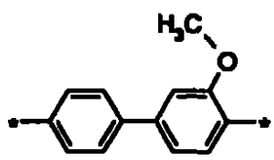
(2.6.6)



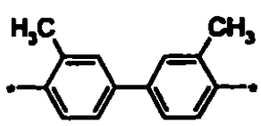
(2.6.7)



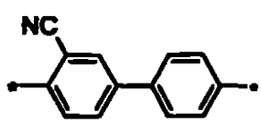
(2.6.8)



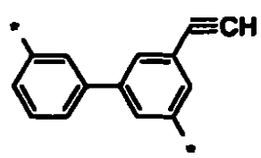
(2.6.9)



(2.6.10)



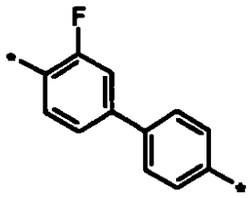
(2.6.11)



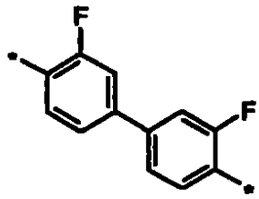
(2.6.12)

5.3.2 Q^2 in Specific Embodiments

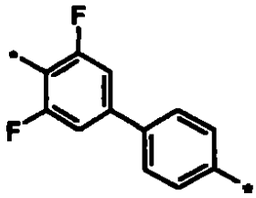
The present invention is also further concerned especially with a compound of Formula (1.0.0) wherein particularly Q^2 and the substituents R^1 and R^2 are selected in such a way that this portion of the right-hand terminus of said compound of Formula (1.0.0) is represented by the following partial Formulas (3.0.1) through (3.0.29) set out below.



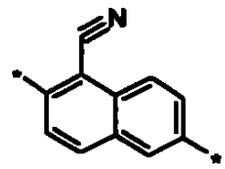
(3.0.1)



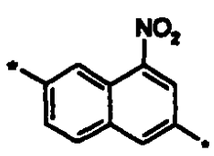
(3.0.2)



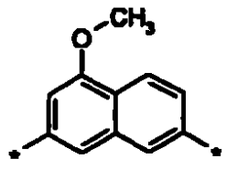
(3.0.3)



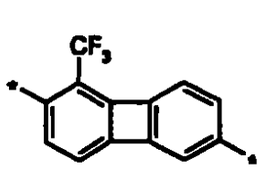
(3.0.4)



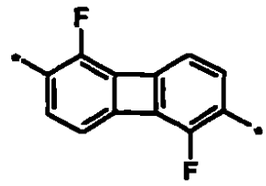
(3.0.5)



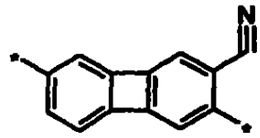
(3.0.6)



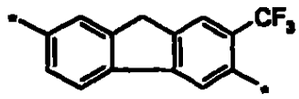
(3.0.7)



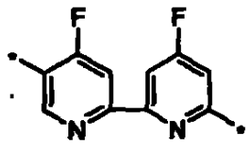
(3.0.8)



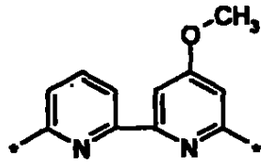
(3.0.9)



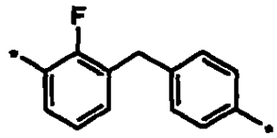
(3.0.10)



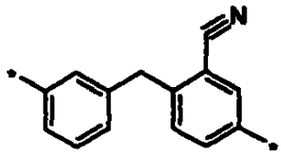
(3.0.11)



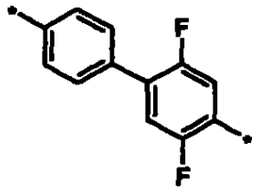
(3.0.12)



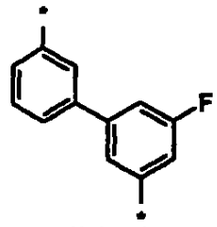
(3.0.13)



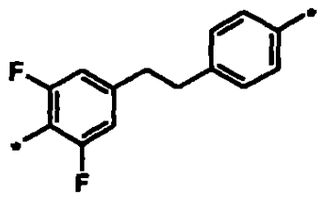
(3.0.14)



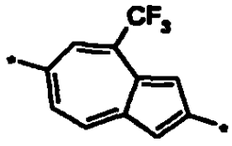
(3.0.15)



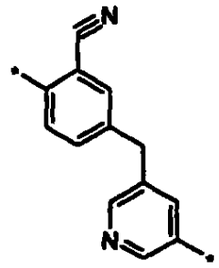
(3.0.16)



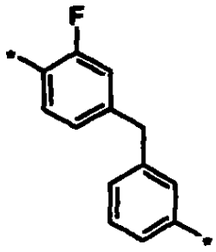
(3.0.17)



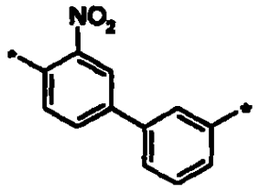
(3.0.18)



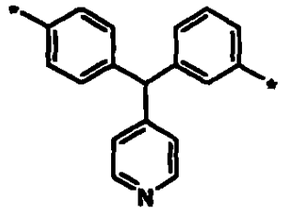
(3.0.19)



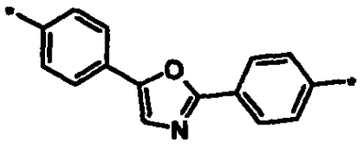
(3.0.20)



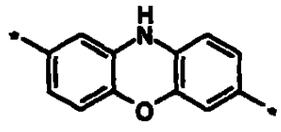
(3.0.21)



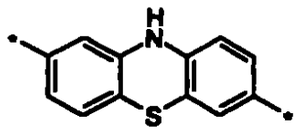
(3.0.22)



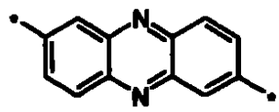
(3.0.23)



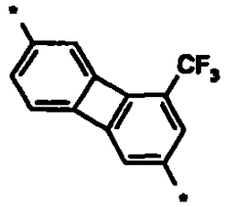
(3.0.24)



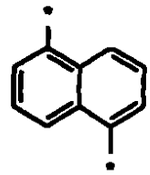
(3.0.25)



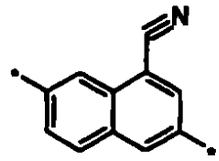
(3.0.26)



(3.0.27)



(3.0.28)



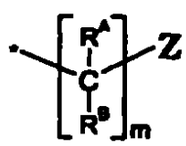
(3.0.29)

5.4.0 The Moiety $[W^2]_g$

The moiety $[W^2]_g$ in Formula (1.0.0) provides for the possibility of ether, thioether, amine, and carbon-linked derivatives of the compounds of the present invention. Thus, in the case where g is 1, W^2 is -O-; $-S(=O)_t-$, where t is 0, 1, or 2; $-N(R^3)-$ where R^3 has the same meaning as defined herein, or $-CR^{29}R^{30}-$. Where W^2 has the meaning of $-N(R^3)-$, R^3 is preferably -H and a simple amino linkage results. Where W^2 has the meaning of $-S(=O)_t-$, t is preferably 0, and a simple thioether linkage results. In the case where g is 1, it is most preferred that W^2 have the meaning of -O-, whereby a simple ether linkage results. In the case where g is 1, it is also a meaning of W^2 that it is a carbon moiety $-CR^{29}R^{30}-$ where R^{29} and R^{30} are each selected from -H; -F; $-CF_3$; $-(C_1-C_3)$ alkyl; $-(C_3-C_6)$ cycloalkyl; phenyl; benzyl; and pyridyl; wherein said alkyl, cycloalkyl, phenyl, benzyl, and pyridyl moieties are each independently substituted with 0 to 3 substituents R^{10}, where R^{10} has the same meaning as defined herein. In the case where W^2 has the meaning of $-CR^{29}R^{30}-$, it is preferred that R^{29} and R^{30} both have the meaning of -H, whereby a simple methylene linkage results.

5.4.1 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 Z, R^A, and R^B, which may be represented by partial Formula (1.1.15):

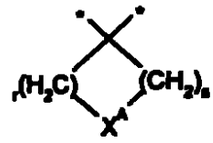


(1.1.15)

where m is 0, 1, or 2. 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,

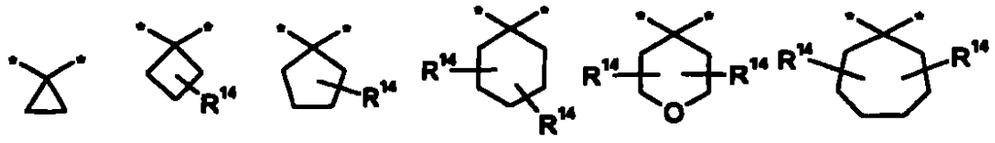
and R^A and R^B are preferably each a member independently selected from the group consisting of -H; and (C_1-C_4) alkyl.

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):

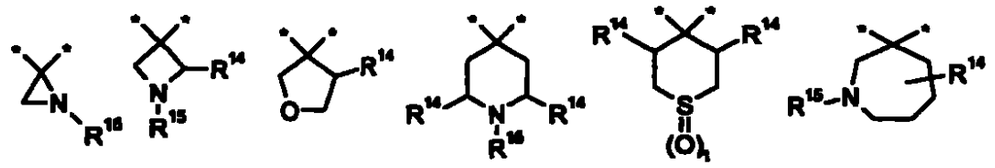


(1.2.0)

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^{12} 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 (1.5.1) through (1.5.12):



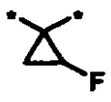
(1.5.1) (1.5.2) (1.5.3) (1.5.4) (1.5.5) (1.5.6)



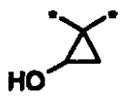
(1.5.7) (1.5.8) (1.5.9) (1.5.10) (1.5.11) (1.5.12)

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

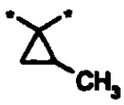
Preferred meanings of the R^{14} substituent include -F; -Cl; =O; -OH; $-CH_3$; $-CH_2OH$; $-CH(CH_3)OH$; $-C(CH_3)_2OH$; $-OCH_3$; -C(=O)OH; $-C(=O)NH_2$; $-NH_2$; $-NHCH(CH_3)_2$; $-NHC(=O)CH_3$; $-NHC(=O)OCH_2CH_3$; $-NHS(=O)_2CH_3$; and $-S(=O)_2NH_2$, resulting in moieties such as those of partial Formulas (3.1.1) through (3.1.34):



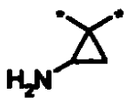
(3.1.1)



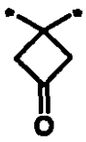
(3.1.2)



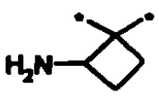
(3.1.3)



(3.1.4)



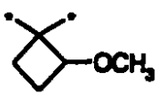
(3.1.5)



(3.1.6)



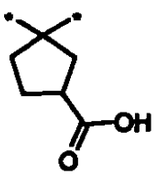
(3.1.7)



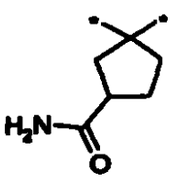
(3.1.8)



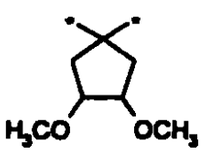
(3.1.9)



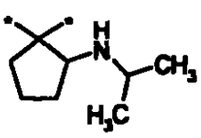
(3.1.10)



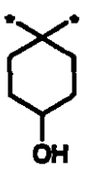
(3.1.11)



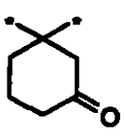
(3.1.12)



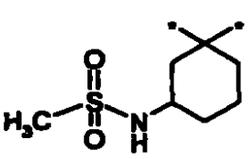
(3.1.13)



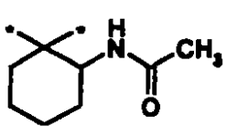
(3.1.14)



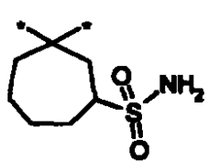
(3.1.15)



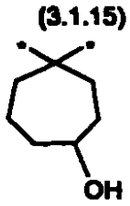
(3.1.16)



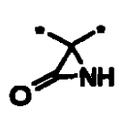
(3.1.17)



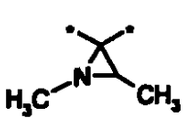
(3.1.18)



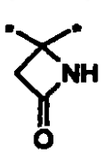
(3.1.19)



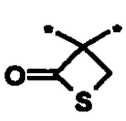
(3.1.20)



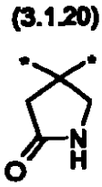
(3.1.21)



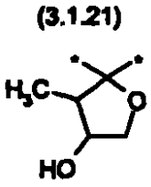
(3.1.22)



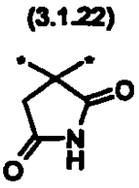
(3.1.23)



(3.1.24)



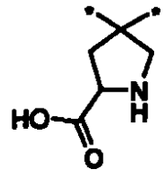
(3.1.25)

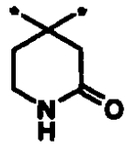


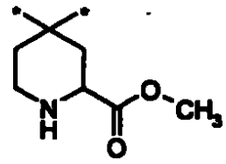
(3.1.26)

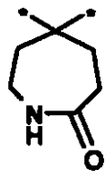


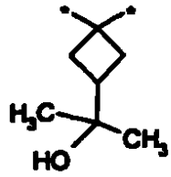
(3.1.27)

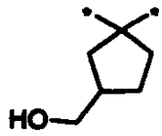

(3.1.28)

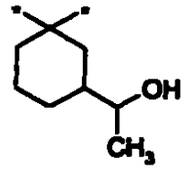

(3.1.29)


(3.1.30)


(3.1.31)


(3.1.32)


(3.1.33)


(3.1.34)

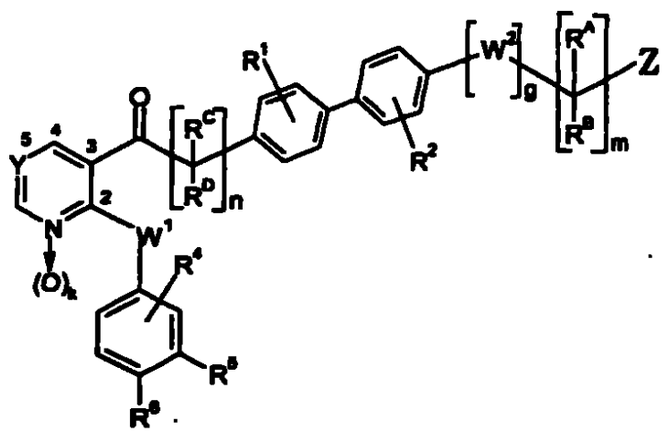
5.4.2 The R^C and R^D Substituents

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.

5.5 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. The nitrogen atom substituent R^3 is preferably selected from –H; –(C_1-C_3) alkyl; and –(C_1-C_3) 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 Q^1 has the preferred meaning of phenyl; Q^2 has the preferred meaning of biphenyl; 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. This ketone structure of the compounds of Formula (1.0.0) is represented by Formula (1.0.7):



(1.0.7)

where all of the substituents and components thereof, *i.e.*, Z; W^1; W^2; Y; g, 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 where j is 1 and the compounds are nicotinamides in structure.

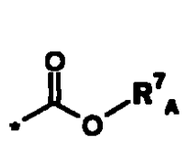
5.6.0 Z Is a Moiety of Partial Formulas (1.1.1) – (1.1.15)

Z is a member selected from the group of moieties defined by partial Formulas (1.1.1) through (1.1.15) illustrated further above. The moieties of partial Formulas (1.1.1) through (1.1.5) which define the Z 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 Z 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. The moieties of partial Formulas (1.1.10) through (1.1.15) which define the Z group are typically but not necessarily inverse amides and their mimetics, 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 bioisostereic 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, alcohol, and inverse amide moieties.

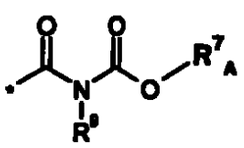
Accordingly, Z is a member selected from the group of moieties defined by partial Formulas (1.1.1) through (1.1.15), and said moieties include substituents R^{7A}, R^{7B}, and R^{7C}, as well as R^8, R^9, R^{16}, and R^{17}, and in the case of partial Formula (1.1.15) the moiety consists of a nitrogen-containing heterocyclic ring system. All of the moieties of partial Formulas (1.1.1) through (1.1.15) are attached to the remaining portion of Formula (1.0.0).

5.6.1 Z is a Moiety of Partial Formulas (1.1.1), (1.1.2), or (1.1.3)

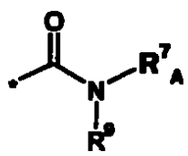
Embodiments of the present invention wherein the definition of the Z group is illustrated by partial Formulas (1.1.1); (1.1.2); and (1.1.3), are as follows:



(1.1.1)



(1.1.2)



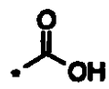
(1.1.3)

One of a number of preferred moieties for defining the Z group is that of partial Formula (1.1.1) where R^7_A 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.

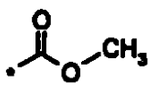
R^{10} is an optional substituent of the moieties that define R^7_A, and there may be up to three such substituents when present. The meaning of the R^{10} substituent includes phenyl or pyridyl where said phenyl or pyridyl is in turn optionally substituted by up to 3 substituents R^{11} where R^{11} 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 $–CH_3$.

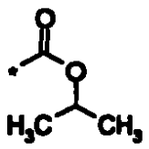
These and other preferred embodiments of the compounds of Formula (1.0.0) comprising the moieties of partial Formula (1.1.1) based on the preferred meanings of R^7_A as described above, include, *inter alia*, the following groups illustrated by partial Formulas (3.5.1) through (3.5.15):



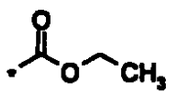
(3.5.1)



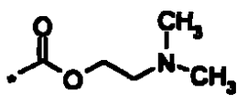
(3.5.2)



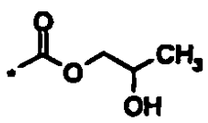
(3.5.3)



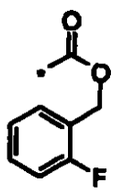
(3.5.4)



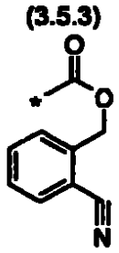
(3.5.5)



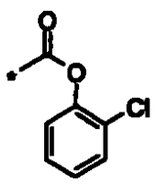
(3.5.6)



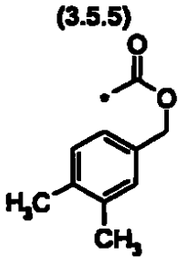
(3.5.7)



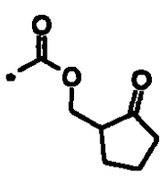
(3.5.8)



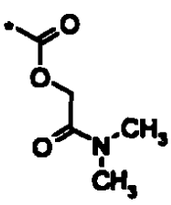
(3.5.9)



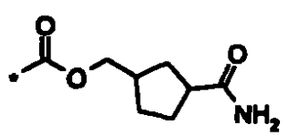
(3.5.10)



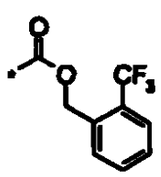
(3.5.11)



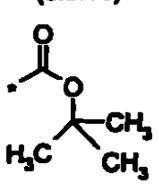
(3.5.12)



(3.5.13)



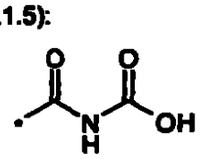
(3.5.14)



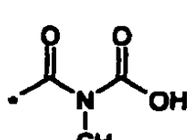
(3.5.15)

The Z 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^{16}; –C(=O)R^{16}; –OR^{16}; -(C_1-C_2) alkyl–OR^{16}; or –(C_1-C_2) alkyl–C(=O)OR^{16}; where R^{16} is –H or -(C_1-C_4) alkyl. R^{16} is preferably –H or –CH_3.

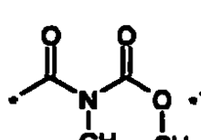
Accordingly, embodiments of the present invention where the Z group is represented by partial Formula (1.1.2) may be illustrated as follows by partial Formulas (4.1.1) through (4.1.5):



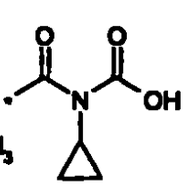
(4.1.1)



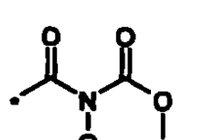
(4.1.2)



(4.1.3)

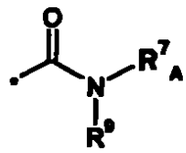


(4.1.4)



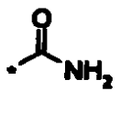
(4.1.5)

Those embodiments wherein the definition of Z is that of an amide group, are illustrated by partial Formula (1.1.3):

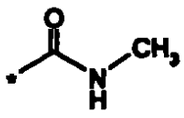


(1.1.3)

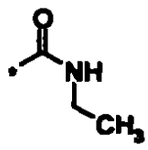
These and other preferred embodiments of the compounds of Formula (1.0.0) comprising moieties of partial Formula (1.1.3), based on the meanings of R^7_A and R^9 described above, include, *inter alia*, the following groups illustrated by partial Formulas (4.5.1) through (4.5.20):



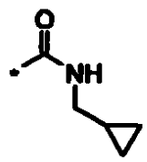
(4.5.1)



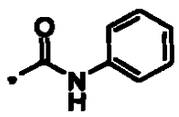
(4.5.2)



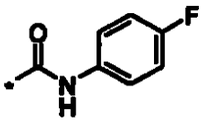
(4.5.3)



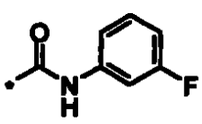
(4.5.4)



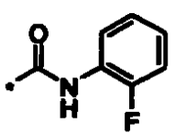
(4.5.5)



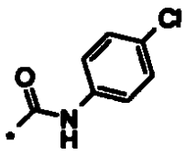
(4.5.6)



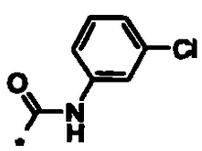
(4.5.7)



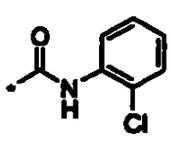
(4.5.8)



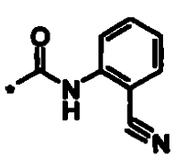
(4.5.9)



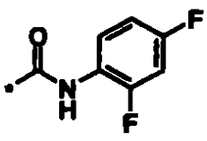
(4.5.10)



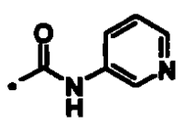
(4.5.11)



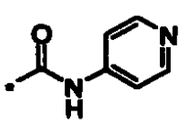
(4.5.12)



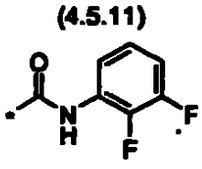
(4.5.13)



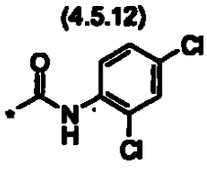
(4.5.14)



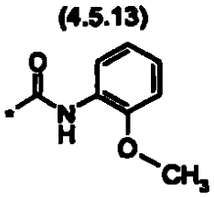
(4.5.15)



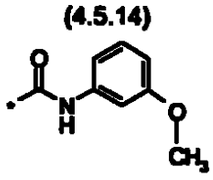
(4.5.16)



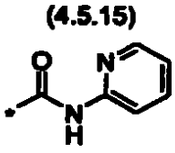
(4.5.17)



(4.5.18)



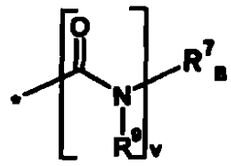
(4.5.19)



(4.5.20)

<u>5.6.2 Z Is a Moiety of Partial Formula (1.1.4)</u>

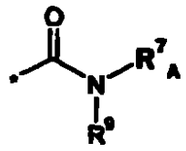
Preferred embodiments of the present invention also comprise those compounds of Formula (1.0.0) wherein terminal moiety Z falls within the scope of partial Formula (1.1.4), *i.e.*, embodiments of this type are encompassed within the scope of the Z moiety when it has the meaning of partial Formula (1.1.4):



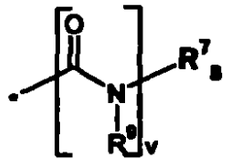
(1.1.4)

wherein R^7_B 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; perathiazinyl; 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^7_B 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_A 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^7_B and the R^7_A 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^7_B and the R^7_A 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}.

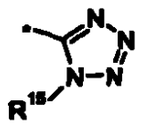
The sub-substituent R^{12} comprises –F; –Cl; $-CO_2R^{18}$; $-OR^{18}$; –CN; $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$; $-NR^{18}C(=O)OR^{19}$; $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, where p is 1 or 2, preferably 2; $-(C_1-C_4)$ alkyl, preferably $-CH_3$; and $-(C_1-C_4)$ alkoxy, where R^{12} has the meaning of $-OR^{16}$ above and R^{16} 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 (1.3.1) through (1.3.20) 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^9 and R^{15}, both of which are attached only to nitrogen atoms in any of the meanings of the moiety $\mathcal{Z}$. The substituent R^{15} is attached only to a nitrogen atom that is an integral, component part of any heterocyclic moiety that may be defined *via* the R^7 substituent of partial Formula (1.1.4) and

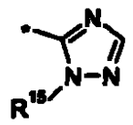
in particular with reference to the more specific heterocyclic moieties of partial Formulas (1.3.1) through (1.3.20), shown above as well as further below. The R^9 substituent, on the other hand, is attached only to a nitrogen atom that in turn is attached to, but is not an integral, component part of any of the heterocyclic moieties that is defined by partial Formulas (1.1.2), (1.1.3), and (1.1.5). The R^{15} 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 Z 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 (1.4.1) through (1.4.28):



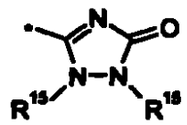
tetrazol-5-yl

(1.4.1)



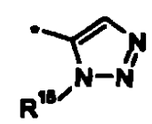
1,2,4-triazol-3-yl

(1.4.2)



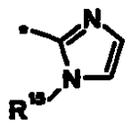
1,2,4-triazol-3-on-5-yl

(1.4.3)



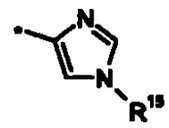
1,2,3-triazol-5-yl

(1.4.4)



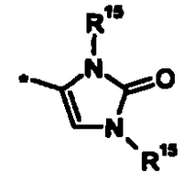
imidazol-2-yl

(1.4.5)



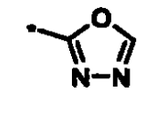
imidazol-4-yl

(1.4.6)



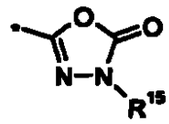
imidazolidin-2-on-4-yl

(1.4.7)



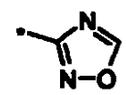
1,3,4-oxadiazolyl

(1.4.8)



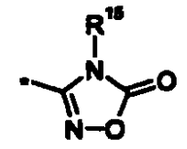
1,3,4-oxadiazol-2-on-5-yl

(1.4.9)



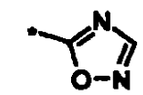
1,2,4-oxadiazol-3-yl

(1.4.10)



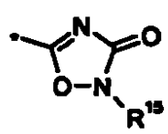
1,2,4-oxadiazol-5-on-3-yl

(1.4.11)



1,2,4-oxadiazol-5-yl

(1.4.12)



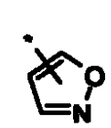
1,2,4-oxadiazol-3-on-5-yl

(1.4.13)



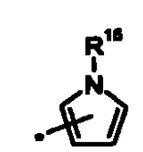
oxazolyl

(1.4.14)



isoxazolyl

(1.4.15)



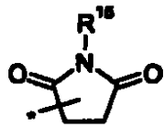
pyrrolyl

(1.4.16)



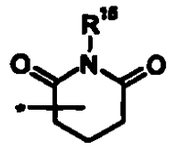
pyrazolyl

(1.4.17)



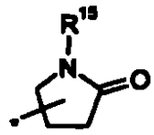
succinimidyl

(1.4.18)



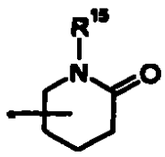
glutarimidyl

(1.4.19)



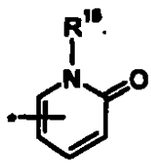
pyrrolidonyl

(1.4.20)



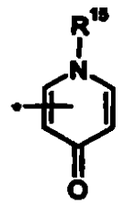
2-piperidonyl

(1.4.21)



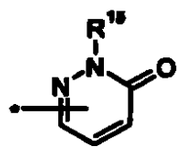
2-pyridonyl

(1.4.22)



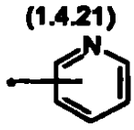
4-pyridonyl

(1.4.23)



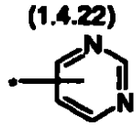
pyridazin-3-onyl

(1.4.24)



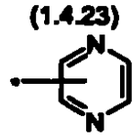
pyridyl

(1.4.25)



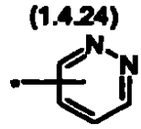
pyrimidinyl

(1.4.26)



pyrazinyl

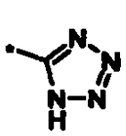
(1.4.27)



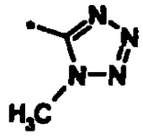
pyridazinyl

(1.4.28)

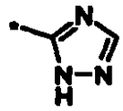
In order to provide another demonstration of preferred embodiments of the compounds of Formula (1.0.0) with reference to the Z group where it is a moiety of partial Formula (1.1.4) and v is 0 or 1, and R^7_B is a monocyclic heterocyclic group, there is set out below the groups consisting of partial Formulas (4.8.1) through (4.8.80) from which the Z moiety is selected in such preferred embodiments:



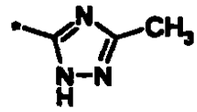
(4.8.1)



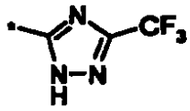
(4.8.2)



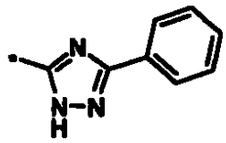
(4.8.3)



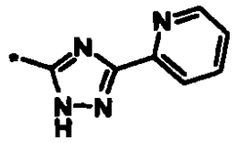
(4.8.4)



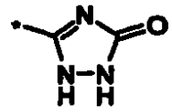
(4.8.5)



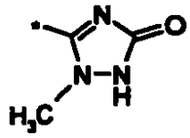
(4.8.6)



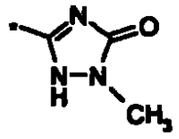
(4.8.7)



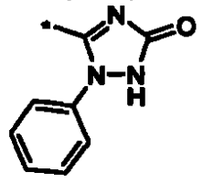
(4.8.8)



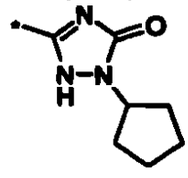
(4.8.9)



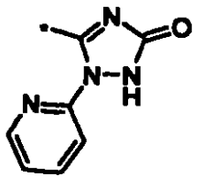
(4.8.10)



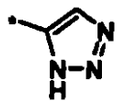
(4.8.11)



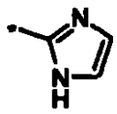
(4.8.12)



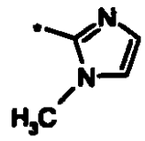
(4.8.13)



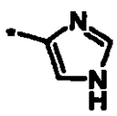
(4.8.14)



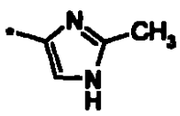
(4.8.15)



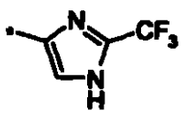
(4.8.16)



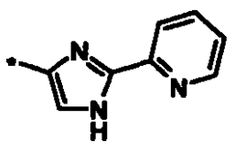
(4.8.17)



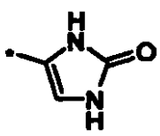
(4.8.18)



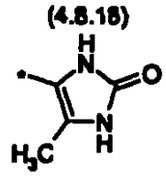
(4.8.19)



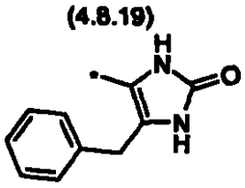
(4.8.20)



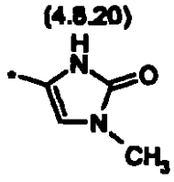
(4.8.21)



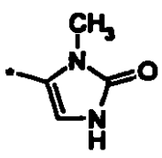
(4.8.22)



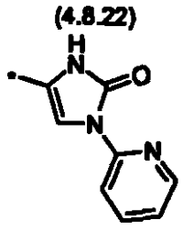
(4.8.23)



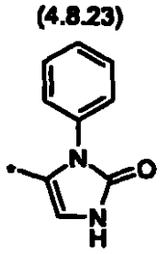
(4.8.24)



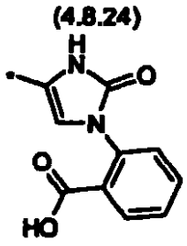
(4.8.25)



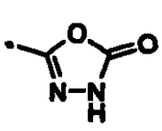
(4.8.26)



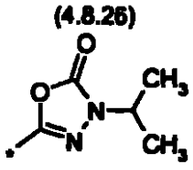
(4.8.27)



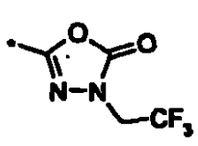
(4.8.28)



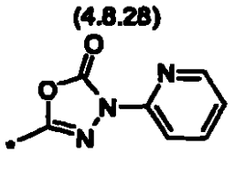
(4.8.29)



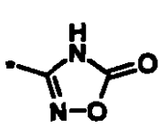
(4.8.30)



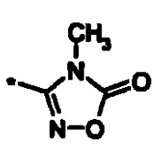
(4.8.31)



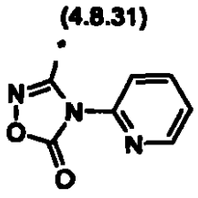
(4.8.32)



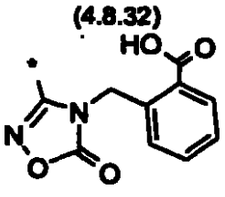
(4.8.33)



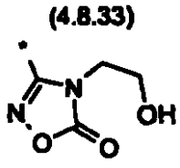
(4.8.34)



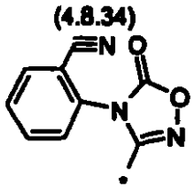
(4.8.35)



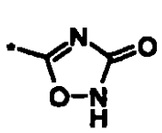
(4.8.36)



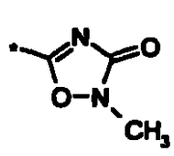
(4.8.37)



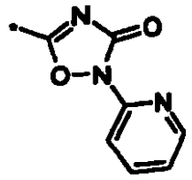
(4.8.38)



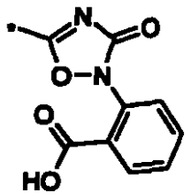
(4.8.39)



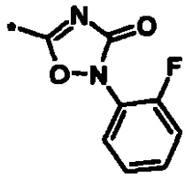
(4.8.40)



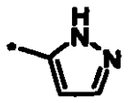
(4.8.41)



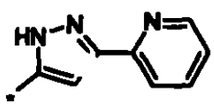
(4.8.42)



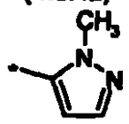
(4.8.43)



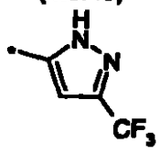
(4.8.44)



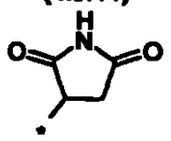
(4.8.45)



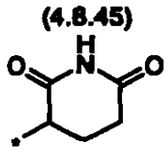
(4.8.46)



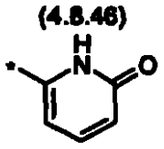
(4.8.47)



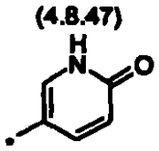
(4.8.48)



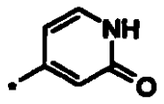
(4.8.49)



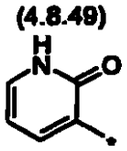
(4.8.50)



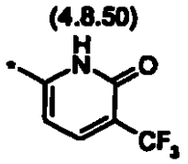
(4.8.51)



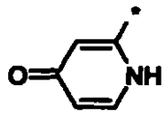
(4.8.52)



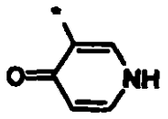
(4.8.53)



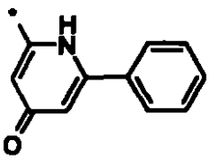
(4.8.54)



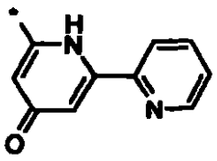
(4.8.55)



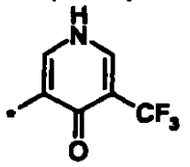
(4.8.56)



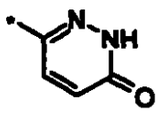
(4.8.57)



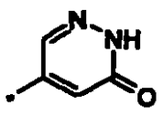
(4.8.58)



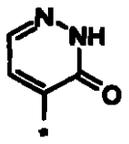
(4.8.59)



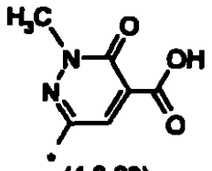
(4.8.60)



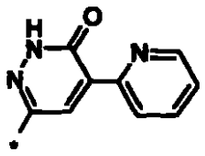
(4.8.61)



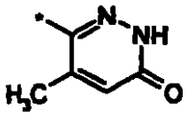
(4.8.62)



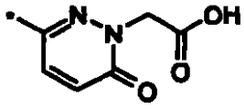
(4.8.63)



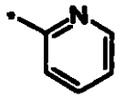
(4.8.64)



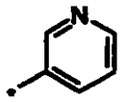
(4.8.65)



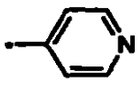
(4.8.66)



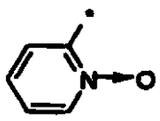
(4.8.67)



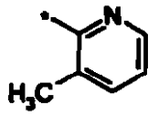
(4.8.68)



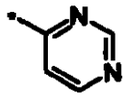
(4.8.69)



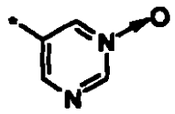
(4.8.70)



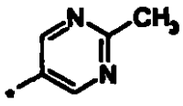
(4.8.71)



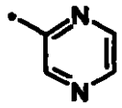
(4.8.72)



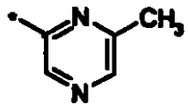
(4.8.73)



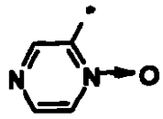
(4.8.74)



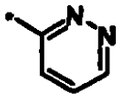
(4.8.75)



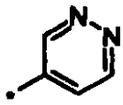
(4.8.76)



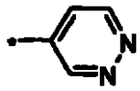
(4.8.77)



(4.8.78)



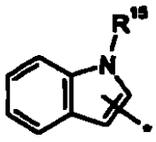
(4.8.79)



(4.8.80)

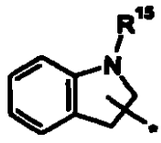
Preferred embodiments of the present invention where the group Z is a moiety of partial Formula (1.1.4) and v is 0 or 1, also include those wherein the moiety R^7_a is a bicyclic heterocyclic group selected from the group consisting of indolyl; indolinyl; isoindolinyl; benzo[*b*]furanyl; 2,3-dihydrobenzofuranyl; 1,3-dihydroisobenzofuranyl; 2*H*-1-benzopyranyl; 2-*H*-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.

In order to provide a still further demonstration of preferred embodiments of the compounds of Formula (1.0.0) with reference to the Z group where it is a moiety of partial Formula (1.1.4), v is 0 or 1, and R^7_a 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 Z moiety is selected in such preferred embodiments:



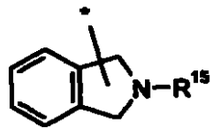
indolyl

(5.0.1)



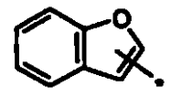
indolinyl

(5.0.2)



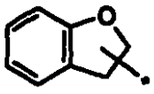
isoindolinyl

(5.0.3)



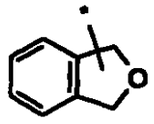
benzo[*b*]furanyl

(5.0.4)



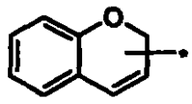
2,3-dihydrobenzo-furanyl

(5.0.5)



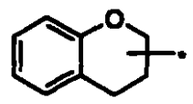
1,3-dihydroisobenzo-furanyl; phthalanyl

(5.0.6)



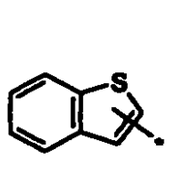
2*H*-1-benzopyranyl

(5.0.7)



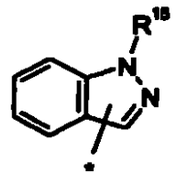
chromanyl

(5.0.8)



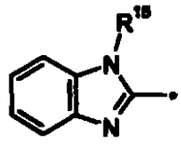
benzothienyl

(5.0.9)



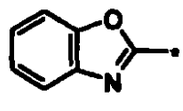
1*H*-indazolyl

(5.0.10)



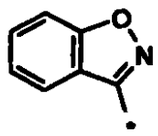
benzimidazolyl

(5.0.11)



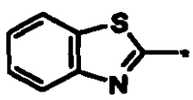
benzoxazolyl

(5.0.12)



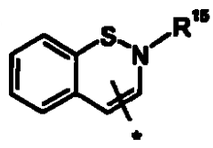
benzisoxazolyl

(5.0.13)



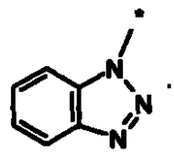
benzothiazolyl

(5.0.14)



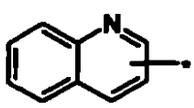
2H-1,2-benzothiazinyl

(5.0.15)



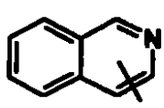
benzotriazolyl

(5.0.16)



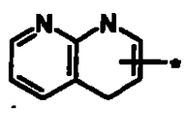
quinolinyl

(5.0.17)



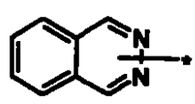
isoquinolinyl

(5.0.18)



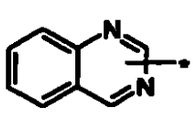
1,8-naphthyridinyl

(5.0.19)



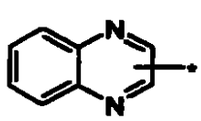
phthalazinyl

(5.0.20)



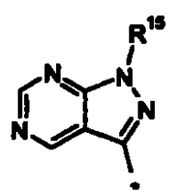
quinazolinyl

(5.0.21)



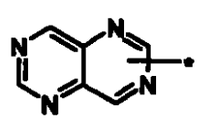
quinoxalinyl

(5.0.22)



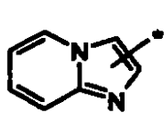
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(5.0.23)



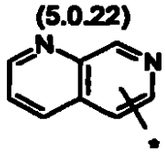
pyrimido[5,4-*d*]-pyrimidinyl

(5.0.24)



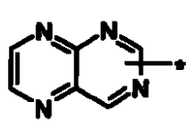
imidazo-[1,2-*a*]-pyridinyl

(5.0.25)



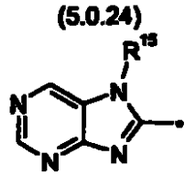
pyridopyridinyl

(5.0.26)



pteridinyl

(5.0.27)



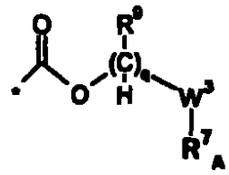
1*H*-purinyl

(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.

5.6.3 Z Is a Moiety of Partial Formula (1.1.5)

There are further embodiments of the compounds of Formula (1.0.0) in which the Z moiety comprises a group falling within the scope of partial Formula (1.1.5):

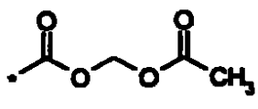


(1.1.5)

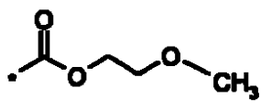
wherein q is 1, 2, or 3, provided that where q is 2 or 3, R^9 has the meaning of –H in at least one instance, or two instances, respectively; W^3 is –O–; –N(R^9)–; or –OC(=O)– where R^9 has the same meaning as defined above; and R^7_A has the same meaning as defined above.

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_A is one of the preferred moieties already described above.

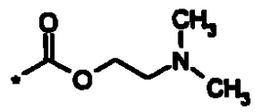
Representative embodiments of the compounds of Formula (1.0.0) in which the Z moiety falls within the scope of partial Formula (1.1.5) are those illustrated by partial Formulas (6.0.1) through (6.0.6):



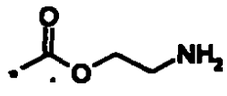
(6.0.1)



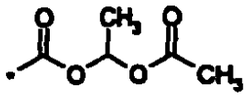
(6.0.2)



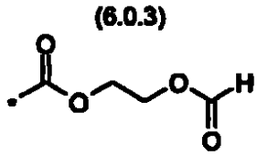
(6.0.3)



(6.0.4)



(6.0.5)



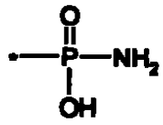
(6.0.6)

5.6.4 Z Is Other Than a Carboxylic Acid

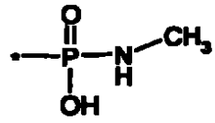
Embodiments of the compounds of Formula (1.0.0) include those wherein the Z moiety is other than a carboxylic acid and is, instead, a phosphorus or sulfur acid or a derivative thereof. There are a significant number of such derivatives from which the Z moiety may be selected, and they include the following: $-O-P(=O)(OH)_2$ (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); $-O-S(=O)_2OH$ (sulfuric); $–S(=O)_2OH$ (sulfonic); $–S(=O)_2NHR^{28}$ or

-NHS(=O)$_2$R^{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)$_2$R^{25}; -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^{25}; -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^{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.

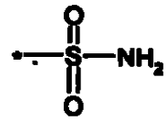
Preferred embodiments of the compounds of Formula (1.0.0) wherein Z is a phosphorus or sulfur acid or a derivative thereof, are those wherein Z is -P(=O)(OH)NHR^{25} (substituted phosphoramido); –S(=O)$_2$NHR^{25} or -NHS(=O)$_2$R^{25} (sulfonamido); or -C(=O)NHS(=O)$_2$R^{25} (acylsulfonamido); where R^{25} and R^{25} 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):



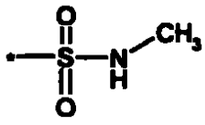
(6.5.1)



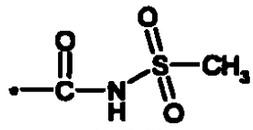
(6.5.2)



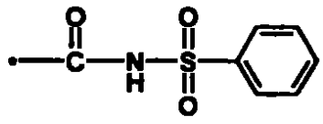
(6.5.3)



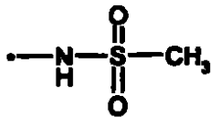
(6.5.4)



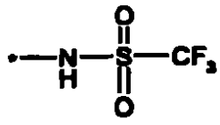
(6.5.5)



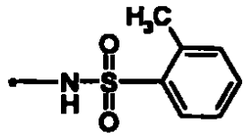
(6.5.6)



(6.5.7)



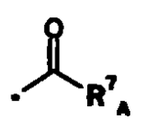
(6.5.8)



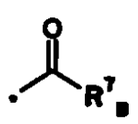
(6.5.9)

5.6.5 Z is a Moiety of Partial Formulas (1.1.6) through (1.1.9)

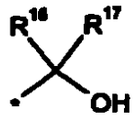
In other embodiments of the compounds of Formula (1.0.0), the terminal group Z is a moiety that is a member selected from the group consisting of partial Formulas (1.1.6), (1.1.7), (1.1.8), and (1.1.9):



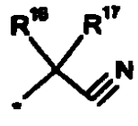
(1.1.6)



(1.1.7)



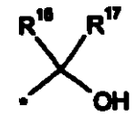
(1.1.8)



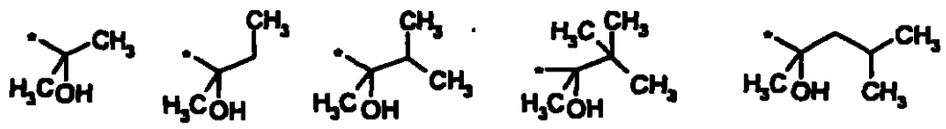
(1.1.9)

where " * " indicates the point of attachment of the moiety of partial Formula (1.1.6), (1.1.7), (1.1.8), or (1.1.9) to the remaining portion of a compound of Formula (1.0.0); and R^{7}_{A} and R^{7}_{B} both have the same meanings as described above. R^{16} and R^{17} also have the same meanings as described above, *i.e.*, each is 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.

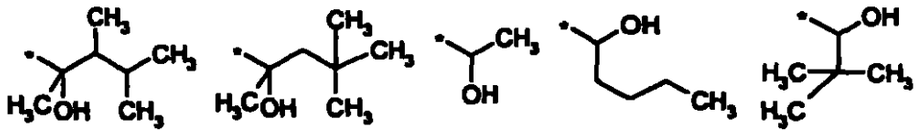
In order to illustrate further meanings of Z that fall within the scope of partial Formulas (1.1.6), (1.1.7), (1.1.8), and (1.1.9), there are depicted below moieties of partial Formulas (3.3.1) through (3.3.15) that represent different meanings that fall within the scope partial Formula (1.1.8):



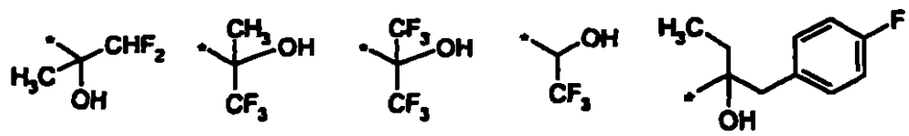
(1.1.8)



(3.3.1) (3.3.2) (3.3.3) (3.3.4) (3.3.5)

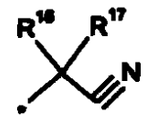


(3.3.6) (3.3.7) (3.3.8) (3.3.9) (3.3.10)

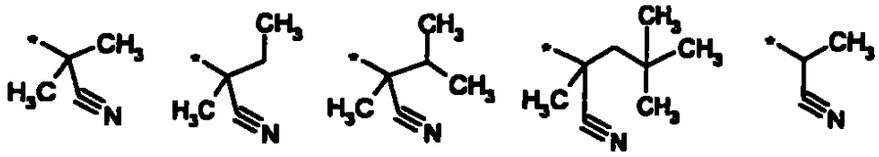


(3.3.11) (3.3.12) (3.3.13) (3.3.14) (3.3.15)

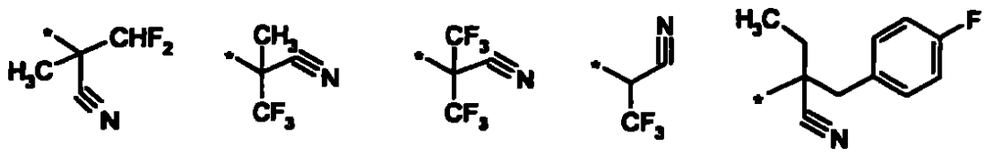
Further meanings of Z are those that fall within the scope of partial Formula (1.1.9), in which a nitrile group, –C≡N, replaces for the hydroxyl group of partial Formula (1.1.8). Accordingly, there are depicted below moieties of partial Formulas (3.8.1) through (3.8.10) that represent different meanings that fall within the scope partial Formula (1.1.9):



(1.1.9)

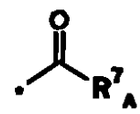


(3.8.1) (3.8.2) (3.8.3) (3.8.4) (3.8.5)



(3.8.6) (3.8.7) (3.8.8) (3.8.9) (3.8.10)

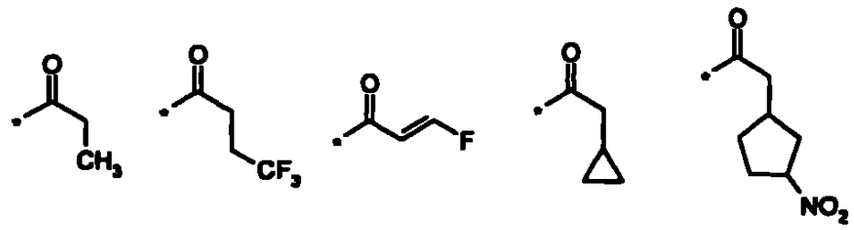
In order to illustrate additional meanings of Z that fall within the scope of partial Formulas (1.1.6), (1.1.7), (1.1.8), and (1.1.9), there are depicted below moieties of partial Formulas (3.9.1) through (3.9.9) that represent different meanings that fall within the scope partial Formula (1.1.6):



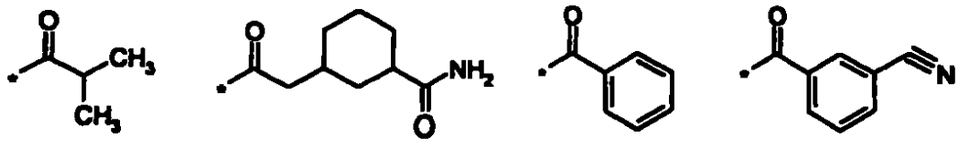
(1.1.6)

where R^7_A is selected from –H; –(C_1-C_8) alkyl; –(C_2-C_8) alkenyl; or –(C_2-C_8) alkynyl; substituted by 0 to 3 substituents R^{10}. Preferably, R^7_A is –H. R^7_A may also be –(C_1-C_4) alkyl which is unsubstituted or is substituted by 3 of –F, or 1 of R^{10} which is preferably –F; -Cl; -CF_3; –NO_2; –CN; -C(=O)$NR^{16}R^{17}$; or –$NR^{16}R^{17}$. R^7_A is also selected from -CH_2)$_u$-(C_3-C_7) cycloalkyl where u is 0, 1 or 2 substituted by 0 to 3 substituents R^{10}, which has the same preferred meanings as defined above. R^7_A is further selected from phenyl or benzyl substituted by 0 to 3 substituents R^{10} which has the same preferred meanings as defined above.

Accordingly, preferred embodiments of Z that fall within the scope of partial Formula (1.1.6) are illustrated in partial Formulas (3.9.1) through (3.9.9):



(3.9.1) (3.9.2) (3.9.3) (3.9.4) (3.9.5)



(3.9.6) (3.9.7) (3.9.8) (3.9.9)

5.6.6 Z Is a Moiety of Partial Formulas (1.1.10) through (1.1.15)

Z is also a member selected from the group of moieties defined by partial Formulas (1.1.10) through (1.1.15) illustrated further above. In the moieties of partial Formulas (1.1.10) through (1.1.14) the meaning of Z consists of a terminal group R^7_C attached to the remaining portion of Formula (1.0.0) *via* what may be termed a linking group that comprises the remaining portion of said partial Formulas (1.1.10) through (1.1.14). R^7_C in turn has the meaning of a member independently selected from the group consisting of the meanings of R^7_A and the meanings of R^7_B defined above.

The linking group of partial Formula (1.1.10) comprises a carbamoyl or reverse amide structure which may be represented by the formula: —N(R^9)—C(=O)—, which is read from left-to-right. The substituent R^9 most frequently has the meaning of –H, so that said reverse amide linking group may be represented as follows, reading from left-to-right: —NHC(=O)—. Accordingly, where Z has the meaning of partial Formula (1.1.10), preferred embodiments of the compounds of Formula (1.0.0) will have the following right-hand terminus: -NHC(=O)-R^7_C.

Z may also be selected as the moiety defined by partial Formula (1.1.10). Where both occurrences of the substituent R^9 have the meaning of –H as is preferred, then the resulting embodiments of the compounds of Formula (1.0.0) will have the following right-hand terminus: —NHC(=O)NH—R^7_C. Similarly, where Z is selected as the moiety defined by partial Formula (1.1.12) and the substituent R^9 has the meaning of –H, then the resulting

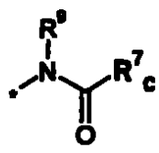
embodiments of the compounds of Formula (1.0.0) will have the following right-hand terminus: —NHC(=O)O—R^7_c.

Z may also be selected as a moiety defined by partial Formulas (1.1.13) or (1.1.14), and in the case where the substituent R^9 has the preferred meaning of –H, the resulting embodiments of the compounds of Formula (1.0.0) will have the following right-hand termini: —$NHS(=O)_2$—R^7_c and —NH—R^7_c. The meanings of Z defined by partial Formulas (1.1.13) and (1.1.14) are not, however, as preferred as the meanings of Z defined by partial Formulas (1.1.10) and (1.1.11), and sometimes (1.1.12).

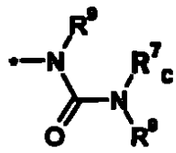
Finally, Z may be selected as the moiety defined by partial Formula (1.1.6) in which a nitrogen atom of a heterocycle is attached by a direct bond to the remaining portion of a compound of Formula (1.0.0). In some preferred embodiments, a carbon atom in said nitrogen-containing heterocycle that is α to said nitrogen atom may be carbonyl, *i.e.*, oxo (=O) substituted. Preferred meanings of Z in the compounds of Formula (1.0.0) are those defined by partial Formulas (1.1.10) and (1.1.15).

5.6.7 Z is a Moiety of Partial Formulas (1.1.10) through (1.1.14)

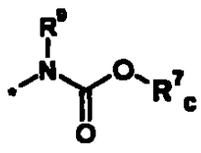
Embodiments of the present invention wherein the definition of the Z group is illustrated by partial Formulas (1.1.10); (1.1.11); (1.1.12); (1.1.13); and (1.1.14), are as follows:



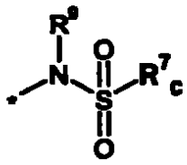
(1.1.10)



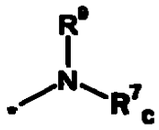
(1.1.11)



(1.1.12)



(1.1.13)



(1.1.14)

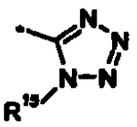
One of a number of preferred moieties for defining the Z group is that of partial Formula (1.1.10) where R^7_c has the meaning of –(C_1-C_4) alkyl, preferably methyl, ethyl, *n*-propyl, *iso*-propyl, or *tert*-butyl; cyclo(C_3-C_6) alkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, all of which are attached directly or *via* a methylene bridge; phenyl; benzyl; or a heterocycle, preferably pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl; tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, indazolyl, indolyl, isoindolyl, benzimidazolyl, benzisoxazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, 1,6-naphthyridinyl, 1,8-naphthyridinyl, or quinazolinyl.

R^9 is a substituent appearing in each of the Z moieties represented by partial Formulas (1.1.10); (1.1.11); (1.1.12); (1.1.13); and (1.1.14). R^9 has the meaning of –H; -(C_1-C_4) alkyl, preferably methyl; -(C_3-C_7) cycloalkyl, preferably cyclopropyl or cyclopentyl; phenyl; benzyl; pyridyl; -OR^{18}; -(C_1-C_2) alkyl–OR^{18}; and –(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 $–CH_3$.

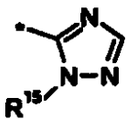
R^{10} is an optional substituent of the above-described preferred moieties that define R^7c, and there may be up to three such substituents when present. The meaning of the R^{10} substituent includes phenyl or pyridyl where said phenyl or pyridyl is in turn optionally substituted by up to 3 substituents R^{12} where R^{12} 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^{12} substitution, there will be 1 or 2 substituents R^{12} that have the meaning of –F, –Cl, $–CH_3$, $–OCH_3$, –OH, –CN, or $–N(CH_3)_2$. 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 $–S(=O)_2NR^{16}R^{17}$. Preferred among the above-recited meanings of the R^{10} substituent are –F, –Cl, $–CF_3$, oxo (=O), –OH, $–OCH_3$, $–NO_2$, –CN, -C(=O)OH, $–C(=O)NH_2$, $–NH_2$, $–N(CH_3)_2$, or $–NHS(=O)_2CH_3$.

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.

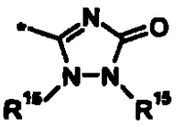
As an illustration of preferred subgeneric embodiments of the present invention wherein the Z group has the meaning of a moiety of partial Formulas (1.1.10) through (1.1.14), there is set out below cycloalkyl, phenyl, benzyl, o-toluyl that is a preferred meaning of R^7c in sulfonamido moieties of partial Formula (1.1.12), and monocyclic heterocyclic groups which define R^7c, of partial Formulas (7.0.1) through (7.0.39):



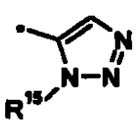
tetrazol-5-yl (7.0.1)



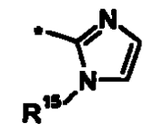
1,2,4-triazol-3-yl (7.0.2)



1,2,4-triazol-3-on-5-yl (7.0.3)

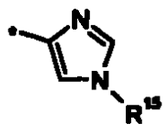


1,2,3-triazol-5-yl (7.0.4)



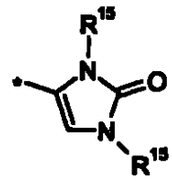
imidazol-2-yl

(7.0.5)



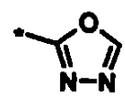
imidazol-4-yl

(7.0.6)



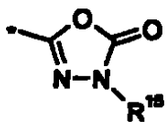
imidazolidin-2-on-4-yl

(7.0.7)



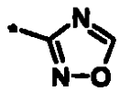
1,3,4-oxadiazolyl

(7.0.8)



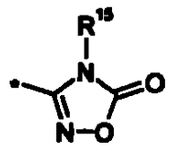
1,3,4-oxadiazol-2-on-5-yl

(7.0.9)



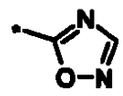
1,2,4-oxadiazol-3-yl

(7.0.10)



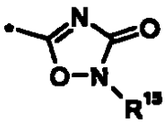
1,2,4-oxadiazol-5-on-3-yl

(7.0.11)



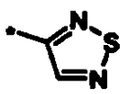
1,2,4-oxadiazol-5-yl

(7.0.12)



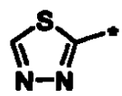
1,2,4-oxadiazol-3-on-5-yl

(7.0.13)



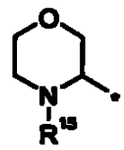
1,2,5-thiadiazol-2-yl

(7.0.14)



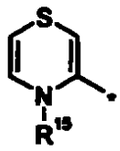
1,3,4-thiadiazolyl

(7.0.15)



morpholin-3-yl

(7.0.16)



parathiazin-3-yl

(7.0.17)



oxazolyl

(7.0.18)



isoxazolyl

(7.0.19)



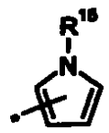
thiazolyl

(7.0.20)



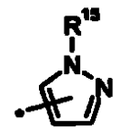
isothiazolyl

(7.0.21)



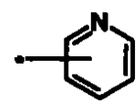
pyrrolyl

(7.0.22)



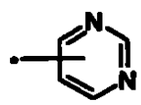
pyrazolyl

(7.0.23)



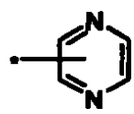
pyridyl

(7.0.24)



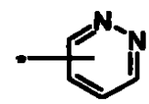
pyrimidinyl

(7.0.25)



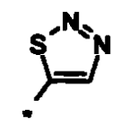
pyrazinyl

(7.0.26)



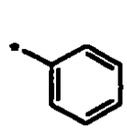
pyridazinyl

(7.0.27)

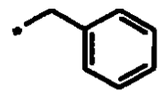


1,2,3-thiadiazol-5-yl

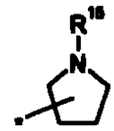
(7.0.28)



phenyl
(7.0.29)



benzyl
(7.0.30)



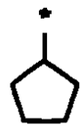
pyrrolidinyl
(7.0.31)



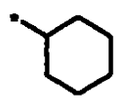
cyclopropyl
(7.0.32)



cyclobutyl
(7.0.33)



cyclopentyl
(7.0.34)



cyclohexyl
(7.0.35)



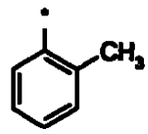
furanyl
(7.0.36)



tetrahydrofuranyl
(7.0.37)



thienyl
(7.0.38)



o-toluyl
(7.0.39)

where "*" indicates the point of attachment of each partial Formula (7.0.1) through (7.0.39) to the remaining portion of Formula (1.0.0); and where each carbon atom of partial Formulas (7.0.1) through (7.039) 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.

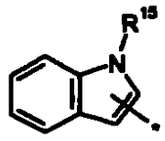
No R^9 substituents are shown in partial Formulas (7.0.1) through (7.0.39) above because the R^9 substituent is attached only to a nitrogen atom that does not form an integral, component part of an attached heterocyclic moiety. The R^9 substituent is optional in character in that "–H" is included as 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^9 and R^{15}, both of which are attached only to nitrogen atoms in any of the meanings of the moiety Z. The substituent R^{15} is attached only to a nitrogen atom that is an integral, component part of any heterocyclic moiety that may be defined *via* the R^7c substituent in partial Formulas (1.1.10) through (1.1.14) and in particular with reference to the more specific heterocyclic moieties of partial Formulas (7.0.1) through (7.0.28) and (7.0.31).. The R^9 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 (1.1.10) through (1.1.14). The R^{15} 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 Formulas (1.1.10) through (1.1.14) that can be characterized as containing or comprising a nitrogen-containing heterocyclic moiety.

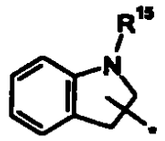
Preferred embodiments of the present invention where the group **Z** is a moiety of partial Formulas (1.1.10) through (1.1.14) also include those wherein the moiety R^7c is a bicyclic heterocyclic group selected from the group consisting of indolyl; indolinyl; isoindolinyl; benzo[*b*]furanyl; 2,3-dihydrobenzofuranyl; 1,3-dihydroisobenzofuranyl; 2*H*-1-benzopyranyl; chromanyl; benzothienyl; 1*H*-indazolyl; benzimidazolyl; benzoxazolyl; benzisoxazolyl; benzothiazolyl; benzotriazolyl; phthalazinyl; 1,6-naphthyridinyl; 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 **Z** group where it is a moiety of partial Formulas (1.1.10) through (1.1.14) and R^7c is a bicyclic heterocyclic group, there is set out below the groups consisting of partial Formulas (7.5.1) through (7.5.29) from which the **Z** moiety is selected in such preferred embodiments:



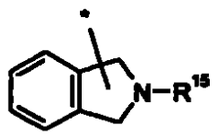
indolyl

(7.5.1)



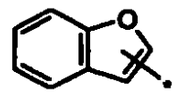
indolinyl

(7.5.2)



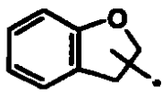
isoindolinyl

(7.5.3)



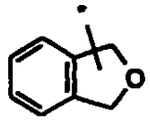
benzo[*b*]furanyl

(7.5.4)



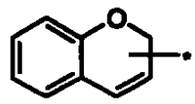
2,3-dihydrobenzo-furanyl

(7.5.5)



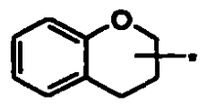
1,3-dihydroisobenzo-furanyl; phthalanyl

(7.5.6)



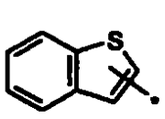
2*H*-1-benzopyranyl

(7.5.7)



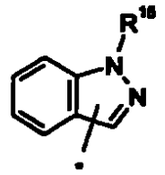
chromanyl

(7.5.8)



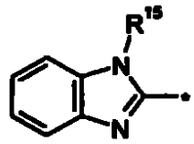
benzothienyl

(7.5.9)



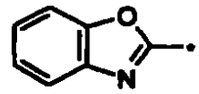
1*H*-indazolyl

(7.5.10)



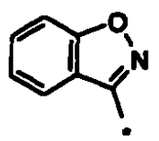
benzimidazolyl

(7.5.11)



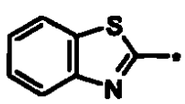
benzoxazolyl

(7.5.12)



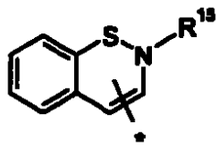
benzisoxazolyl

(7.5.13)



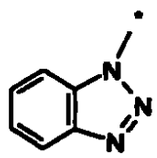
benzothiazolyl

(7.5.14)



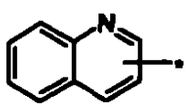
2H-1,2-benzothiazinyl

(7.5.15)



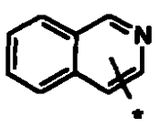
benzotriazolyl

(7.5.16)



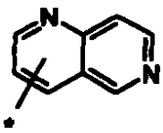
quinolinyl

(7.5.17)



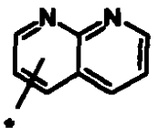
isoquinolinyl

(7.5.18)



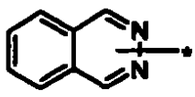
1,6-naphthyridinyl

(7.5.19)



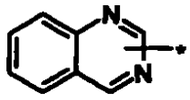
1,8-naphthyridinyl

(7.5.20)



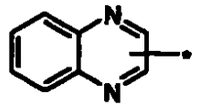
phthalazinyl

(7.5.21)



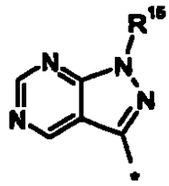
quinazolinyl

(7.5.22)



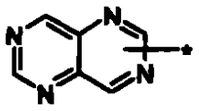
quinoxalinyl

(7.5.23)



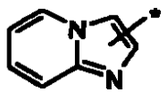
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(7.5.24)



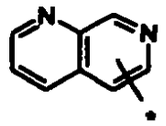
pyrimido[5,4-*d*]-pyrimidinyl

(7.5.25)



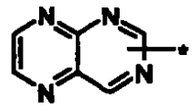
imidazo-[1,2-*a*]-pyridinyl

(7.5.26)



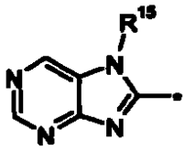
1,7-naphthyridinyl

(7.5.27)



pteridinyl

(7.5.28)



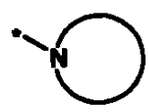
1*H*-purinyl

(7.5.29)

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.

5.6.8 Z is a Moiety of Partial Formula (1.1.15)

Preferred embodiments of the present invention also comprise those compounds of Formula (1.0.0) wherein the terminal moiety Z falls within the scope of partial Formula (1.1.15), *i.e.*, embodiments of this type are encompassed within the scope of the Z moiety when it has the meaning of partial Formula (1.1.15):



(1.1.15)

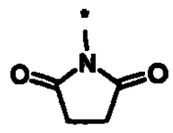
It will be understood that where the terminal moiety Z is defined by partial Formula (1.1.15), that it inherently comprises a nitrogen-containing heterocyclic group. Any one or more of the carbon atoms of said heterocyclic group is substituted by 0 to 3 substituents R^{14}. Consequently, R^{14} is an optional substituent of any one or more, up to a total of three, of the carbon atoms of the moieties that are included within the scope of partial Formula (1.1.6). Said R^{14} substituent comprises -(C_1-C_4) alkyl, preferably -CH_3; -(C_3-C_7) cycloalkyl, preferably cyclopropyl; phenyl; benzyl; pyridyl; or quinolinyl; where said alkyl, cycloalkyl, phenyl, benzyl, pyridyl, or quinolinyl moiety is in turn optionally substituted by 1 or 2 substituents –F, -Cl, -CH_3, –OCH_3, –OR^{16}, -CN, or –$NR^{16}R^{17}$. In preferred embodiments R^{16} and R^{17} are independently –H or –CH_3. When R^{14} is substituted, it is preferred that the substituent be –F or –Cl. The R^{14} substituent further comprises –F; -Cl; -CF_3; oxo (=O); –OR^{16}; -CN; –NO_2, -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 -$S(=O)_2NR^{16}R^{17}$. In addition to those preferred embodiments indicated above, when R^{14} is present it is also preferred that it have the meaning of –F, –Cl, –CF_3, -OCH_3, –CN, or –NO_2.

Any one or more of the nitrogen atoms included in said nitrogen-containing heterocyclic groups included within the scope of partial Formula (1.1.15), provided that they are not a point of attachment of said heterocyclic group, are optionally substituted by up to 3 substituents R^{15}. Any sulfur atom which happens to occur in said heterocyclic group, provided that it is not a point of attachment of said heterocyclic group, is substituted by 0, 1, or 2 oxygen atoms.

The optional nitrogen heterocyclyl substituent R^{15} comprises –H; -C(=O)OR^{16}; -C(=O)$NR^{16}R^{17}$; –(C_1-C_4) alkyl, preferably –CH_3; –(C_2-C_4) alkenyl; -(C_1-C_2) alkoxy, preferably –OCH_3; -(C_3-C_7) cycloalkyl, preferably cyclopropyl; phenyl; or benzyl, wherein said alkyl, alkenyl, alkoxy, cycloalkyl, phenyl, or benzyl are optionally substituted with up to 2 substituents R^{11}.

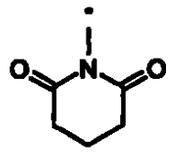
The sub-substituent R^{11} comprises –F; –Cl; $-CO_2R^{18}$; $-OR^{18}$; –CN; $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$; $-NR^{18}C(=O)OR^{19}$; $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, where p is 1 or 2, preferably 2; $-(C_1-C_4)$ alkyl, preferably $-CH_3$; and $-(C_1-C_4)$ alkoxy, where R^{11} has the meaning of $-OR^{18}$ above and R^{18} is defined as $-(C_1-C_4)$ alkyl, preferably $-OCH_3$; 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 comprise –H; or $-(C_1-C_2)$ alkyl, preferably $-CH_3$; optionally substituted with up to 3 –F; or –Cl.

The present invention is also concerned with a compound of Formula (1.0.0) wherein the terminal group $\mathbf{Z}$ has the meaning of a moiety of partial Formula (1.1.15) where the number and position of carbon atoms and replacement thereof by one or more heteroatoms, as well as the substitution of one or more said carbon atoms thereof by R^{14} where R^{14} is oxo (=O), are selected in such a way that $\mathbf{Z}$ comprises a member selected from the group consisting of partial Formulas (1.7.1) through (1.7.46):



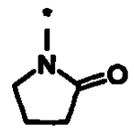
succinimid-1-yl

(1.7.1)



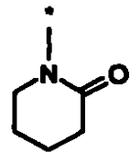
glutarimid-1-yl

(1.7.2)



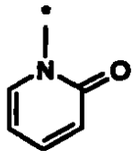
pyrrolidin-2-on-1-yl

(1.7.3)



piperid-2-on-1-yl

(1.7.4)



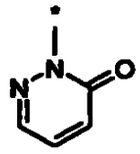
pyrid-2-on-1-yl

(1.7.5)



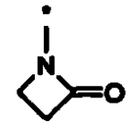
pyrid-4-on-1-yl

(1.7.6)



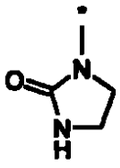
pyridazin-3-on-2-yl

(1.7.7)



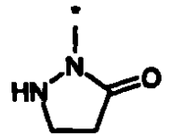
azetidin-2-on-1-yl

(1.7.8)



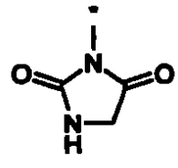
imidazolidin-2-on-1-yl

(1.7.9)



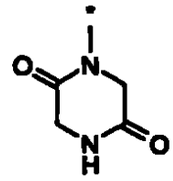
pyrazol-5-on-1-yl

(1.7.10)



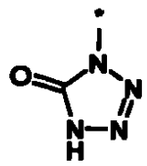
imidazolidin-2,4-dion-1-yl

(1.7.11)



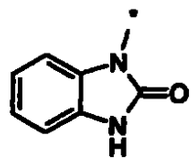
piperazin-2,5-dion-1-yl

(1.7.12)



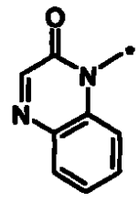
4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl

(1.7.13)



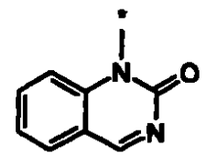
benzimidazolin-2-on-1-yl

(1.7.14)



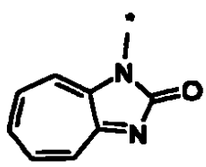
1*H*-quinoxalin-2-on-1-yl

(1.7.15)



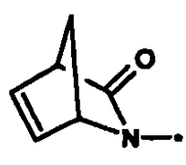
1*H*-quinazolin-2-on-1-yl

(1.7.16)



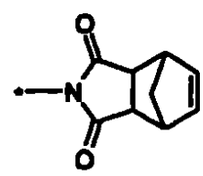
1H-cycloheptimid-azol-2-on-1-yl

(1.7.17)



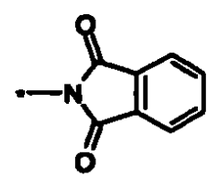
2-azabicyclo[2.2.1]-hept-5-en-3-on-1-yl

(1.7.18)



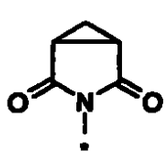
norbom-5-en-2,3-dicarboximid-1-yl

(1.7.19)



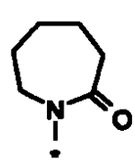
phthalimid-1-yl; 1*H*-isoindole-1,3(2*H*)-dion-1-yl

(1.7.20)



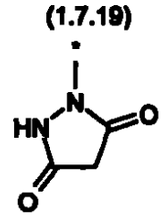
3-azabicyclo[3.1.0]-hexane-2,4-dion-3-yl

(1.7.21)



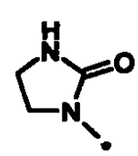
2*H*-azepin-2-on-1-yl

(1.7.22)



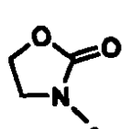
pyrazolidin-3,5-dion-1-yl

(1.7.23)



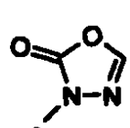
imidazolidin-2-on-1-yl

(1.7.24)



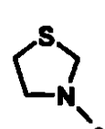
oxazolidin-2-on-1-yl

(1.7.25)



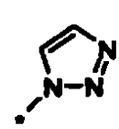
1,3,4-oxadiazol-2(3*H*)-on-3-yl

(1.7.26)



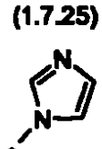
thiazolidin-3-yl

(1.7.27)



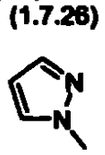
1*H*-1,2,3-triazol-1-yl

(1.7.28)



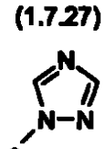
imidazol-1-yl

(1.7.29)



pyrazol-1-yl

(1.7.30)



1*H*-1,2,4-triazol-1-yl

(1.7.31)



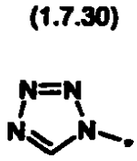
azetidin-1-yl

(1.7.32)



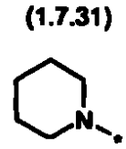
pyrrolidin-1-yl

(1.7.33)



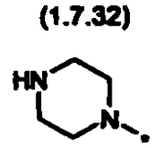
tetrazol-1-yl

(1.7.34)



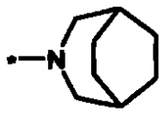
piperidin-1-yl

(1.7.35)



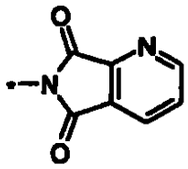
piperazin-1-yl

(1.7.36)



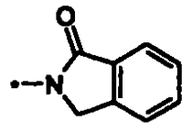
3-azabicyclo[3.2.2]-non-3-yl

(1.7.37)



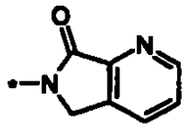
pyrrolo[3,4-*b*]pyridin-5,7-dion-6-yl

(1.7.38)



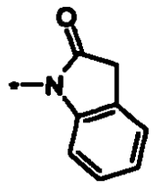
2,3-dihydro-*iso*-indol-1-on-2-yl

(1.7.39)



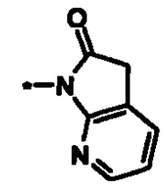
pyrrolo[3,4-*b*]pyridin-7-on-6-yl

(1.7.40)



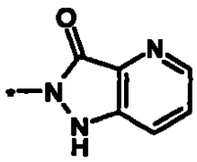
1,3-dihydro-indol-2-on-1-yl

(1.7.41)



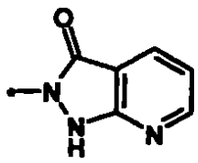
pyrrolo[4,5-*b*]pyridin-3-on-2-yl

(1.7.42)



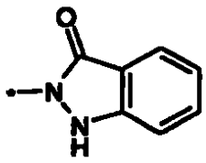
1*H*-pyrazolo[4,5-*e*]pyridin-7-on-2-yl

(1.7.43)



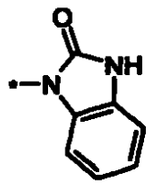
1*H*-pyrazolo[4,5-*b*]pyridin-4-on-2-yl

(1.7.44)



1*H*-indazol-3-on-2-yl

(1.7.45)

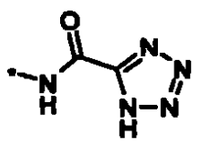


1*H*-benzimidazol-2-on-3-yl

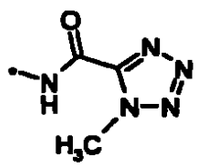
(1.7.46)

Any moiety that is a member selected from the group consisting of partial Formulas (1.7.1) through (1.7.46) depicted above, includes optional substitution thereof with respect to *(1)* any one or more carbon atoms thereof, by a substituent R^{14} where R^{14} has the same meaning as defined above; *(2)* any one or more nitrogen atoms thereof by a substituent R^{15} where R^{15} has the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms thereof; or *(3)* any sulfur atom thereof by 0, 1, or 2 oxygen atoms.

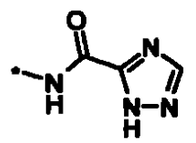
The present invention is further illustrated regarding preferred subgeneric groups comprising compounds of Formula (1.0.0) wherein $R^{7}c$ and R^{8} of partial Formulas (1.1.10) through (1.1.15) are all selected in such a way that Z comprises a member selected from the group consisting of the following partial Formulas (8.0.1) through (8.0.139):



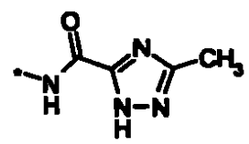
(8.0.1)



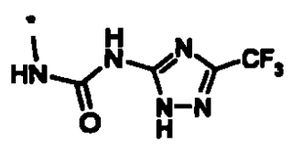
(8.0.2)



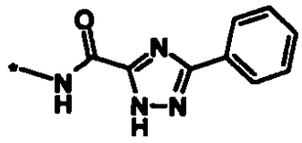
(8.0.3)



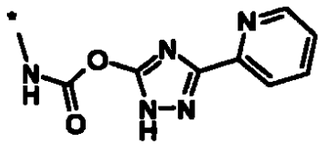
(8.0.4)



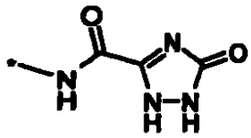
(8.0.5)



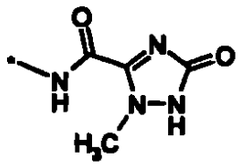
(8.0.6)



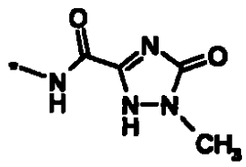
(8.0.7)



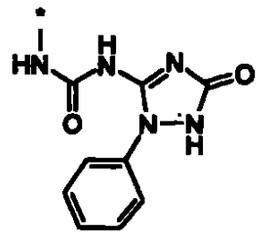
(8.0.8)



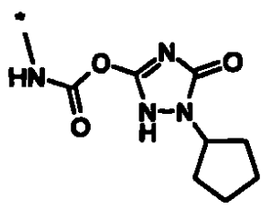
(8.0.9)



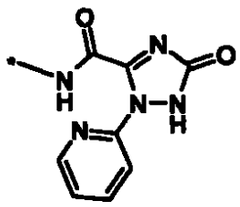
(8.0.10)



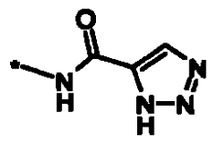
(8.0.11)



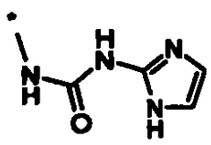
(8.0.12)



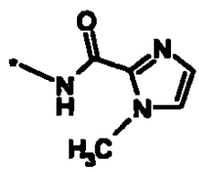
(8.0.13)



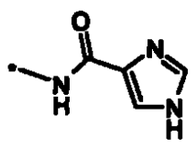
(8.0.14)



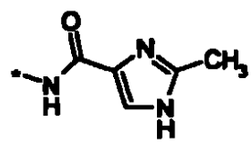
(8.0.15)



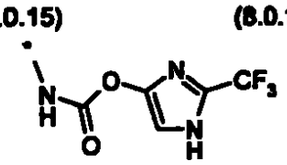
(8.0.16)



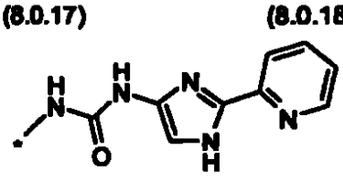
(8.0.17)



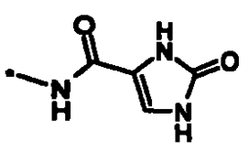
(8.0.18)



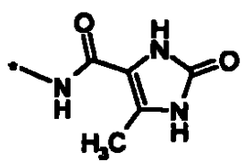
(8.0.19)



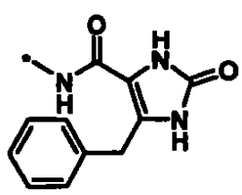
(8.0.20)



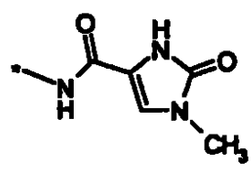
(8.0.21)



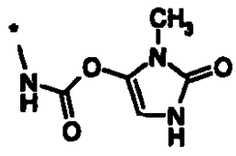
(8.0.22)



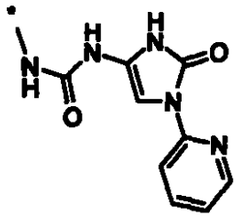
(8.0.23)



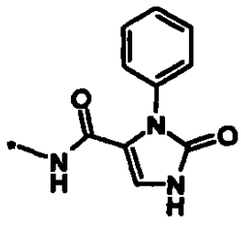
(8.0.24)



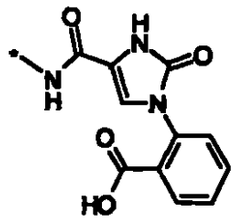
(8.0.25)



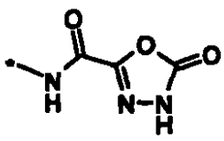
(8.0.26)



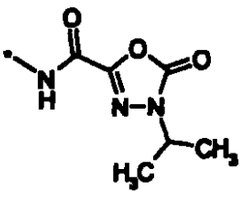
(8.0.27)



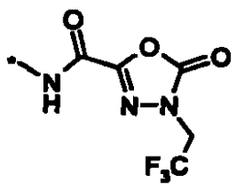
(8.0.28)



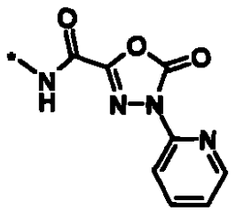
(8.0.29)



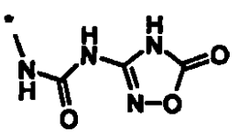
(8.0.30)



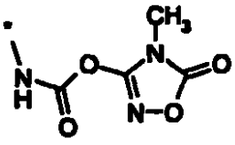
(8.0.31)



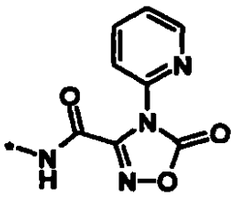
(8.0.32)



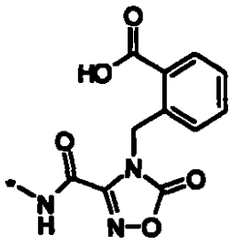
(8.0.33)



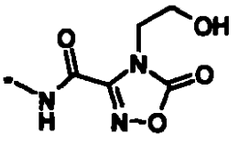
(8.0.34)



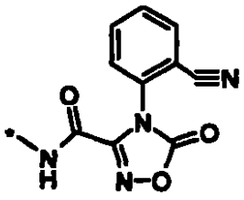
(8.0.35)



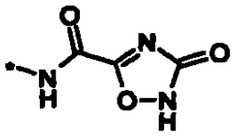
(8.0.36)



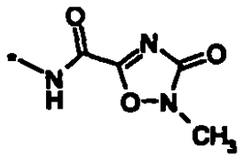
(8.0.37)



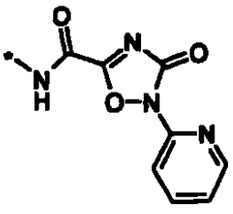
(8.0.38)



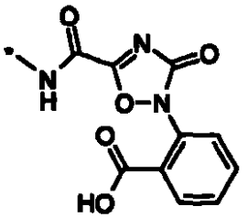
(8.0.39)



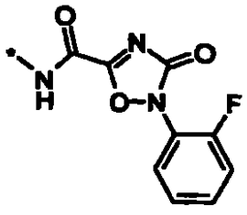
(8.0.40)



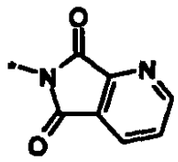
(8.0.41)



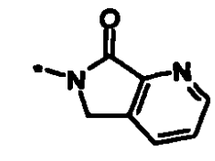
(8.0.42)



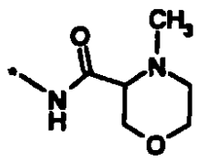
(8.0.43)



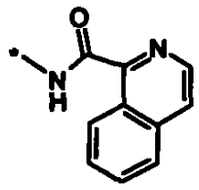
(8.0.44)



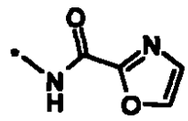
(8.0.45)



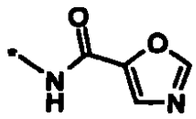
(8.0.46)



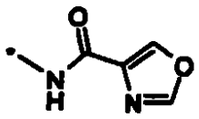
(8.0.47)



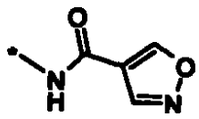
(8.0.48)



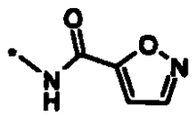
(8.0.49)



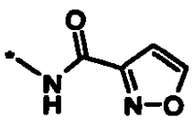
(8.0.50)



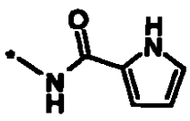
(8.0.51)



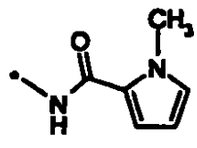
(8.0.52)



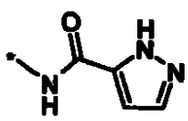
(8.0.53)



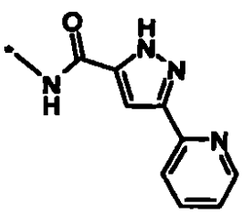
(8.0.54)



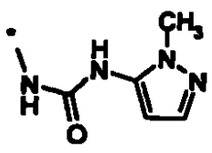
(8.0.55)



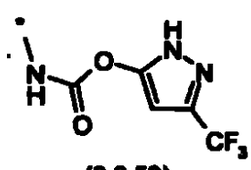
(8.0.56)



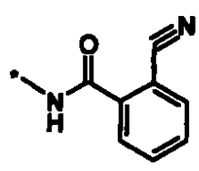
(8.0.57)



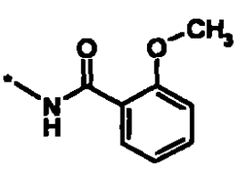
(8.0.58)



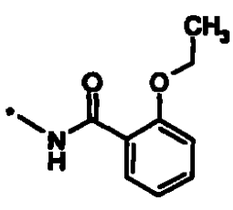
(8.0.59)



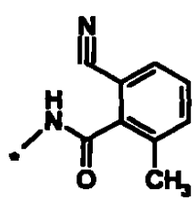
(8.0.60)



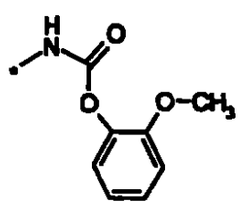
(8.0.61)



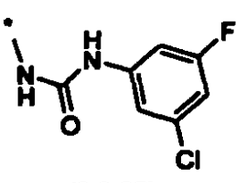
(8.0.62)



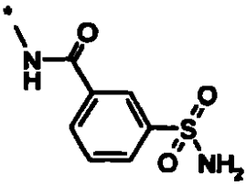
(8.0.63)



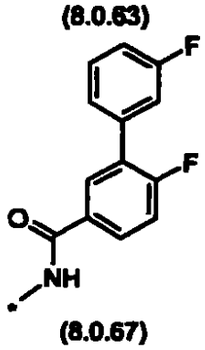
(8.0.64)



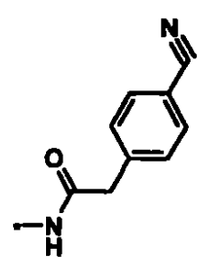
(8.0.65)



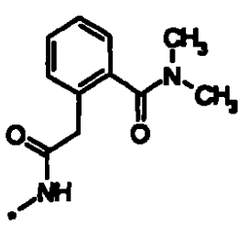
(8.0.66)



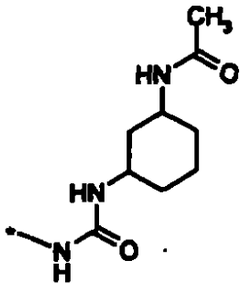
(8.0.67)



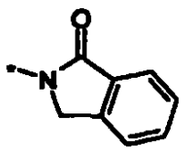
(8.0.68)



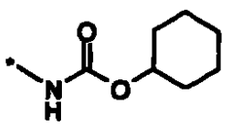
(8.0.69)



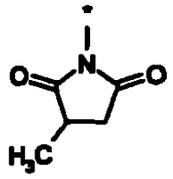
(8.0.70)



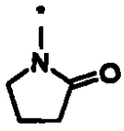
(8.0.71)



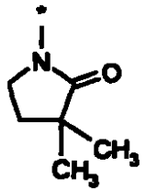
(8.0.72)



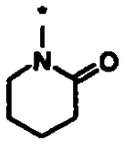
(8.0.73)



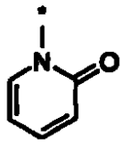
(8.0.74)



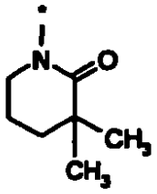
(8.0.75)



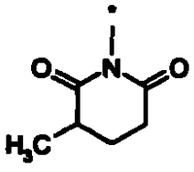
(8.0.76)



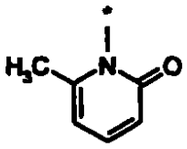
(8.0.77)



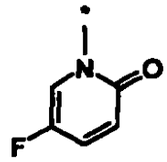
(8.0.78)



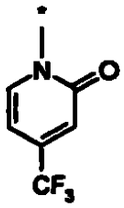
(8.0.79)



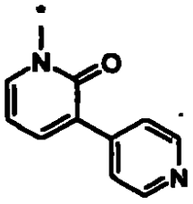
(8.0.80)



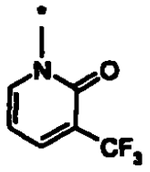
(8.0.81)



(8.0.82)



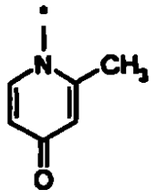
(8.0.83)



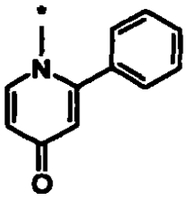
(8.0.84)



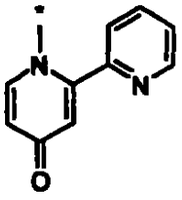
(8.0.85)



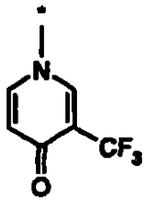
(8.0.86)



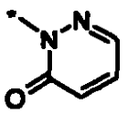
(8.0.87)



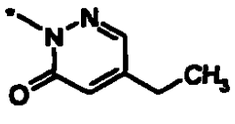
(8.0.88)



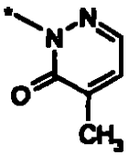
(8.0.89)



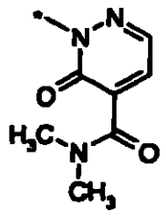
(8.0.90)



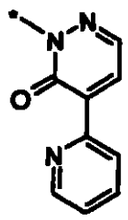
(8.0.91)



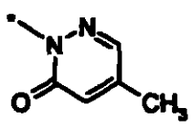
(8.0.92)



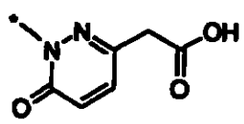
(8.0.93)



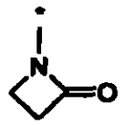
(8.0.94)



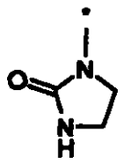
(8.0.95)



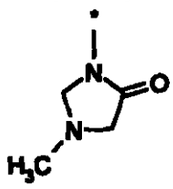
(8.0.96)



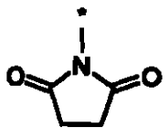
(8.0.97)



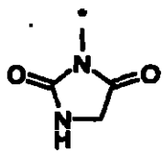
(8.0.98)



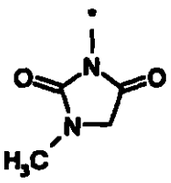
(8.0.99)



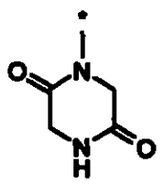
(8.0.100)



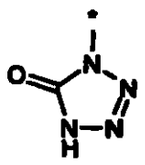
(8.0.101)



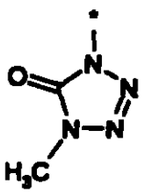
(8.0.102)



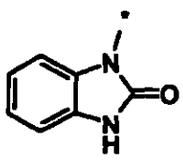
(8.0.103)



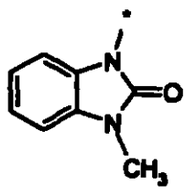
(8.0.104)



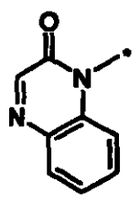
(8.0.105)



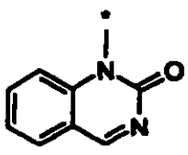
(8.0.106)



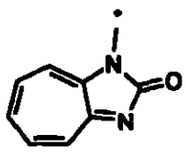
(8.0.107)



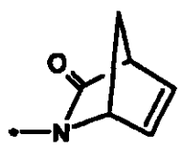
(8.0.108)



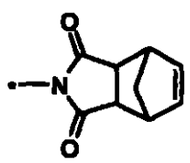
(8.0.109)



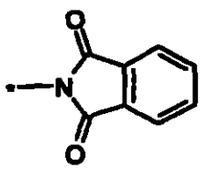
(8.0.110)



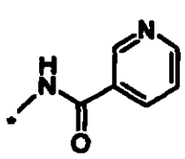
(8.0.111)



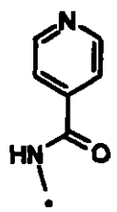
(8.0.112)



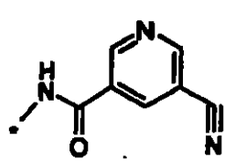
(8.0.113)



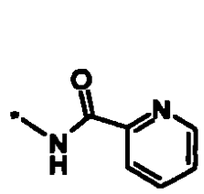
(8.0.114)



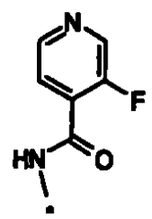
(8.0.115)



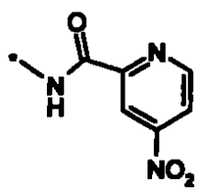
(8.0.116)



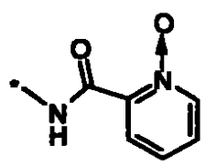
(8.0.117)



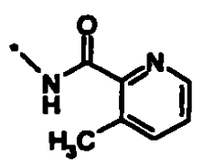
(8.0.118)



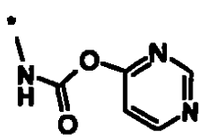
(8.0.119)



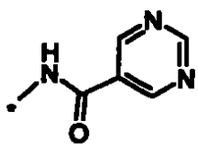
(8.0.120)



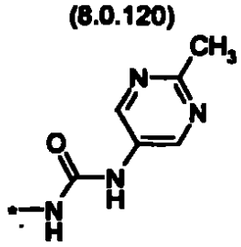
(8.0.121)



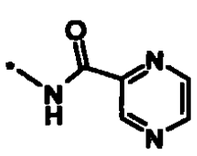
(8.0.122)



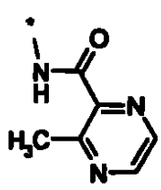
(8.0.123)



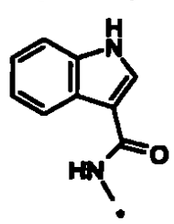
(8.0.124)



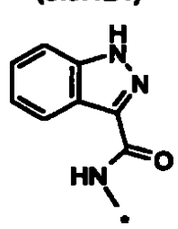
(8.0.125)



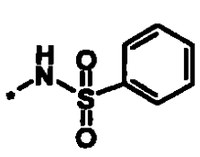
(8.0.126)



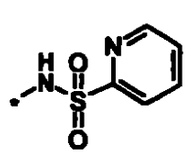
(8.0.127)



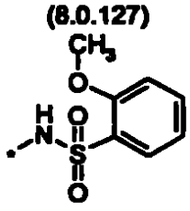
(8.0.128)



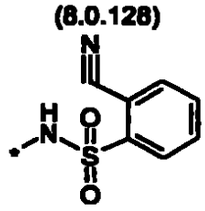
(8.0.129)



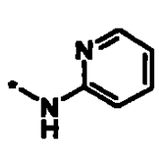
(8.0.130)



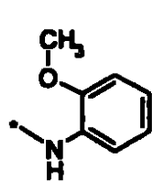
(8.0.131)



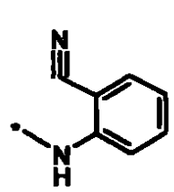
(8.0.132)



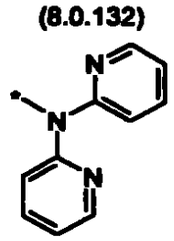
(8.0.133)



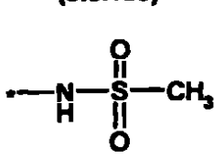
(8.0.134)



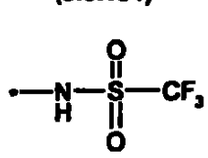
(8.0.135)



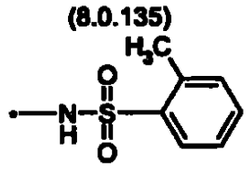
(8.0.136)



(8.0.137)



(8.0.138)



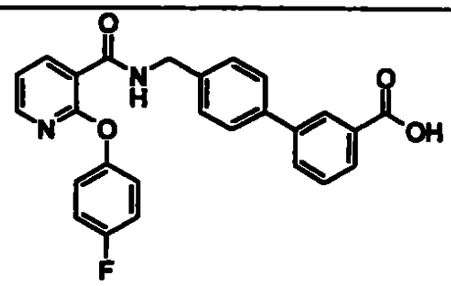
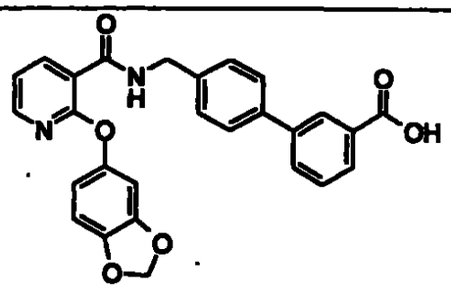
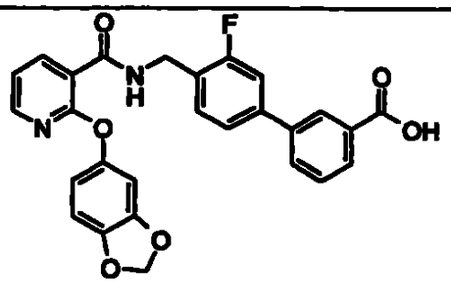
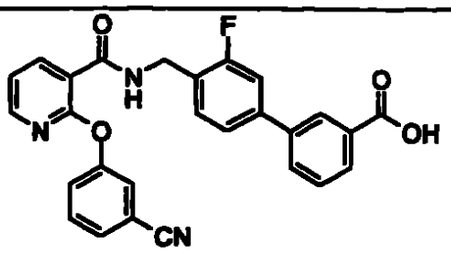
(8.0.139)

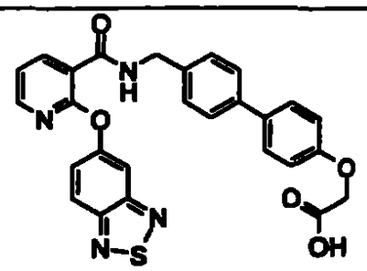
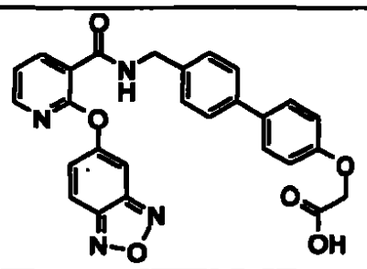
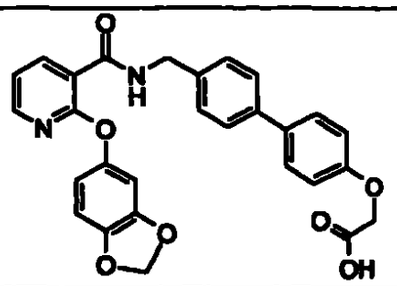
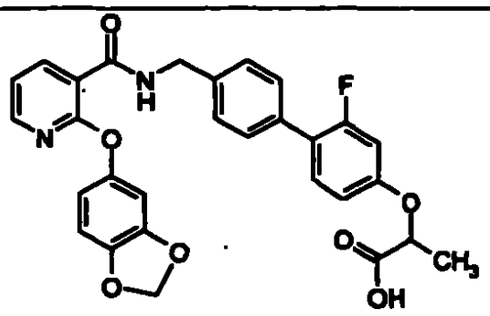
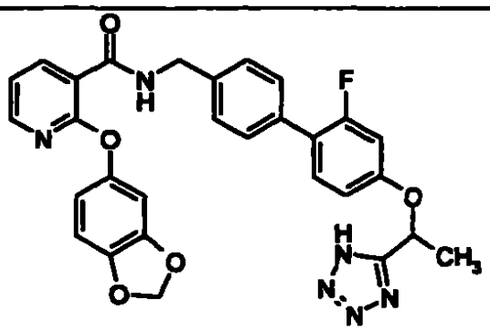
Any moiety that is a member selected from the group consisting of partial Formulas (8.0.1) through (8.0.139) depicted above, includes optional substitution thereof with respect to *(1)* any one or more carbon atoms thereof, by a substituent R^{14} where R^{14} has the same meaning as defined above; *(2)* any one or more nitrogen atoms thereof by a substituent R^{15}

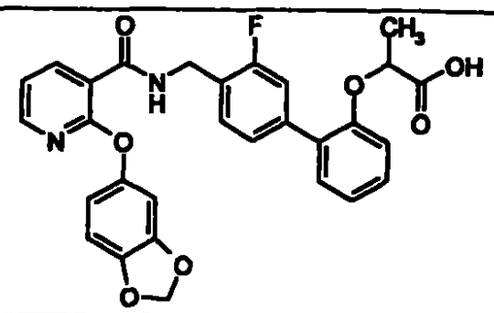
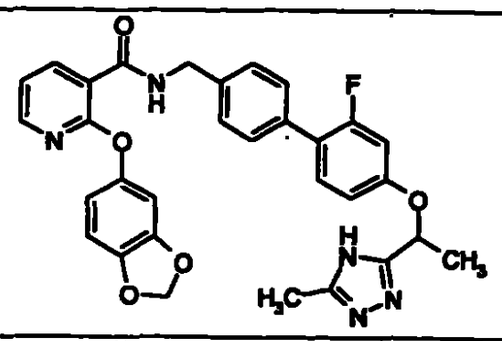
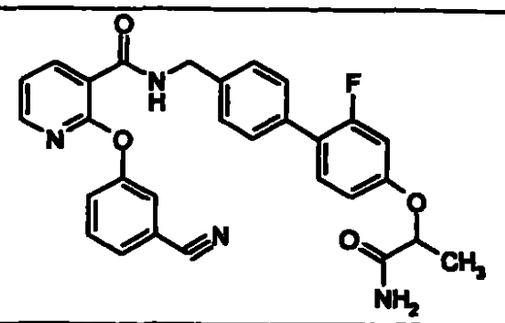
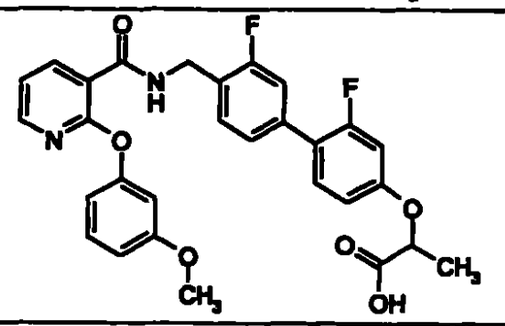
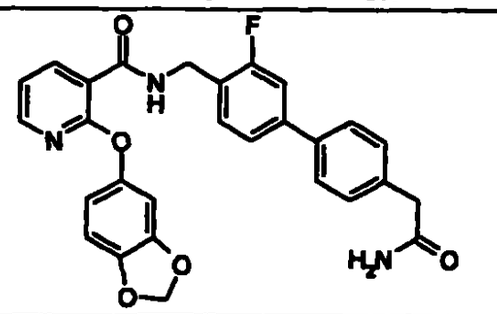
where R^{15} has the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms thereof; or *(3)* any sulfur atom thereof by 0, 1, or 2 oxygen atoms.

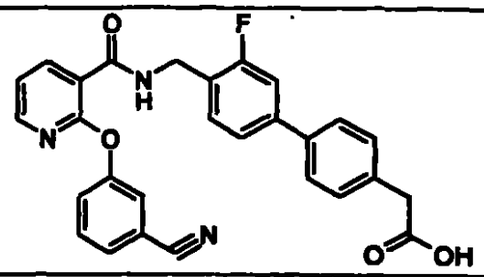
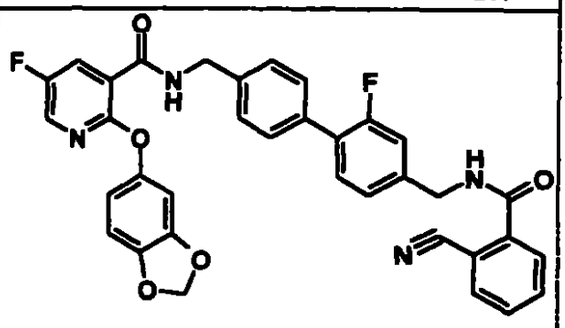
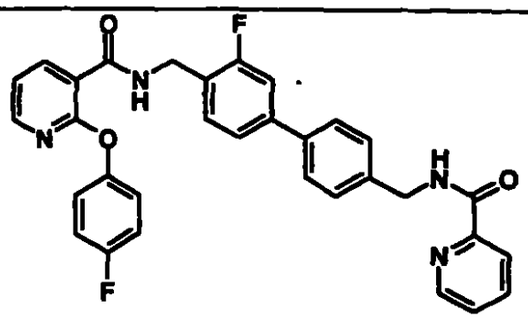
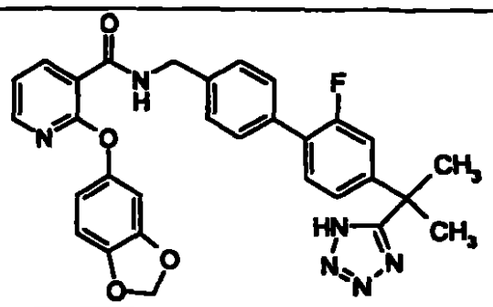
5.7 Representative Species of Formula (1.0.0)

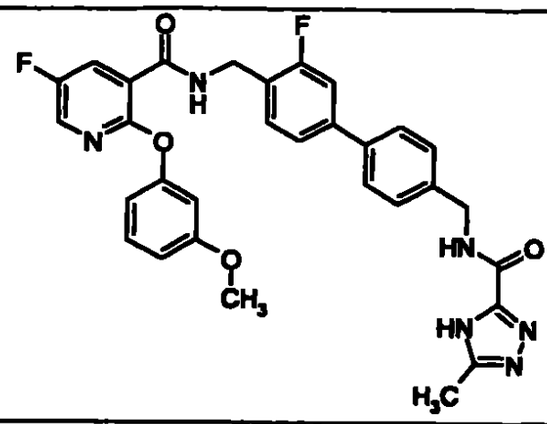
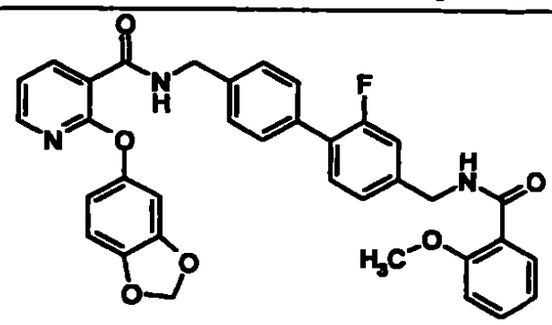
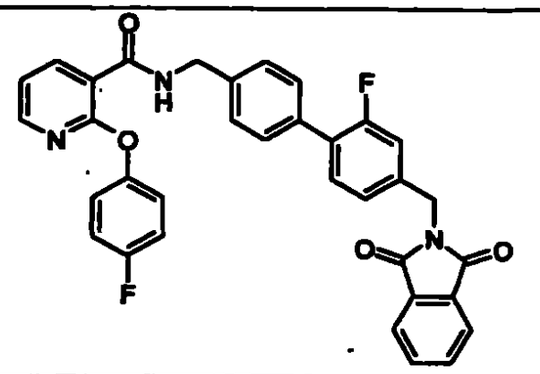
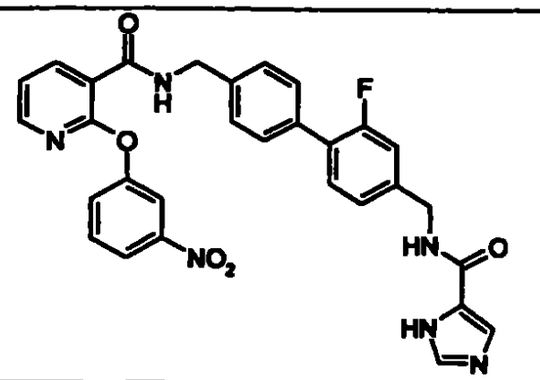
In the above description various preferred aspects of the compounds of Formula (1.0.0) have been set forth. As a further demonstration of the scope and content of the present invention, specific compounds comprising embodiments of the compounds of Formula (1.0.0) are presented. Such species of Formula (1.0.0) include, but are not limited to the following compounds of Formulas (8.5.1) through (8.5.28):

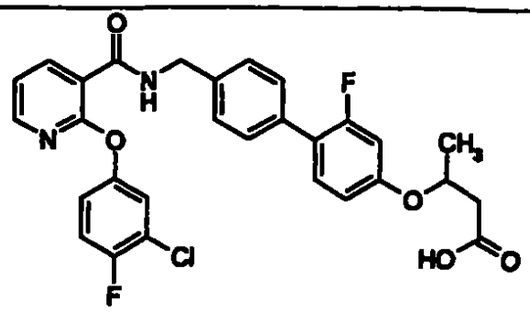
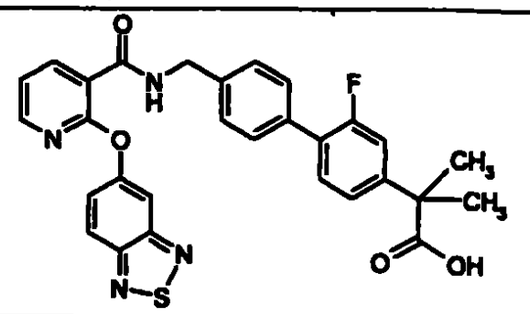
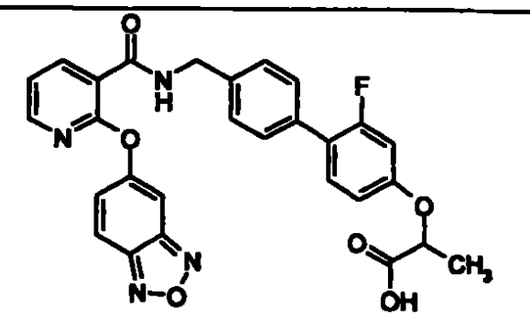
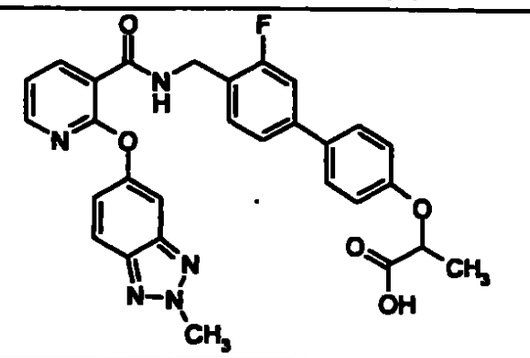
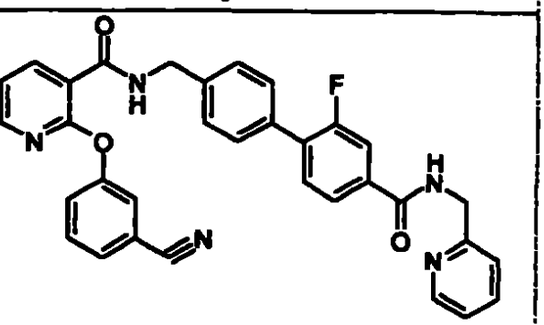
4'-[[[2-[4-Fluorophenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid of Formula (8.5.1);	
4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid of Formula (8.5.2);	
4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8.5.3);	
4'-[[[2-[3-Cyano-phenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8.5.4);	

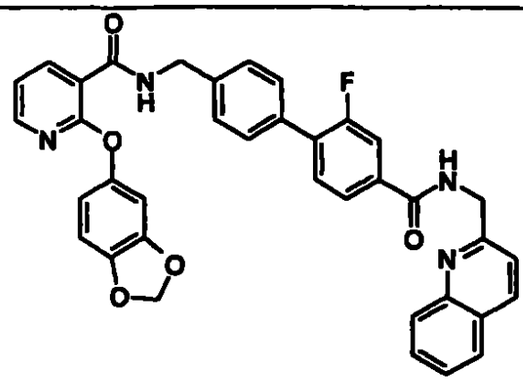
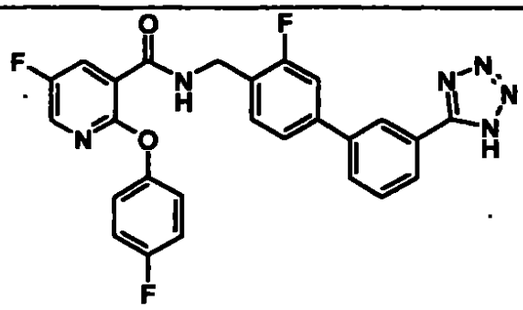
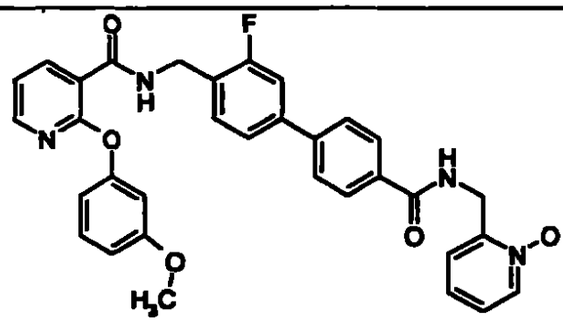
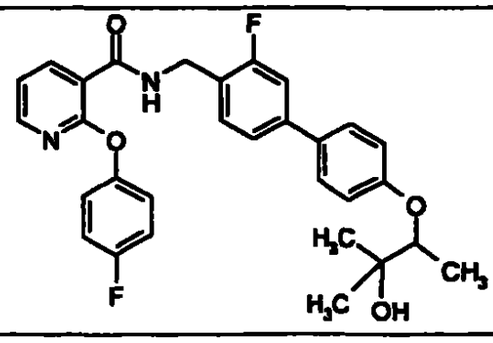
[4'-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-acetic acid of Formula (8.5.5);	
[4'-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-acetic acid of Formula (8.5.6);	
[4'-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-acetic acid of Formula (8.5.7);	
(±)-2-[4'-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-propionic acid of Formula (8.5.8);	
(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-(2'-fluoro-4'[1-(1H-tetrazol-5-yl)-ethoxy]-biphenyl-4-ylmethyl)-nicotinamide of Formula (8.5.9);	

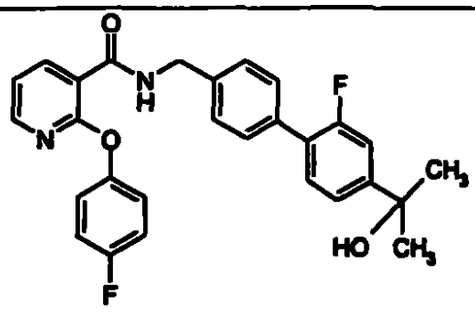
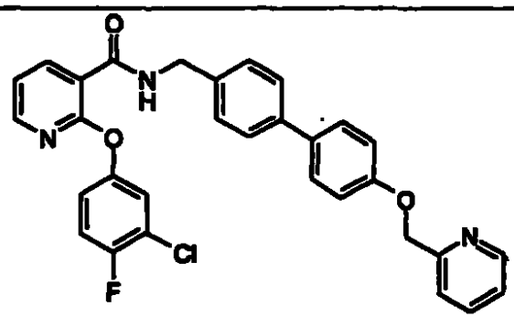
(±)-2-[4'-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-2-yloxy]-propionic acid of Formula (8.5.10);	
(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-(2'-fluoro-4'[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-biphenyl-4-ylmethyl}-nicotinamide of Formula (8.5.11);	
(±)-N-[4'-(1-Carbamoyl-ethoxy)-2'-fluoro-biphenyl-4-ylmethyl]-2-(3-cyano-phenoxy)-nicotinamide of Formula (8.5.12);	
(±)-2-[2,3'-Difluoro-4'-({[2-(3-methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-propionic acid of Formula (8.5.13);	
2-(Benzo[1,3]dioxol-5-yloxy)-N-(4'-carbamoylmethyl-3-fluoro-biphenyl-4-ylmethyl)-nicotinamide of Formula (8.5.14);	

[4'-({[2-(3-Cyano-phenoxy)-3-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-4-yl]-acetic acid of Formula (8.5.15);	
2-(Benzo[1,3]dioxol-5-yloxy)-N-[4'-[(2-cyano-benzoylamino)-methyl]-2'-fluoro-biphenyl-4-ylmethyl)-5-fluoro-nicotinamide of Formula (8.5.16);	
Pyridine-2-carboxylic acid (3'-fluoro-4'-{[2-(4-fluoro-phenoxy)-nicotinamide]-methyl}-biphenyl-4-ylmethyl)-amide of Formula (8.5.17);	
2-[Benzo[1,3]dioxol-5-yloxy)-N-[2'-fluoro-4'-[1-methyl-1-(1H-tetrazol-5-yl)-ethyl]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.18);	

5-Fluoro-N-(3-fluoro-4'-[[(5-methyl-4H-[1,2,4]triazole-3-carbonyl)-amino]-methyl]-biphenyl-4-ylmethyl)-2-(3-methoxy-phenoxy)-nicotinamide of Formula (8.5.19);	
2-(Benzo[1,3]dioxol-5-yloxy)-N-[2'-fluoro-4'-[(2-methoxy-benzoylamino)-methyl]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.20);	
N-[4'-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2'-fluoro-biphenyl-4-ylmethyl]-2-(4-fluoro-phenoxy)-nicotinamide of Formula (8.5.21);	
N-(2'-Fluoro-4'-[[(3H-imidazole-4-carbonyl)-amino]-methyl]-biphenyl-4-ylmethyl)-2-(3-nitro-phenoxy)-nicotinamide of Formula (8.5.22);	

(±)-3-[4'-({[2-(3-Chloro-4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-butyric acid of Formula (8.5.23);	
2-[4'-({[2-Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yl]-2-methyl-propionic acid of Formula (8.5.24);	
(±)-2-[4'-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-propionic acid of Formula (8.5.25);	
(±)-2-[3'-Fluoro-4'-({[2-(2-methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-propionic acid of Formula (8.5.26);	
2-(3-Cyano-phenoxy)-N-[2'-fluoro-4'[(pyridin-2-ylmethyl)-carbamoyl]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.27);	

2-(Benzo[1,3]dioxol-5-yloxy)-N-[2'-fluoro-4'-[(quinolin-2-ylmethyl)-carbamoyl]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.28);	
5-Fluoro-2-(4-fluoro-phenoxy)N-[3-fluoro-3'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.29);	
N-[3-Fluoro-4'-[(1-oxy-pyridin-2-ylmethyl)-carbamoyl]-biphenyl-4-ylmethyl]-2-(3-methoxy-phenoxy)-nicotinamide of Formula (8.5.30);	
(±)-N-[3-Fluoro-4'-(2-hydroxy-1,2-dimethyl-propoxy)-biphenyl-4-ylmethyl]-2-(4-fluoro-phenoxy)-nicotinamide of Formula (8.5.31);	

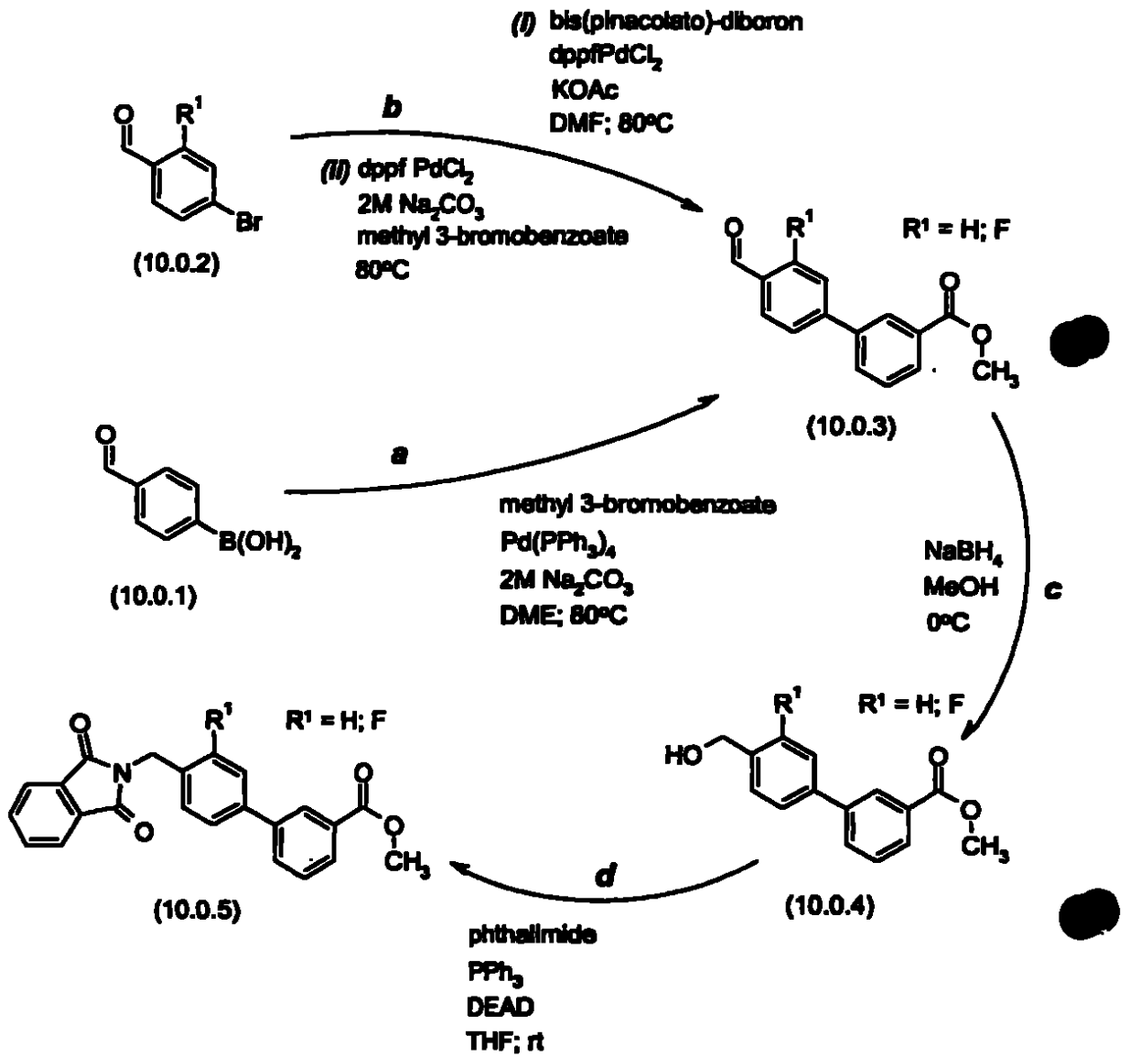
N-[2'-Fluoro-4'-(1-hydroxy-1-methyl-ethyl)-biphenyl-4-ylmethyl]-2-(4-fluoro-phenoxy)-nicotinamide of Formula (8.5.32);	
2-(3-Chloro-4-fluoro-phenoxy)-N-[4'-(pyridin-2-ylmethoxy)-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.33).	

DETAILED DESCRIPTION OF THE INVENTION

6.0 Processes for Making the Compounds of Formula (1.0.0)

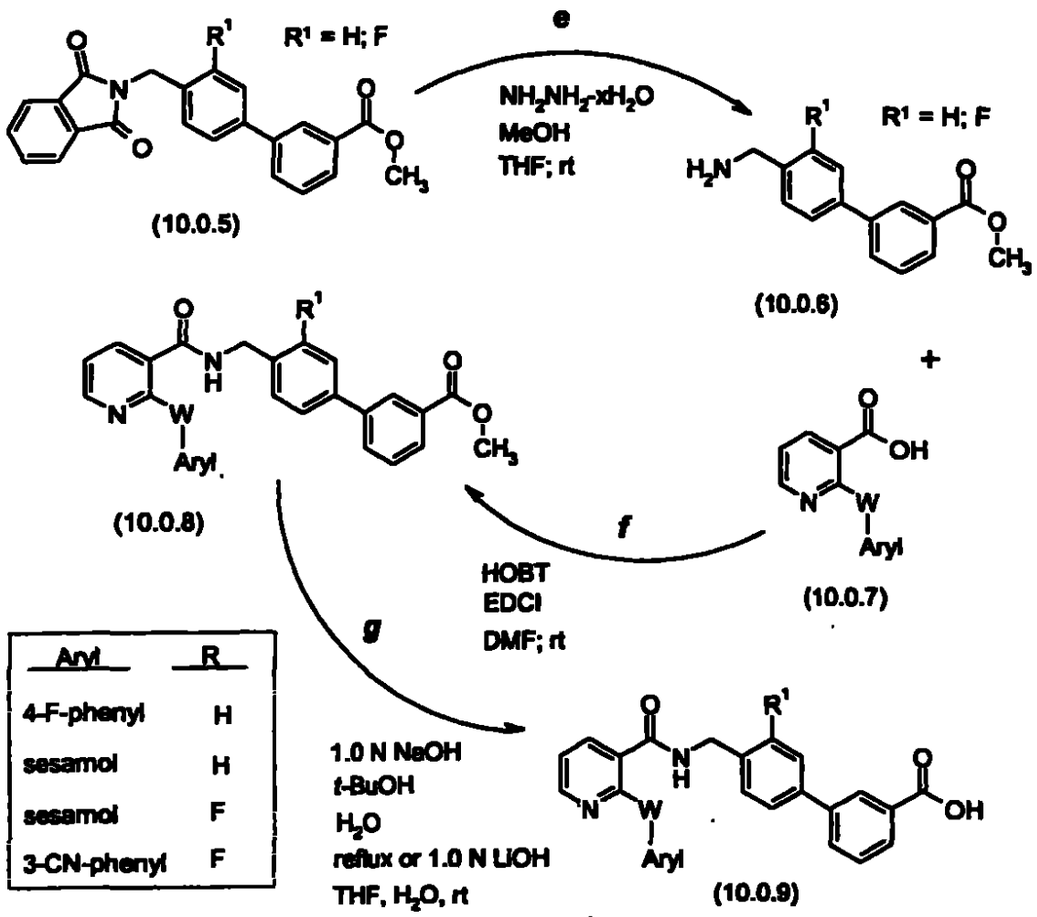
A method suitable for preparing the right-hand side of the compounds of Formula (1.0.0) where the Q^2 group is a biphenyl moiety of partial Formula (1.2.1), and the Z group is a carboxyl moiety of partial Formula (1.1.1), is illustrated in Synthesis Scheme (10.0.0) below.

SYNTHESIS SCHEME (10.0.0)



The left-hand side of the compounds of Formula (1.0.0) is prepared by amide coupling of a suitably substituted phenoxy-, phenylthio-, or phenylsulfonyl-nicotinic acid to the right-hand side moiety prepared as described above, after the intermediate of Formula (10.0.5) is converted into the corresponding amine. These steps are carried out in accordance with SYNTHESIS SCHEME (10.1.0) set out below.

SYNTHESIS SCHEME (10.1.0)



Aryl	R
4-F-phenyl	H
sesamol	H
sesamol	F
3-CN-phenyl	F

Once a compound of Formula (1.0.0) has been prepared in accordance with SYNTHESIS SCHEMES (10.0.0) and (10.1.0) described above, further embodiments of the compounds of Formula (1.0.0) may be prepared by suitable reactions with group **Z** when it is a carboxyl group.

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, hydroiodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, *etc.*; and alkyl- and monoarylsulfonates 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, dihydroganphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, 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, fluorine and chlorine, *e.g.*, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{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 = 2-7 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, i.m.) 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-egonist 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 macrophages; 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 Cai," *Naunyn Schmiedebergs Arch. Pharmacol.* 344 682-690, 1991; and Tenor *et al.*, "Cyclic nucleotide phosphodiesterase isoenzyme activities in human alveolar macrophages," *Clin. Exp. Allergy* 25 625-633, 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.

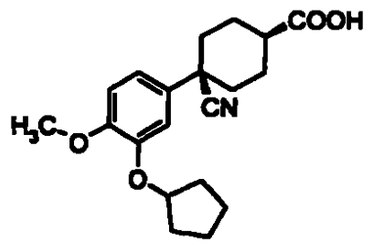
It is also inferred that the compounds of Formula (1.0.0) reduce superoxide anion production mediated by PDE4s in peripheral blood neutrophils, and that they regulate leukotriene synthesis mediated by PDE4s; Wright *et al.*, *Ibid.*; Schudt *et al.*, *Ibid.*; Bloeman *et al.*, *Ibid.*; Al Essa, *et al.*, "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.* 101 502-506, 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 bronchodilaors 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; $MgSO_4 \cdot 7H_2O$ 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 Lipopolysacharide (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 0.08 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

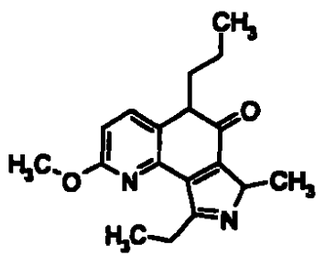
Allergic rhinitis is characterized by nasal obstruction, itching, watery rhinorrhea, sneezing and occasional anosmia. Allergic rhinitis is divided into two disease categories, seasonal and perennial, in which the former is attributed to pollen or outdoor mould spores, while the latter is attributed to 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.

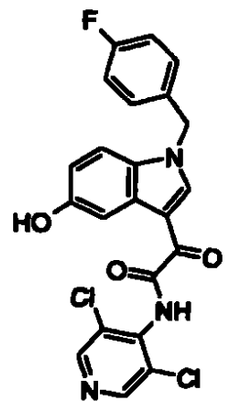
Other types of rhinitis for which the compounds of Formula (1.0.0) may be used as therapeutic agents include acute catarrhal rhinitis which is a cold in the head involving acute congestion of the mucous membrane of the nose, marked by dryness and followed by increased mucous secretion from the membrane, 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 affect 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)



Lotesprednol (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 1356-1361, 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 el 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 *el 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; Souness *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. Souness *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 10^5 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 anglitis, 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 than 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 Carninelli, "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." *Baillieres 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.

8.11 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 dabufylline 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. Thera.*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 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. 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; Waki *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 9169665 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.

8.16 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 Porssmann 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

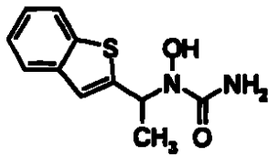
One or more compounds of Formula (1.0.0) is used in combination with leukotriene biosynthesis inhibitors, *i.e.*, 5-lipoxygenase inhibitors and/or 5-lipoxygenase activating protein antagonists, to form embodiments of the present invention. As already adverted to above, 5-lipoxygenase (5-LO) is one of 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 8511-6, 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

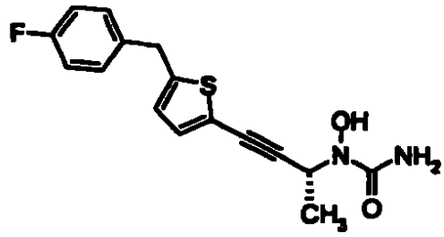
(c) competitive inhibitors of 5-lipoxygenase, based on thiopyranoindole and methoxyalkyl thiazole structures which may act as non-redox inhibitors of 5-lipoxygenase; see Ford-Hutchinson *et al., Ibid.*; and Hamel *et al.*, "Substituted (pyridylmethoxy)naphthalenes as potent and orally active 5-lipoxygenase 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

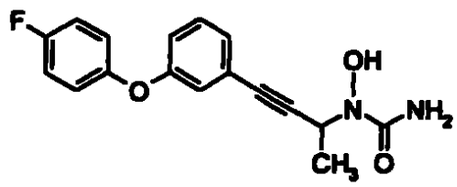
(0.1.14)



ABT-761

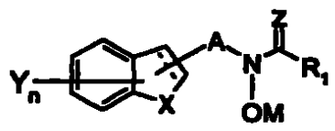
(5.2.1)

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.

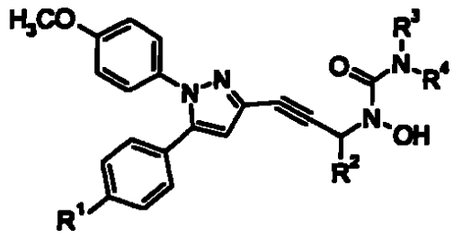
Related compounds are disclosed in US 4,769,387 (Summers *et al.*); US 4,822,811 (Summers); US 4,822,809 (Summers and Stewart); US 4,897,422 (Summers); US 4,992,464 (Summers *et al.*); and US 5,250,565 (Brooks and Summers); each of which is incorporated herein by reference in its entirety as though fully 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.

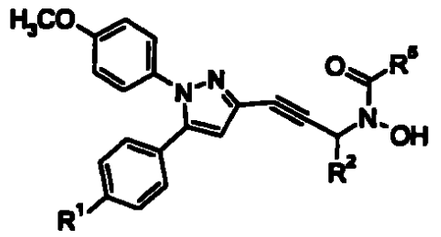
Fenleuton is disclosed in US 5,432,194; US 5,446,062; US 5,484,786; US 5,559,144; US 5,616,596; US 5,668,146; US 5,668,150; US 5,843,968; US 5,407,959; US 5,426,111; US 5,446,055; US 5,475,009; US 5,512,581; US 5,516,795; US 5,476,873; US 5,714,488; US 5,783,586; US 5,399,699; US 5,420,282; US 5,459,150; and US 5,506,261; 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 97/12865; WO 97/12866; WO 97/12867; 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:



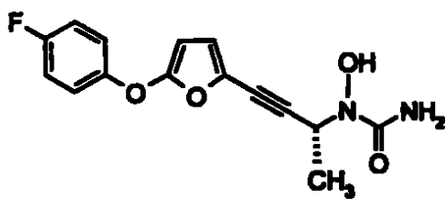
(5.2.4)



(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 $(CH_2)_5$ 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.

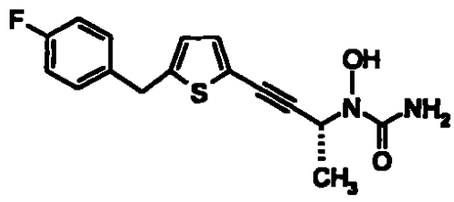
Another *N*-hydroxyurea compound is Abbott-79175 which is represented by Formula (5.2.6):



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):

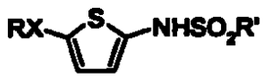


Abbott-85761 (5.2.7)

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.

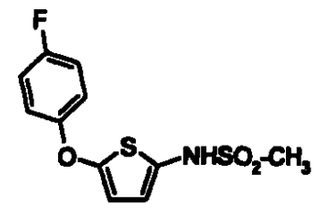
Fenleuton, Abbott-79175, Abbott-85761 or any of the above-described derivatives thereof or of tepoxalin, are combined with the compounds of Formula (1.0.0) to form embodiments of the present invention.

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)

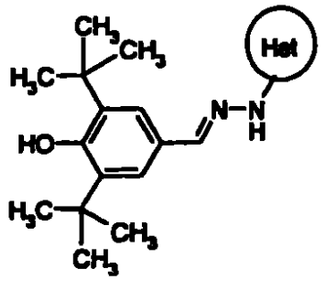
where X is O or S; R' is methyl, *iso*-propyl, *n*-butyl, *n*-octyl, or phenyl; and R is *n*-pentyl, cyclohexyl, phenyl, tetrahydro-1-naphthyl, 1- or 2-naphthyl, or phenyl mono- or di-substituted by Cl, F, Br, CH_3, OCH_3, SCH_3, SO_2CH_3, CF_3, or *iso*-propyl. A preferred compound is that of Formula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

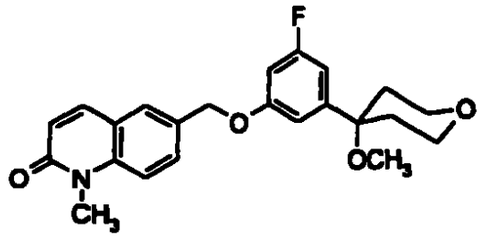


(5.2.10)

where "Het" is benzoxazol-2-yl; benzothizazol-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.

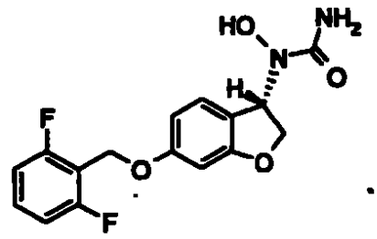
A further distinct class of 5-lipoxygenase inhibitors is that of methoxytetrahydropyrans to which Zeneca ZD-2138 belongs. ZD-2138 is represented by Formula (5.2.11):



(5.2.11)

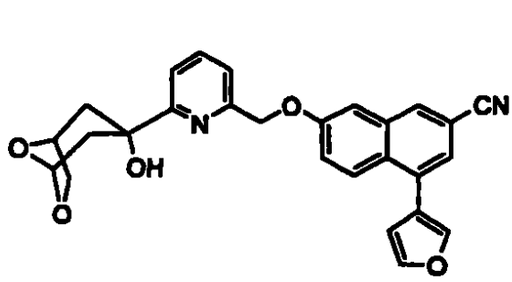
ZD-2138 is highly selective and highly active orally in a number of species and has been evaluated in the treatment of asthma and rheumatoid arthritis by oral admininstration. Further details concerning ZD-2138 and derivatives thereof are disclosed in Crawley *et al.*, *J. Med. Chem.*, 35 2600, 1992;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



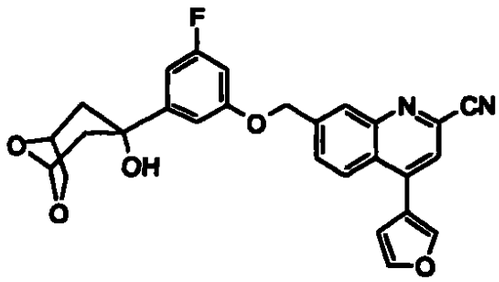
(5.2.12)

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-746,530, represented by Formulas (5.2.13) and (5.2.14) respectively:



L-739,010

(5.2.13)



L-746,530

(5.2.14)

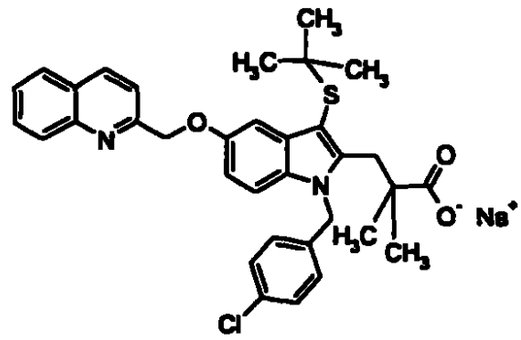
Details concerning L-739,010 and L-746,530 are disclosed in Dubé *et al.*, "Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746,530," *Bioorganic & Medicinal Chemistry* 6 1255-1260, 1998; and in WO 95/03309 (Friesen *et al.*).

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 quiflipon 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

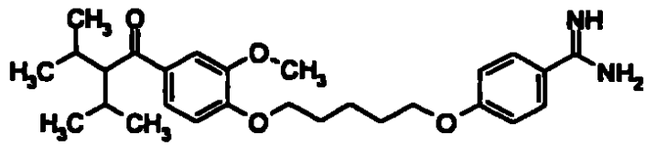
One or more compounds of Formula (1.0.0) is used in combination with receptor antagonists for leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4. The most significant of these leukotrienes in terms of mediating inflammatory response, are LTB_4 and LTD_4. Classes of antagonists for the receptors of these leukotrienes are described in the paragraphs which follow.

4-Bromo-2,7-diemethoxy-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):



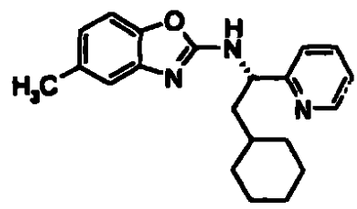
L-651,392 (5.2.16)

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 5,639,768 (Morrissey and Suh). These receptor antagonists for LTB_4 are typified by CGS-25019c, which is represented by Formula (5.2.17):



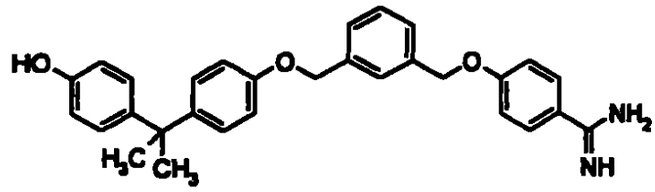
CGS-25019c (5.2.17)

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



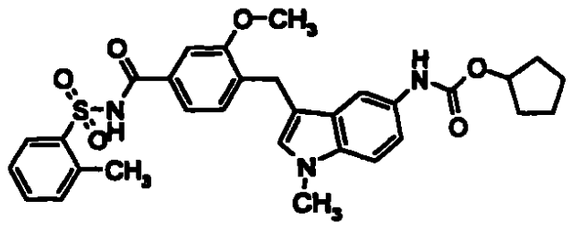
Ontazolast (5.2.18)

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):



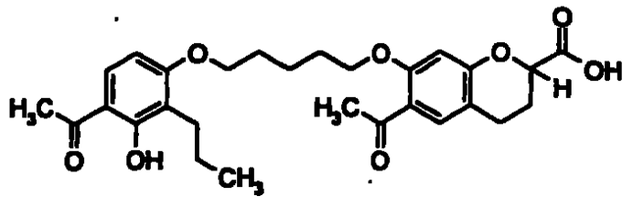
BIIL 284/260 (5.2.19)

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):



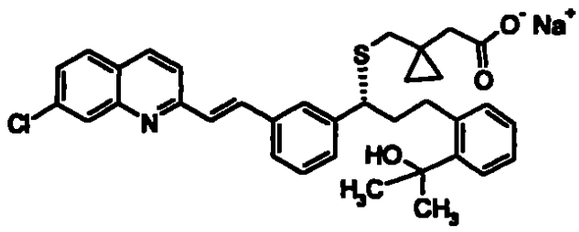
Zafirlukast (5.2.20)

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 benzoxaolamines 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, albuterol, 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.*, protamine 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 temetastine; 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_{30})alkyl sulfates, (C_{10} -C_{30})alkyl sulfonates, and (C_{10} -C_{30})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, parafin, synthetic parafin, 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, tallose, 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 instillation, inhalation or insufflation of a pharmaceutical composition in suitable solid form containing the active ingredient. Instillation 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 respsonse 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.

DETAILED DESCRIPTION OF THE INVENTION

11.0 Preparations and Working Examples

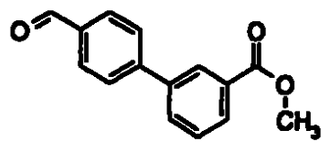
There follows a description of numerous Preparations by which intermediates used in preparing specific compounds of Formula (1.0.0) were made. There also follows numerous Examples showing preparation of specific compounds of Formula (1.0.0). These Preparations and Examples are intended to further illustrate the compounds of the present invention and processes in accordance with which they may be readily prepared by the artisan. The artisan will be aware of many other suitable processes that are also available, as well as acceptable variations in the processes described below.

The description which follows is for the purpose of illustrating the present invention and is not intended to in any way create limitations, express or implied, upon the scope of the present invention. The claims appended hereto are for the purpose of reciting the present invention, of expressing the contemplated scope thereof, and of pointing out particulars thereof.

In the following Preparations, analytical characterizations of the compounds prepared were made by mass spectral analyses determined by GCMS, AMPI, APCI or thermospray methods. All ^{1}H NMR spectra were taken on a 400 MHz instrument.

Preparation 1

4'-Formyl-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.1):



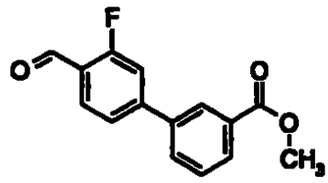
(9.0.1)

A mixture if 2.0 g (9.3. mmol.) methyl-3-bromobenzoate, 1.5 g (10.2 mmol.) 4-formylbenzeneboronic acid and 537 mg (0.47 mmol.) tetrakis(triphenylphosphine)-palladium in 14 mL (27.9 mmol.) 2M Na_2CO_3 and 15 mL dimethoxyethane was heated at 80°C for 4 hours. The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined then washed successively with 1N NaOH, 1N HCl, water, brine then dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Chromatography on Silica Gel eluting with ethyl acetate/hexanes (1:5) gave 1.6 g 4-formyl-biphenyl-3-carboxylic acid methyl ester as an oil.

MS (m/z): 240 (M^+, 100).

Preparation 2

3'-Fluoro-4'-formyl-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.2):



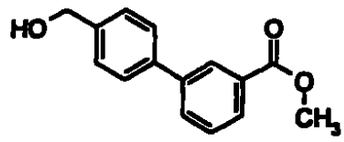
(9.0.2)

A mixture of 2.0 g (9.85 mmol.) 4-bromo-2-fluorobenzaldehyde, 2.8 g (10.8 mmol.) bis(pinacolato)diboron, 2.9 g (29.6 mmol.) potassium acetate and 216 mg (0.3 mmol.) bis(diphenylphosphino)ferrocene palladium dichloride in 60 mL dimethylformamide was heated at 80°C for 4 hours. The mixture was cooled and 4.2 g (19.7 mmol.) methyl 3-bromobenzoate and 216 mg (0.3 mmol.) bis(diphenylphosphino)ferrocene palladium dichloride was added and the mixture heated at 80°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined then washed successively with 1N NaOH, 1N HCl, water, brine then dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Chromatography on Silica Gel eluting with ethyl acetate/hexanes (1:5) gave 1.4 g 3'-fluoro-4'-formyl-biphenyl-3-carboxylic acid methyl ester as an oil.

MS (m/z): 258 (M^+, 100).

Preparation 3

4'Hydroxymethyl-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.3):



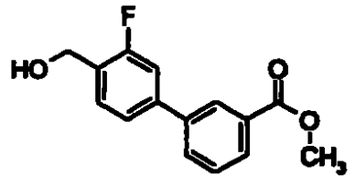
(5.0.3)

To a stirred mixture of 1.56 g (6.5 mmol.) 4-formyl-biphenyl-3-carboxylic acid methyl ester in 30 mL methanol at 0°C was added 307 mg (8.1 mmol.) sodium borohydride. The mixture was stirred at 0°C for 1 hour, then quenched with saturated ammonium chloride solution. The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed successively with water, brine then dried ($MgSO_4$) and concentrated *in vacuo* to yield an oil. Chromatography on Silica Gel eluting with ethyl acetate/hexanes (1:5) afforded 1.5 g 4'-hydroxymethyl-biphenyl-3-carboxylic acid methyl ester as an oil.

^{1}H-NMR ($CDC1_3$)δ 8.3 (dd, 1H, J=2, 3 Hz), 8.0 (ddd, 1H, J=1, 3, 8 Hz) 7.8 (m, 1H), 7.6 (ddd, 2H, J= 2, 4, 8 Hz), 7.5 (m, 3H), 4.7 (d, 2H, J=6 Hz), 3.9 (s, 3H).

Preparation 4

3'-Fluoro-4'-hydroxymethyl-biphenyl-3-carboxylix acid methyl ester of Formula (9.0.4):

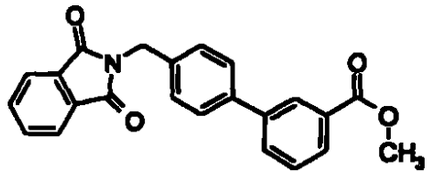


(9.0.4)

This compound was prepared from 3'-Fluoro-4'-formyl-biphenyl-3-carboxyl acid methyl ester in a manner analogous to Preparation 3.

Preparation 5

4'-[1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl]-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.5):



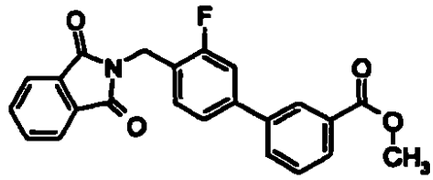
(9.0.5)

To a stirred mixture of 1.4 g (5.8 mmol.) 4'-hydroxymethyl-biphenyl-3-carboxylic acid methyl ester, 1.0 g (6.9 mmol.) phthalimide and 1.8 g (6.9 mmol.) triphenylphosphine in 25 mL tetrahydrofuran at 0°C was added 1.2 ml (7.5 mmol.) diethylazodicarboxylate. The mixture was warmed to ambient temperature and stirred for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined then washed successively with 1N NaOH, 1N HCl, water, brine then dried ($MgSO_4$) and concentrated *in vacuo* to give a solid. Trituration with diethyl ether gave 3.0 g 4'-[1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl]-biphenyl-3-carboxylic acid methyl ester as a solid.

MS (m/z): 371 (M^+, 100).

Preparation 6

4'-[1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl]-3'-fluoro-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.6):



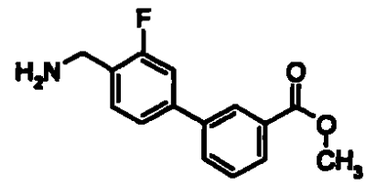
(9.0.6)

This compound was prepared from 3'-Fluoro-4'-hydroxymethyl-biphenyl-3-carboxylic acid methyl ester in a manner analogous to Preparation 5.

MS (m/z): 389 (M^+, 100).

Preparation 7

4'-Aminomethyl-3'-fluoro-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.7):



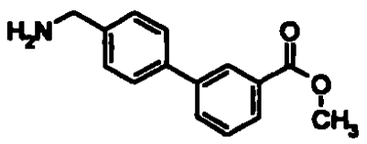
(9.0.7)

To a stirred mixture of 832 mg (2.14 mmol.) 4'-[1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl]-3'-fluoro-biphenyl-3-carboxylic acid methyl ester in 20 ml methanol and 10 ml tetrahydrofuran at ambient temperature was added 0.2 ml (6.42 mmol.) hydrazine hydrate. The mixture was stirred for 18 hours. and the resulting precipitate filtered. The filtrate volume was reduced in vacuo and poured into 0.5 N HCl and washed with diethyl ether. The aqueous extract was basified with 6N NaOH to pH 10 then extracted with ethyl acetate. The ethyl acetate extracts were combined, washed successively with water, brine then dried ($MgSO_4$) and concentrated *in vacuo* to give 400 mg 4'-aminomethyl-3'-fluoro-biphenyl-3-carboxylic acid methyl esters as an oil.

MS (m/z): 258 (M^+, 100).

Preparation 8

4'-Aminomethyl-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.8):



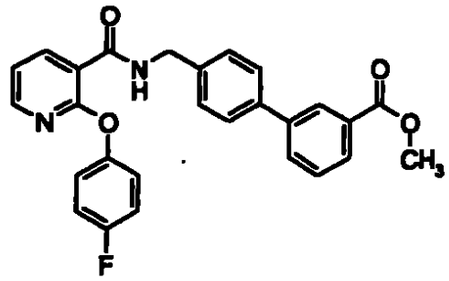
(9.0.8)

This compound was prepared from 4'-[1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl]-biphenyl-3-carboxylic acid methyl ester in a manner analogous to Preparation 7.

MS (m/z): 241 (M^+, 60), 240(100).

Preparation 9

4'[[[2-[4-Fluorophenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.9):



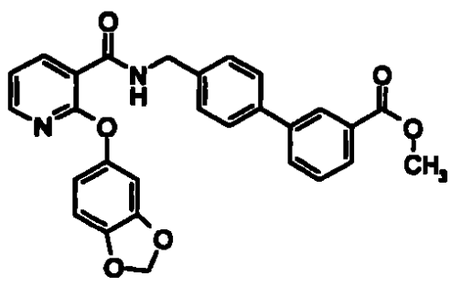
(9.0.9)

To a stirred solution of 290 mg (1.24 mmol.) 2-[4-fluoro-phenoxy]-nicotinic acid, 300mg (1.24 mmol.) 4'-aminomethyl-biphenyl-3-carboxylic acid methyl ester and 184 mg (1.36 mmol.) 1-hydroxybenzotriazole hydrate in 10 mL dimethylformamide at ambient temperature was added 285 mg (1.49 mmol.) 1-[3-[dimethylamino]propyl]-3-ethylcarbodiimide hydrochloride. The mixture was stirred at ambient temperature for 18 hours then poured into water and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed successively with 1N NaOH, water, brine then dried ($MgSO_4$) and concentrated *in vacuo* to give an oil. Chromatography on silica Gel eluting with ethyl acetate/hexanes (1:1) gave 310 mg 4'-[[[2-[4-Fluorophenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid methyl ester as an oil.

^{1}H-NMR($CDCl_3$): δ 8.6 (dd, 1H, J=2, 8 Hz), 8.2 (m, 3H), 8.0 (ddd, 1H, J=1, 3, 8 Hz), 7.7 (dd, 1H, J=1, 3, 8 Hz), 7.6 (dd, 2H, J=2, 6Hz), 7.4 (m, 3H), 7.2(m, 1H), 7.1 (d, 4H, J=7 Hz), 3.9 (s, 3H).

Preparation 10

4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.10):



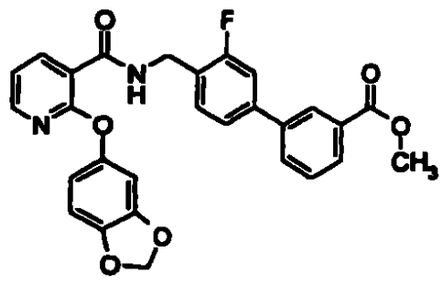
(9.0.10)

This compound was prepared from 2-[Benzo[1,3]dioxol-5-yloxy]-nicotinic acid and 4'-aminomethyl-biphenyl-3-carboxylic acid methyl ester in a manner analogous to Preparation 9.

MS (m/z): 483 (M^+,100).

Preparation 11

4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.11):



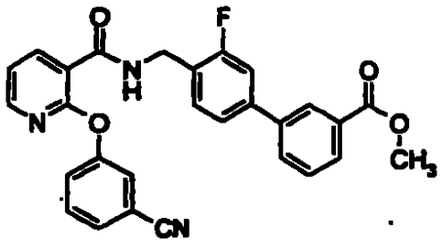
(9.0.11)

This compound was prepared from 2-[Benzo[1,3]dioxol-5-yloxy]-nicotinic acid and 4'-Aminomethyl-3'-fluoro-biphenyl-3-carboxylic acid methyl ester in a manner analogous to Preparation 9.

MS (m/z): 501 (M^+,100).

Preparation 12

4'-[[[2-[3-Cyano-phenoxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid methyl ester of Formula (9.0.12):



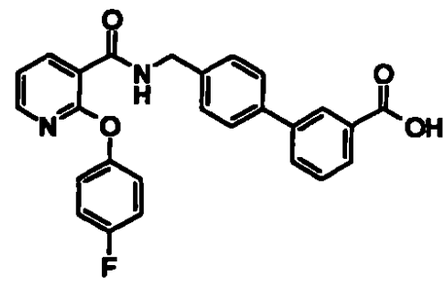
(9.0.12)

This compound was prepared from 2-[3-Cyano-phenoxy]-nicotinic acid and 4'-Aminomethyl-3'-fluoro-biphenyl-3-carboxylic acid methyl ester in a manner analogous to Preparation 9.

MS (m/z): 482 (M^+), 100).

Example 1

4'-[[[2-[4-Fluorophenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid of Formula (8.5.1):



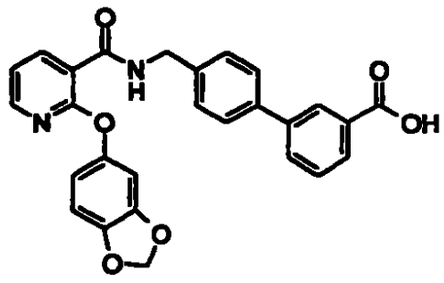
(8.5.1)

A mixture of 300 mg (0.66 mmol.) 4'-[[[2-[4-Fluorophenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid methyl ester and 1.6 mL 1.0 N NaOH in 10 mL t-butanol and 3 mL water and refluxed for 4 hours. The mixture was poured into water, acidified to pH 1 with 2N HCl, then extracted with ethyl acetate. The ethyl acetate extracted were combined, washed successively with water, brine then dried ($MgSO_4$) and concentrated to give an oil. Chromatography on Silica Gel eluting with methanol/dichloromethane (1:40) yielded a foam. Recrystallization from ethyl acetate/hexanes afforded 151 mg 4'-[[[2-[4-Fluorophenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid as a solid, mp 184-6°C.

Anal. Calcd. For $C_{26}H_{19}N_2O_4F$: C, 70.58; H, 4.33; N, 6.33. Found: C, 70.06; H, 4.25; N, 6.25.

Example 2

4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid of Formula (8.5.2)):



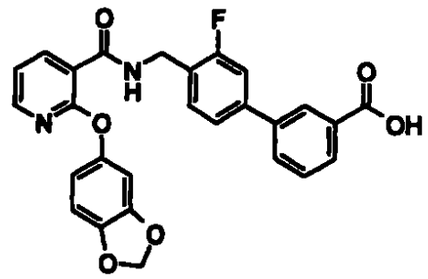
(8.5.2))

This compound was prepared from 4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid methyl ester in a manner analogous to Example 1, mp 175-7°C.

Anal. Calcd. For $C_{27}H_{20}N_2O_6$: C, 69.23; H, 4.30; N, 5.98. Found: C, 69.60; H, 4.59; N, 5.99.

Example 3

4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8.5.3)):



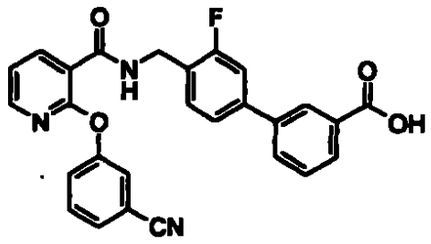
(8.5.3)

This compound was prepared from 4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid methyl ester in a manner analogous to Example 1, mp 190-2°C.

Anal. Calcd. For $C_{27}H_{19}N_2O_6F$: C, 66.67; H, 3.94; N, 5.76. Found: C, 66.68; H, 4.02; N, 5.95.

Example 4

4'-[[[2-[3-Cyano-phenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8.5.4):



(8.5.4)

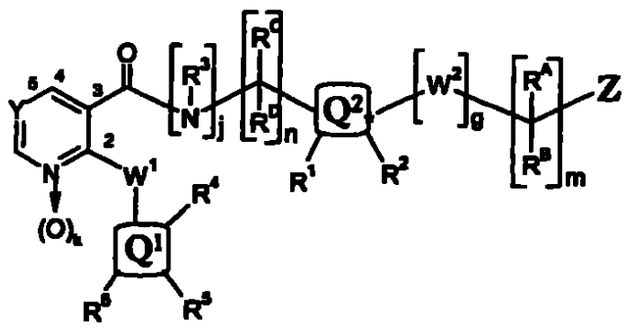
A mixture of 336 mg (0.7 mmol.) 4'-[[[2-[3-Cyano-phenoxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid methyl ester and 0.8 mL (0.8 mmol.) 1.0 N LiOH in 20 mL tetrahydrofuran and 2 mL water was stirred at ambient temperature for 18 hours. The mixture was poured into water, acidified to pH 1 with 1N HCl, then extracted with ethyl acetate. The ethyl acetate extracts were combined, washed successively with water, brine then dried ($MgSO_4$) and concentrated *in vacuo* to give a solid. Chromatography on Silica Gel eluting with methanol/dichloromethane (1:20) yielded a solid. Recrystallization from ethyl

acetate/hexane afforded 280 mg 4'-[[[2-[3-cyano-phenoxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid as a solid, mp 200-2°C.

Anal. Calcd. For $C_{27}H_{18}N_3O_4F$: C, 69.38; H, 3.88; N, 8.99. Found: C, 68.44; H, 3.97; N, 8.91.

WHAT IS CLAIMED IS:

1. A compound of Formula (1.0.0):



(1.0.0)

— wherein —

-g is 0 or 1;

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

-k is 0 or 1

-m is 0, 1, or 2;

-n is 1 or 2;

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

-W^2 is –O–; –S(=O)$_t$–, where t is 0, 1, or 2; –N(R^3)– where R^3 has the same meaning as defined below, or –C$R^{29}R^{30}$–;

— where —

–R^{29} and R^{30} are each a member independently selected from the group consisting of –H; –F; –CF_3; –(C_1-C_3) alkyl; –(C_3-C_6) cycloalkyl; phenyl; benzyl; and pyridyl; wherein said alkyl, cycloalkyl, phenyl, benzyl, and pyridyl moieties are each independently substituted with 0 to 3 substituents R^{10}, where R^{10} 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_3) alkyl; fluorinated-(C_1-C_3) 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 —

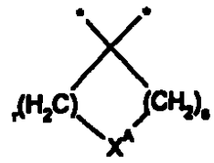
$-R^{11}$ is –F; –Cl; $-CF_3$; –CN; $-NO_2$; –OH; $-(C_1-C_3)$ alkoxy; $-(C_1-C_3)$ alkyl; or $-NR^{16}R^{17}$;

— 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 Q^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 Q^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; -$C(=O)NR^{16}R^{17}$; –$OC(=O)NR^{16}R^{17}$; -$NR^{22}_aC(=O)NR^{16}R^{17}$; -$NR^{22}_aC(=NR^{12})NR^{16}R^{17}$; -$NR^{22}_aC(=NCN)NR^{16}R^{17}$; -$NR^{22}_aC(=N\text{-}NO_2)NR^{16}R^{17}$; -$C(=NR^{22}_a)NR^{16}R^{17}$; -$CH_2C(=NR^{22}_a)NR^{16}R^{17}$; -$OC(=NR^{22}_a)NR^{16}R^{17}$; –$OC(=N\text{–}NO_2)NR^{16}R^{17}$; -$NR^{16}R^{17}$; -$CH_2NR^{16}R^{17}$; -$NR^{22}_aC(=O)R^{16}$; -$NR^{22}_aC(=O)OR^{16}$; =$NOR^{16}$; –$NR^{22}_aS(=O)_pR^{17}$ -$S(=O)_pNR^{16}R^{17}$; 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^{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 —

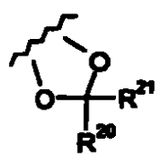
—R^{12} is a member independently selected from the group consisting of –F; –Cl; $-CO_2R^{16}$; $-OR^{16}$; –CN; $-C(=O)NR^{16}R^{19}$; $-NR^{16}R^{19}$; $-NR^{16}C(=O)R^{19}$; $-NR^{16}C(=O)OR^{19}$; $-NR^{16}S(=O)_pR^{19}$; $-S(=O)_pNR^{16}R^{19}$, where p is 1 or 2; $-(C_1-C_4)$ alkyl; and $-(C_1-C_4)$ 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^{16} has the same meaning as defined above; and

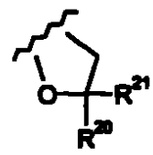
— where —

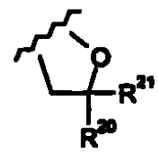
——R^{18} and R^{19} are independently selected from the group consisting of –H; $-(C_1-C_4)$ alkyl; and phenyl; where said alkyl or phenyl is substituted by 0-3 of –F; or –Cl;

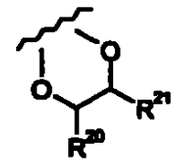
— or in the case where Q^1 is phenyl —

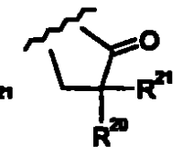
-(d) R^5 and R^6 are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3.1) through (1.3.15):

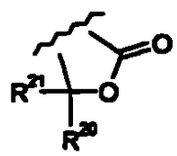

(1.3.1)

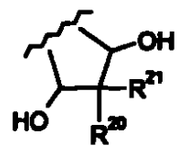

(1.3.2)

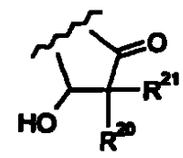

(1.3.3)

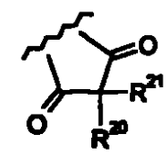

(1.3.4)

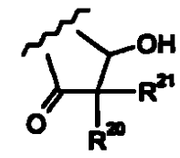

(1.3.5)

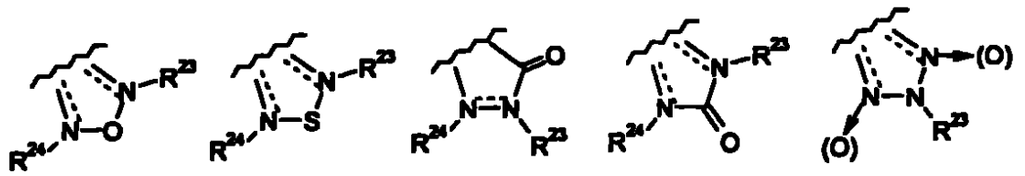

(1.3.6)


(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;

-Q^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 Q^1 is not a discontinuous or restricted biaryl moiety as defined under Q^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 —

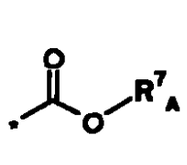
said moiety defining Q^1 is substituted on any ring or rings thereof by R^4, R^5 and R^6, which have the same meaning as defined above;

-Q^2 is a discontinuous or restricted biaryl moiety consisting of 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; 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;

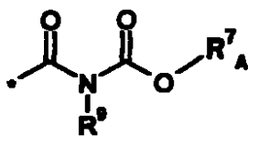
-Z is a member independently selected from the group consisting of

— the following —

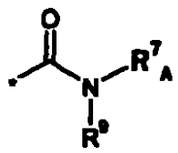
-*(a)* the group consisting of partial Formulas (1.1.1) through (1.1.15):



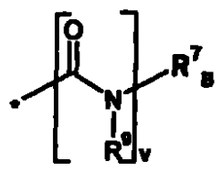
(1.1.1)



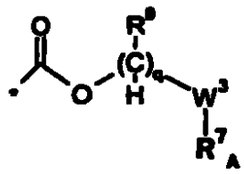
(1.1.2)



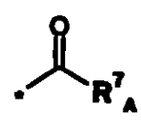
(1.1.3)



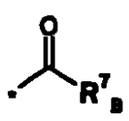
(1.1.4)



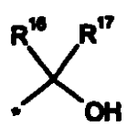
(1.1.5)



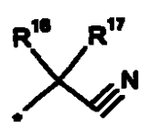
(1.1.6)



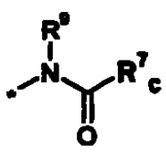
(1.1.7)



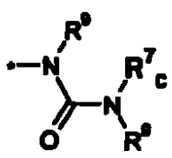
(1.1.8)



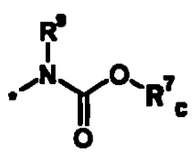
(1.1.9)



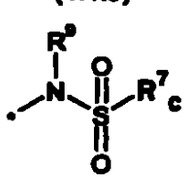
(1.1.10)



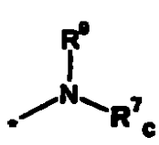
(1.1.11)



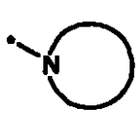
(1.1.12)



(1.1.13)



(1.1.14)



(1.1.15)

— wherein —

where R^{16} and R^{17} have the same meanings as defined above; and R^9 has the same meaning as defined below;

–"*" indicates the point of attachment of each partial Formula (1.1.1) through (1.1.15) 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)—;

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

— the following: —

—(1) 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; parathiazinyl; 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;

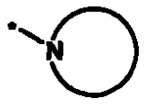
— where —

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^{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^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^{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;

—R^7c is a member independently selected from the group consisting of the meanings of R^7A and the meanings of R^7B defined above;

— and further wherein —



(1.1.15)

—comprises a saturated or unsaturated, 4– to 8–membered monocyclic, or 5– to 10–membered fused or open bicyclic, carbocyclic ring system containing a nitrogen heteroatom as shown in partial Formula (1.1.15); wherein optionally from 1 to 3 carbon atoms of said carbocyclic ring system may be individually replaced by a nitrogen heteroatom; or optionally 1 carbon atom thereof may be replaced by an oxygen heteroatom or by a sulfur heteroatom; or optionally 2 carbon atoms thereof may be individually replaced by a nitrogen heteroatom and an oxygen heteroatom, or by a nitrogen heteroatom and a sulfur heteroatom;

— where —

any moiety of partial Formula (1.1.15) recited above is optionally substituted with respect to *(1)* any one or more carbon atoms thereof, by a substituent R^{14} where R^{14} has the same meaning as defined above; *(2)* any one or more nitrogen atoms thereof by a substituent R^{15} where R^{15} has the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms thereof; or *(3)* any sulfur atom thereof by 0, 1, or 2 oxygen atoms;

— and Z 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)$_2$OH (sulfuric); –S(=O)$_2$OH (sulfonic); –S(=O)$_2$$NHR^{25}$ or -NHS(=O)$_2$$R^{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)$_2$$R^{25}$; -C(=O)NHS(=O)$_2$$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$;

$-S(=O)_2NHC(=O)NH(C_1-C_4)$ 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 $-S(=O)_2NHS(=O)_2R^{25}$;

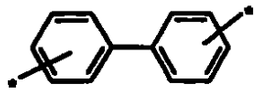
— where —

$-R^{25}$ is –H; $-(C_1-C_4)$ alkyl; phenyl; or $-OR^{18}$, where R^{18} has the same meaning as defined above;

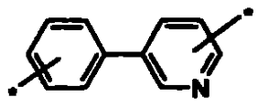
— or —

a pharmaceutically acceptable salt thereof.

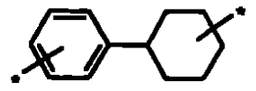
2. A compound according to Claim 1 wherein the group Q^2 comprises a member selected from the group consisting of the following moieties represented by partial Formulas (1.2.1) through (1.2.32):



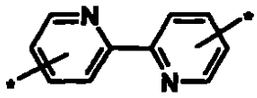
(1.2.1)



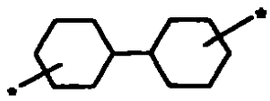
(1.2.2)



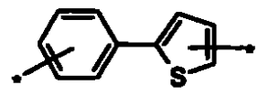
(1.2.3)



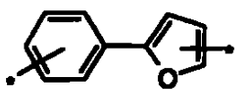
(1.2.4)



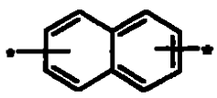
(1.2.5)



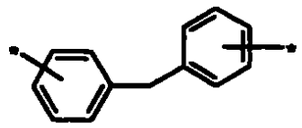
(1.2.6)



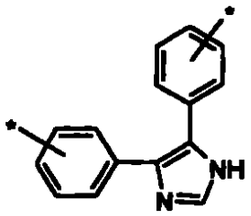
(1.2.7)



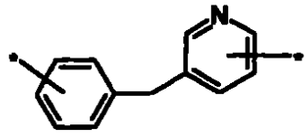
(1.2.8)



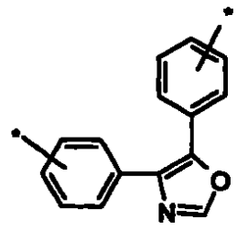
(1.2.9)



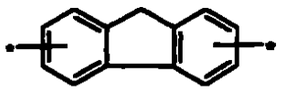
(1.2.10)



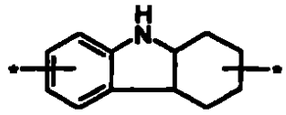
(1.2.11)



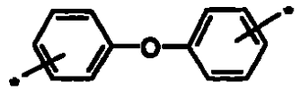
(1.2.12)



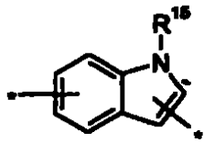
(1.2.13)



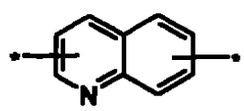
(1.2.14)



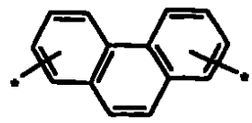
(1.2.15)



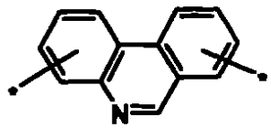
(1.2.16)



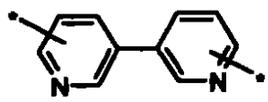
(1.2.17)



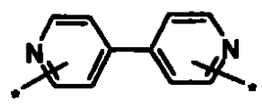
(1.2.18)



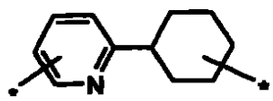
(1.2.19)



(1.2.20)



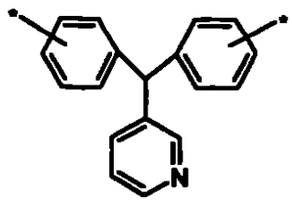
(1.2.21)



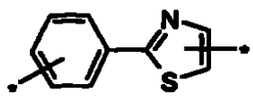
(1.2.22)



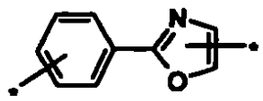
(1.2.23)



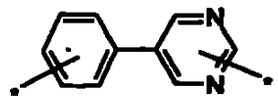
(1.2.24)



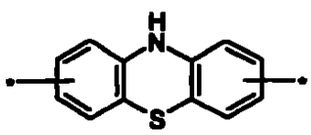
(1.2.25)



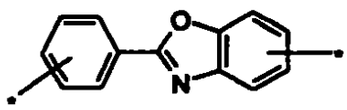
(1.2.26)



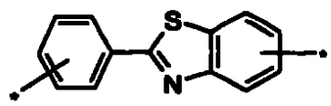
(1.2.27)



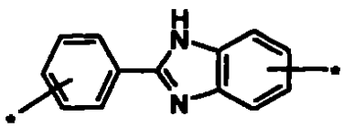
(1.2.28)



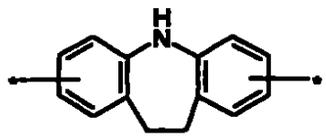
(1.2.29)



(1.2.30)



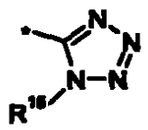
(1.2.31)



(1.2.32)

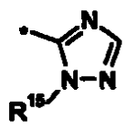
wherein " * " is a symbol indicating the two points of attachment of said group Q^2 to the remaining components of Formula (1.0.0).

3. A compound according to Claim 1 wherein Z comprises partial Formulas (1.1.4) and (1.1.10) through (1.1.14), and the meaning of R^7_B of partial Formula (1.1.4) where v is 0 or 1, or the meaning of R^7_C of partial Formulas (1.1.10) through (1.1.14) is defined as a member selected from the group consisting of partial Formulas (1.4.1) through (1.4.28):



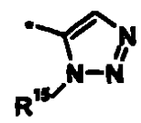
tetrazol-5-yl

(1.4.1)



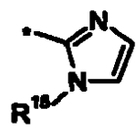
1,2,4-triazol-3-yl

(1.4.2)



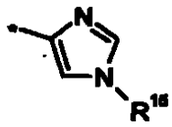
1,2,3-triazol-5-yl

(1.4.3)



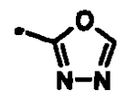
imidazol-2-yl

(1.4.4)



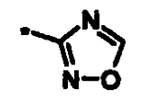
imidazol-4-yl

(1.4.5)



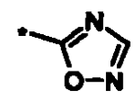
1,3,4-oxadiazolyl

(1.4.6)



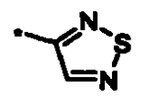
1,2,4-oxadiazol-3-yl

(1.4.7)



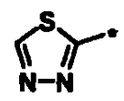
1,2,4-oxadiazol-5-yl

(1.4.8)



1,2,5-thiadiazol-2-yl

(1.4.9)



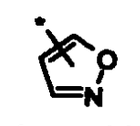
1,3,4-thiadiazolyl

(1.4.10)



oxazolyl

(1.4.11)



isoxazolyl

(1.4.12)



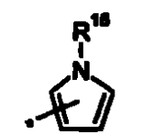
thiazolyl

(1.4.13)



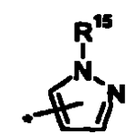
isothiazolyl

(1.4.14)



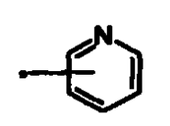
pyrrolyl

(1.4.15)



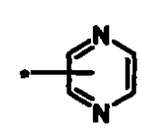
pyrazolyl

(1.4.16)



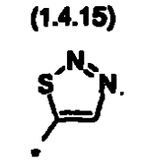
pyridyl

(1.4.17)



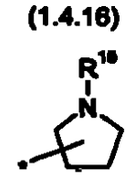
pyrazinyl

(1.4.18)



1,2,3-thiadiazol-5-yl

(1.4.19)



pyrrolidinyl

(1.4.20)



furanyl

(1.4.21)



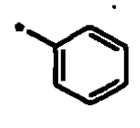
tetrahydrofuranyl

(1.4.22)



thienyl

(1.4.23)



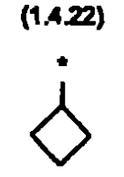
phenyl

(1.4.24)



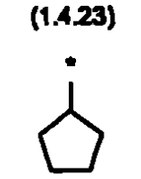
cyclopropyl

(1.4.25)



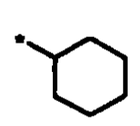
cyclobutyl

(1.4.26)



cyclopentyl

(1.4.27)



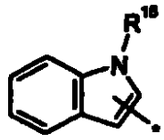
cyclohexyl

(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}

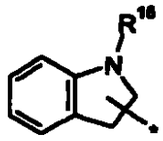
have the same meaning as defined in Claim 1; and all tautomer forms, and optionally N-oxide forms, thereof.

4. A compound according to Claim 1 wherein Z comprises partial Formulas (1.1.4) and (1.1.10) through (1.1.14) and the meanings of R^7_B and R^7_C in said partial Formulas are each independently a member selected from the group consisting of partial Formulas (1.5.1) through (1.5.29):



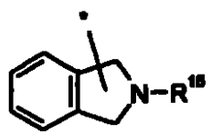
indolyl

(1.5.1)



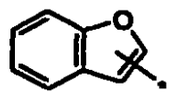
indolinyl

(1.5.2)



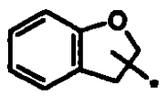
isoindolinyl

(1.5.3)



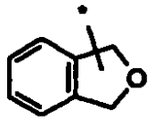
benzo[*b*]furanyl

(1.5.4)



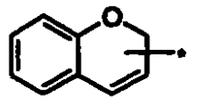
2,3-dihydrobenzofuranyl

(1.5.5)



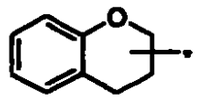
1,3-dihydroisobenzofuranyl; phthalanyl

(1.5.6)



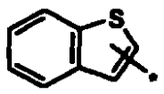
2*H*-1-benzopyranyl

(1.5.7)



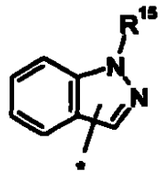
chromanyl

(1.5.8)



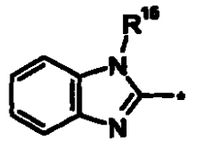
benzothienyl

(1.5.9)



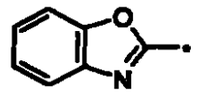
1*H*-indazolyl

(1.5.10)



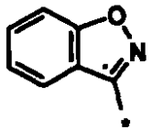
benzimidazolyl

(1.5.11)



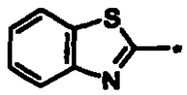
benzoxazolyl

(1.5.12)



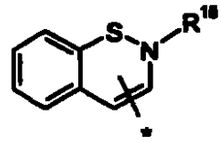
benzisoxazolyl

(1.5.13)



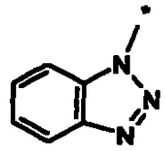
benzothiazolyl

(1.5.14)



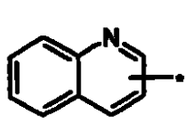
2H-1,2-benzothiazinyl

(1.5.15)



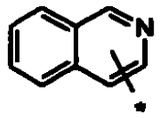
benzotriazolyl

(1.5.16)



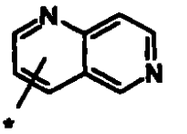
quinolinyl

(1.5.17)



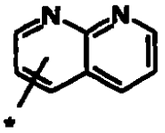
isoquinolinyl

(1.5.18)



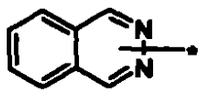
1,6-naphthyridinyl

(1.5.19)



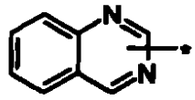
1,8-naphthyridinyl

(1.5.20)



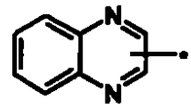
phthalazinyl

(1.5.21)



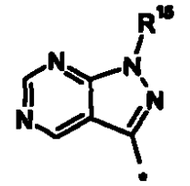
quinazolinyl

(1.5.22)



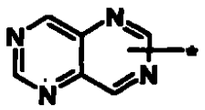
quinoxalinyl

(1.5.23)



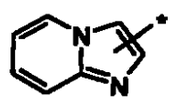
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(1.5.24)



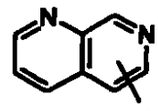
pyrimido[5,4-*d*]-pyrimidinyl

(1.5.25)



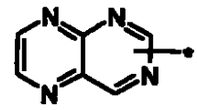
imidazo-[1,2-*a*]-pyridinyl

(1.5.26)



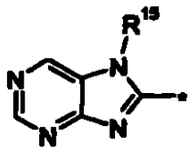
1,7-naphthyridinyl

(1.5.27)



pteridinyl

(1.5.28)

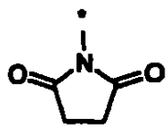


1*H*-purinyl

(1.5.29)

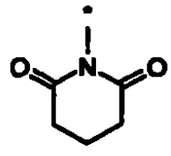
where "*" indicates the point of attachment to the remaining portion of Formula (1.0.0); and where each carbon atom is optionally substituted by a substituent R^{14}; and where R^{14} and R^{15} have the same meaning as defined in Claim 1; and all tautomer forms, and optionally N-oxide forms, thereof.

5. A compound according to Claim 1 wherein Z comprises a member selected from the group consisting of partial Formulas (1.7.1) through (1.7.46):



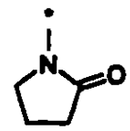
Succinimid-1-yl

(1.7.1)



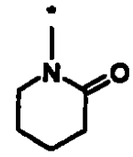
glutarimid-1-yl

(1.7.2)



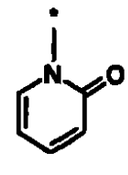
pyrrolidin-2-on-1-yl

(1.7.3)



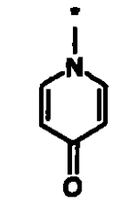
piperid-2-on-1-yl

(1.7.4)



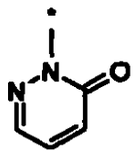
Pyrid-2-on-1-yl

(1.7.5)



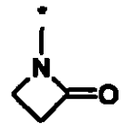
pyrid-4-on-1-yl

(1.7.6)



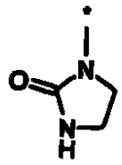
pyridazin-3-on-2-yl

(1.7.7)



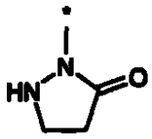
azetidin-2-on-1-yl

(1.7.8)



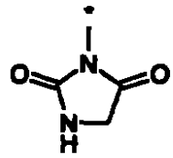
Imidazolidin-2-on-1-yl

(1.7.9)



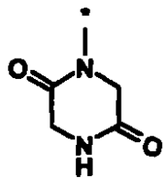
pyrazol-5-on-1-yl

(1.7.10)



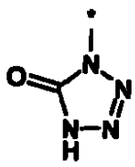
imidazolidin-2,4-dion-1-yl

(1.7.11)



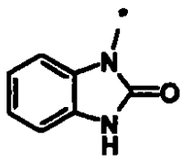
piperazin-2,5-dion-1-yl

(1.7.12)



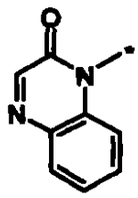
4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl

(1.7.13)



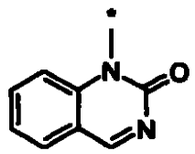
benzimidazolin-2-on-1-yl

(1.7.14)



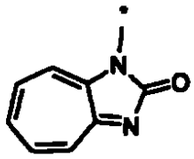
1*H*-quinoxalin-2-on-1-yl

(1.7.15)



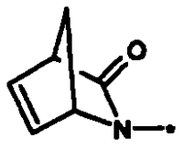
1*H*-quinazolin-2-on-1-yl

(1.7.16)



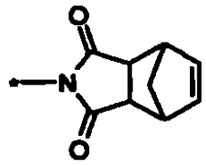
1H-cycloheptimid-azol-2-on-1-yl

(1.7.17)



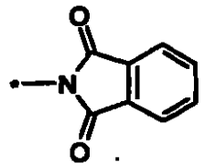
2-azabicyclo[2.2.1]-hept-5-en-3-on-1-yl

(1.7.18)



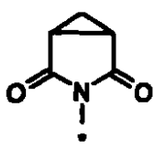
norborn-5-en-2,3-dicarboximid-1-yl

(1.7.19)



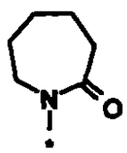
phthalimid-1-yl; 1*H*-isoindole-1,3(2*H*)-dion-1-yl

(1.7.20)



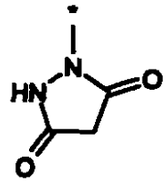
3-azabicyclo[3.1.0]-hexane-2,4-dion-3-yl

(1.7.21)



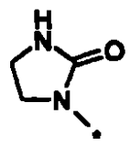
2*H*-azepin-2-on-1-yl

(1.7.22)



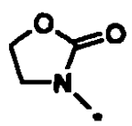
pyrazolidin-3,5-dion-1-yl

(1.7.23)



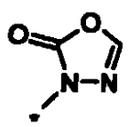
imidazolidin-2-on-1-yl

(1.7.24)



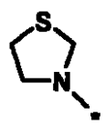
Oxazolidin-2-on-1-yl

(1.7.25)



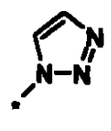
1,3,4-oxadiazol-2(3*H*)-on-3-yl

(1.7.26)



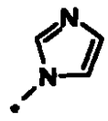
thiazolidin-3-yl

(1.7.27)



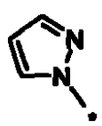
1*H*-1,2,3-triazol-1-yl

(1.7.28)



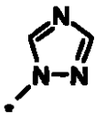
Imidazol-1-yl

(1.7.29)



pyrazol-1-yl

(1.7.30)



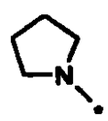
1*H*-1,2,4-triazol-1-yl

(1.7.31)



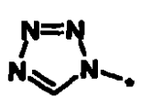
azetidin-1-yl

(1.7.32)



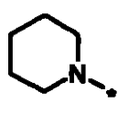
Pyrrolidin-1-yl

(1.7.33)



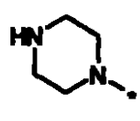
tetrazol-1-yl

(1.7.34)



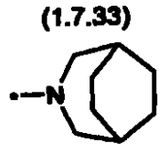
piperidin-1-yl

(1.7.35)



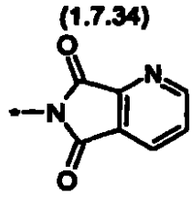
piperazin-1-yl

(1.7.36)



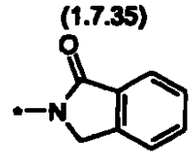
3-azabicyclo[3.2.2]-non-3-yl

(1.7.37)



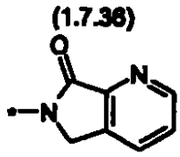
pyrrolo[3,4-*b*]pyridin-5,7-dion-6-yl

(1.7.38)



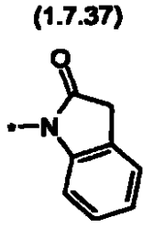
2,3-dihydro-*iso*-indol-1-on-2-yl

(1.7.39)



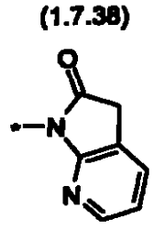
pyrrolo[3,4-*b*]pyridin-7-on-6-yl

(1.7.40)



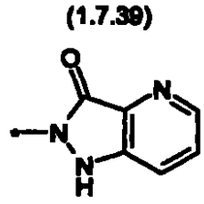
1,3-dihydro-indol-2-on-1-yl

(1.7.41)



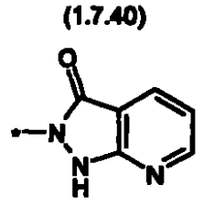
pyrrolo[4,5-*b*]pyridin-3-on-2-yl

(1.7.42)



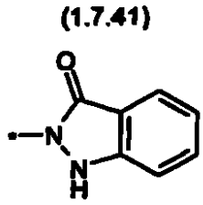
1*H*-pyrazolo[4,5-*e*]pyridin-7-on-2-yl

(1.7.43)



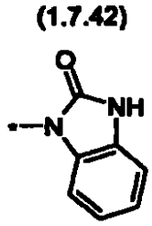
1*H*-pyrazolo[4,5-*b*]pyridin-4-on-2-yl

(1.7.44)



1*H*-indazol-3-on-2-yl

(1.7.45)



1*H*-benzimidazol-2-on-3-yl

(1.7.46)

where "*" indicates the point of attachment to the remaining portion of Formula (1.0.0); where each carbon atom is optionally substituted by a substituent R^{14}; and where each nitrogen atom is optionally substituted by a substituent R^{15}; where R^{14} and R^{15} have the same meaning as defined in Claim 1; and all tautomer forms, and optionally N-oxide forms, thereof.

6. A compound according to Claim 1 wherein said compound is a member selected from the group consisting of the following:

4'-[[[2-[4-Fluorophenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid of Formula (8.5.1);

4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3-carboxylic acid of Formula (8.5.2);

4'-[[[2-Benzo[1,3]dioxol-5-yloxy]-pyridine-3-carbonyl]-amino]-methyl]-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8.5.3);

4'-[[[2-[3-Cyano-phenoxy]-pyridine-3-carbonyl]-amino]-methyl]-biphenyl-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8.5.4);

[4'-({[2-(Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-acetic acid of Formula (8.5.5);

[4'-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-acetic acid of Formula (8.5.6);

[4'-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-acetic acid of Formula (8.5.7);

(±)-2-[4'-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-propionic acid of Formula (8.5.8);

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-(2'-fluoro-4'[1-(1H-tetrazol-5-yl)-ethoxy]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.9);

(±)-2-[4'-({[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-2-yloxy]-propionic acid of Formula (8.5.10);

(±)-2-(Benzo[1,3]dioxol-5-yloxy)-N-(2'-fluoro-4'[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.11);

(±)-N-[4'-(1-Carbamoyl-ethoxy)-2'-fluoro-biphenyl-4-ylmethyl]-2-(3-cyano-phenoxy)-nicotinamide of Formula (8.5.12);

(±)-2-[2,3'-Difluoro-4'-({[2-(3-methoxy-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-propionic acid of Formula (8.5.13);

2-(Benzo[1,3]dioxol-5-yloxy)-N-(4'-carbamoylmethyl-3-fluoro-biphenyl-4-ylmethyl)-nicotinamide of Formula (8.5.14);

[4'-({[2-(3-Cyano-phenoxy)-3-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-4-yl]-acetic acid of Formula (8.5.15);

2-(Benzo[1,3]dioxol-5-yloxy)-N-{4'-[(2-cyano-benzoylamino)-methyl]-2'-fluoro-biphenyl-4-ylmethyl}-5-fluoro-nicotinamide of Formula (8.5.16);

Pyridine-2-carboxylic acid (3'-fluoro-4'-{[2-(4-fluoro-phenoxy)-nicotinamide]-methyl}-biphenyl-4-ylmethyl)-amide of Formula (8.5.17);

2-(Benzo[1,3]dioxol-5-yloxy)-N-[2'-fluoro-4'-[1-methyl-1-(1H-tetrazol-5-yl)-ethyl]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.18);

5-Fluoro-N-(3-fluoro-4'-{[(5-methyl-4H-[1,2,4]triazole-3-carbonyl)-amino]-methyl}-biphenyl-4-ylmethyl)-2-(3-methoxy-phenoxy)-nicotinamide of Formula (8.5.19);

2-(Benzo[1,3]dioxol-5-yloxy)-N-[2'-fluoro-4'-[(2-methoxy-benzoylamino)-methyl]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.20);

N-[4'-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2'-fluoro-biphenyl-4-ylmethyl]-2-(4-fluoro-phenoxy)-nicotinamide of Formula (8.5.21);

N-(2'-Fluoro-4'-{[(3H-imidazole-4-carbonyl)-amino]-methyl}-biphenyl-4-ylmethyl)-2-(3-nitro-phenoxy)-nicotinamide of Formula (8.5.22);

(±)-3-[4'-({[2-(3-Chloro-4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-butyric acid of Formula (8.5.23);

2-[4'-({[2-Benzo[2,1,3]thiadiazol-5-yloxy)-pyridine3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yl]-2-methyl-propionic acid of Formula (8.5.24);

(±)-2-[4'-({[2-(Benzo[2,1,3]oxadiazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-propionic acid of Formula (8.5.25);

(±)-2-[3'-Fluoro-4'-({[2-(2-methyl-2H-benzotriazol-5-yloxy)-pyridine-3-carbonyl]-amino}-methyl)-biphenyl-4-yloxy]-propionic acid of Formula (8.5.26);

2-(3-Cyano-phenoxy)-N-[2'-fluoro-4'(pyridin-2-ylmethyl)-carbamoyl]-biphenyl-4-ylmethyl}-nicotinamide of Formula (8.5.27);

2-(Benzo[1,3]dioxol-5-yloxy)-N-[2'-fluoro-4'-[(quinolin-2-ylmethyl)-carbamoyl]-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.28);

5-Fluoro-2-(4-fluoro-phenoxy)N-[3-fluoro-3'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.29);

N-[3-Fluoro-4'-[(1-hydroxy-pyridin-2-ylmethyl)-carbamoyl]-biphenyl-4-ylmethyl]-2-(3-methoxy-phenoxy)-nicotinamide of Formula (8.5.30);

(±)-N-[3-Fluoro-4'-(2-hydroxy-1,2-dimethyl-propoxy)-biphenyl-4-ylmethyl]-2-(4-fluoro-phenoxy)-nicotinamide of Formula (8.5.31);

N-[2'-Fluoro-4'-(1-hydroxy-1-methyl-ethyl)-biphenyl-4-ylmethyl]-2-(4-fluoro-phenoxy)-nicotinamide of Formula (8.5.32); and

2-(3-Chloro-4-fluoro-phenoxy)-N-[4'-(pyridin-2-ylmethoxy)-biphenyl-4-ylmethyl]-nicotinamide of Formula (8.5.33).

7. A method of treating a subject suffering from a disease, disorder or condition mediated by the PDE4 isozyme, including the D subtype thereof, whereby it regulates the activation and degranulation of 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.

8. A pharmaceutical composition for use in treating a subject suffering from a disease, disorder or condition mediated by the PDE4 isozyme, including the D subtype thereof, 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.

9. A method according to Claim 8 wherein said disease, disorder, or condition comprises one or more members selected from the group 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 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-□ in their host, or wherein such viruses are sensitive to upregulation of TNF-□ 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-□ or elicit TNF-□ production in their host, when administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections, including but not limited to, polymixins, Polymycin B; lmidazoles, clotrimazole, econazole, miconazole, and ketoconazole; triazoles, fluconazole and itranazole; and amphotericins, 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.

10. 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); 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-748,530 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;

(l) β_1— to β_4—adrenoceptor agonists including isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol;

(m) 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 flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate;

(t) Tryptase inhibitors;

(u) Platelet activating factor (PAF) antagonists;

(v) Monoclonal antibodies 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) Anti-emetic agents including NK-1 receptor antagonists and D-4418; and

(vv) Anti-depressants.

DERIVADOS BIARÍLICOS DE NICOTINAMIDA DE UTILIDAD COMO INHIBIDORES DE ISOZIMAS PDE4

1.0 REFERENCIA A LAS SOLICITUDES DE PATENTE EN TRAMITACIÓN CON LA PRESENTE

Se hace referencia a la solicitud de patente internacional en tramitación con la presente y a la solicitud de patente de Estados Unidos basada en ella, con el nº de serie PCT/IB98/315, ambas presentadas el 10 de marzo de 1998 (expediente del abogado nº PC9762A) y publicada como documento WO 98/45268 el 15 de octubre, 1998; reivindicando la prioridad de la solicitud de patente con nº de serie 60/043403 presentada el 4 de abril de 1997 (expediente del abogado nº PC9762), a la que se ha renunciado; que describe derivados de nicotinamida que tienen actividad biológica como inhibidores selectivos de la isozima PDE4D, y son por tanto de utilidad en el tratamiento de enfermedades y afecciones inflamatorias, respiratorias y alérgicas. Nada de lo que se describe en las solicitudes mencionadas anteriormente podría enseñar a los expertos en la técnica pertinente los compuestos novedosos de la presente invención o el nivel inesperadamente elevado de selectividad de inhibición por la isozima PDE4D que poseen dichos compuestos novedosos.

Se hace referencia también a la solicitud de patente en tramitación con la presente con nº de serie 09/345.185 presentada el 30 de junio de 1999 (expediente del abogado nº PC10096A); que reivindica prioridad de la solicitud de patente con nº de serie 60/105.120, presentada el 21 de octubre de 1998 (expediente del abogado nº PC10096), que describe compuestos y procesos para preparar derivados de nicotinamida sustituida en N. Sin embargo, los compuestos y procesos descritos no son los mismos que los de la presente invención.

Se hace referencia adicionalmente a las solicitudes de patentes en tramitación con la presente presentadas el mismo día que la presente solicitud, expediente del abogado nº PC11712; PC11848; PC11893; PC11894; PC11895; y PC11896, que implican otras clases de derivados de nicotinamida de utilidad como inhibidores de isozimas PDE4. Las descripciones de todas las solicitudes de patentes en tramitación con la presente se incorporan a la presente como referencia en su totalidad.

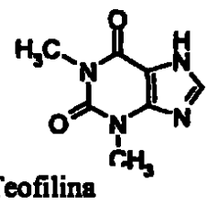
2.0 ANTECEDENTES DE LA INVENCIÓN

Las 3',5'- nucleótido fosfodiesterasas cíclicas (PDE) comprenden una gran clase de enzimas divididas en al menos once familias diferentes que son estructural, bioquímica y farmacológicamente diferentes las unas de las otras. Las enzimas de cada familia se denominan comúnmente isoenzimas o isozimas. En esta clase está incluido un total de más de quince productos génicos, y el empalme diferencial y procesamiento posttraslacional de esos productos génicos dan como resultado una mayor diversidad. La presente invención concierne principalmente a los cuatro productos génicos de la cuarta familia de PDE, es decir, PDE4A, PDE4B, PDE4C, y PDE4D. Estas enzimas se denominan colectivamente isoformas o subtipos de la familia de isozimas PDE4. Más adelante se encontrará un análisis más detallado de la organización genómica, estructura molecular y actividad enzimática, empalme diferencial, regulación y fosforilación transcripcionales, distribución y expresión, e inhibición selectiva de los subtipos de isozimas PDE4.

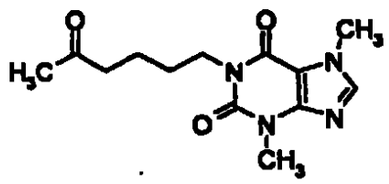
Las PDE4 se caracterizan por la degradación hidrolítica selectiva de afinidad elevada del segundo nucleótido cíclico mensajero, adenosin 3',5'-monofosfato cíclico (AMPc), y por la sensibilidad a la inhibición por rolipram. En los últimos años se han descubierto numerosos inhibidores selectivos de las PDE4, y se han demostrado efectos

farmacológicos beneficiosos como resultado de dicha inhibición en una diversidad de modelos de enfermedades. Véase, p. e., Torphy y cols., *Environ. Health Perspect.* 102 Supl. 10, 79-84, 1994; Duplantier y cols, *J. Med. Chem.* 39 120-125, 1996; Schneider y cols., *Pharmacol. Biochem. Behav.* 50 211-217, 1995; Banner y Page, *Br. J. Pharmacol.* 114 93-98, 1995; Barnette y cols., *J. Pharmacol. Exp. Ther.* 273 674-679, 1995 ; Wright y cols., " 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 y cols. "Anti-inflammatory and bronchodilator properties of KF19514, a phosphodiesterase 4 and 1 inhibitor ," *Eur. J. Pharmacol.* 332 97-107, 1997; y Ukita y cols. "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. En consecuencia, continúa habiendo un interés considerable en la técnica en lo que respecta al descubrimiento de más inhibidores selectivos de las PDE4 adicionales.

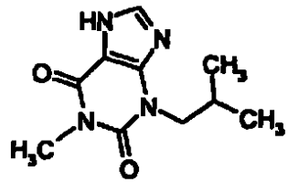
La presente invención concierne también al uso de inhibidores selectivos de PDE4 para el tratamiento terapéutico mejorado de numerosas enfermedades y afecciones inflamatorias respiratorias y alérgicas, pero especialmente para el tratamiento del asma; enfermedad pulmonar obstructiva crónica (COPD) incluyendo bronquitis crónica, enfisema, y bronquiectasia; rinitis crónica; y sinusitis crónica. Hasta la fecha en la técnica, sin embargo, la terapia de primera línea para el tratamiento del asma y otras enfermedades de obstrucción de las vías respiratorias ha sido el inhibidor de PDE no selectivo teofilina, así como pentoxifilina e IBMX, que pueden representarse mediante 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)

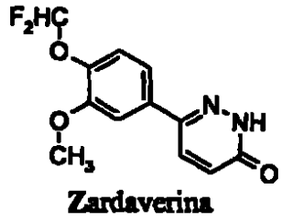
La teofilina, que tiene las PDE como una de sus dianas bioquímicas, además de su bien caracterizada actividad broncodilatadora, afecta los vasos sanguíneos de los pacientes aumentando la presión arterial pulmonar, suprime las respuestas inflamatorias celulares, e induce la apoptosis de los eosinófilos. Sin embargo, los efectos adversos de la teofilina, más comúnmente arritmias cardíacas y nauseas, están mediados también por la inhibición de PDE, lo que lleva a la búsqueda de inhibidores más selectivos de las PDE que sean capaces de suprimir tanto las funciones celulares inmunitarias *in vitro* como la inflamación pulmonar alérgica *in vivo*, teniendo a la vez unos perfiles de efectos secundarios mejorados. En las vías respiratorias de los pacientes que sufren de asma y otras enfermedades de obstrucción de las vías respiratorias, PDE4 es la más importante de las isozimas PDE como diana para el descubrimiento de fármacos debido a su distribución en las células del músculo liso e inflamatorias de las vías respiratorias. Los diversos inhibidores de PDE4 introducidos en la técnica hasta la fecha han sido diseñados para tener un índice terapéutico mejorado en lo que se refiere a los efectos

secundarios cardiovasculares, gastrointestinales y del sistema nervioso central de las xantinas no selectivas mencionadas anteriormente.

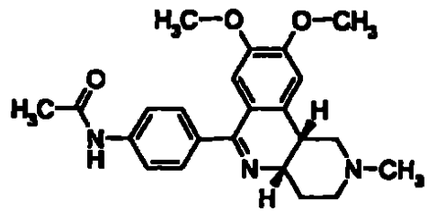
La obstrucción del flujo de aire y la inflamación de las vías respiratorias son características del asma así como de la COPD. Aunque el asma bronquial está predominantemente caracterizada por una inflamación eosinófila, los neutrófilos parecen desempeñar un papel fundamental en la patogénesis de la COPD. Por lo tanto, las PDE que están implicadas en la relajación de los músculos lisos y que se encuentran también en eosinófilos así como neutrófilos probablemente constituyen un elemento esencial del progreso de ambas enfermedades. Las PDE implicadas incluyen las PDE3 así como las PDE4, y se han descubierto inhibidores broncodilatadores que son inhibidores selectivos de PDE3 e inhibidores selectivos duales de PDE3/4. Los ejemplos de éstos son milrinona, un inhibidor selectivo de PDE3, así como zardaverina y benafentrina, ambos inhibidores selectivos duales de PDE3/4, que pueden representarse mediante las Fórmulas (0.0.4), (0.0.5), y (0.0.6), respectivamente:



Milrinona
(0.0.4)



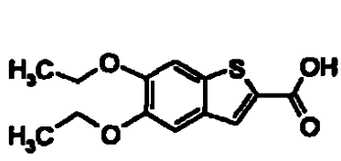
Zardaverina
(0.0.5)



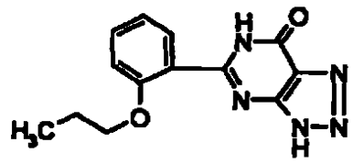
Benafentrina

(0.0.6)

Sin embargo, benafentrina da como resultado la broncodilatación únicamente cuando se administra por inhalación, y zardaverina produce únicamente una broncodilatación modesta y de corta duración. Milrinona, un agente cardiotónico, induce broncodilatación de corta duración y un ligero grado de protección contra la broncoconstricción inducida, pero tiene efectos adversos marcados, por ejemplo, taquicardia e hipotensión. Se han obtenido también resultados no satisfactorios con un inhibidor de PDE4 ligeramente selectivo, tibenelast, y un inhibidor selectivo de PDE5, zaprinast, que pueden representarse mediante las Fórmulas (0.07) y (0.0.8):



Tibenelast
(0.0.7)



Zaprinast

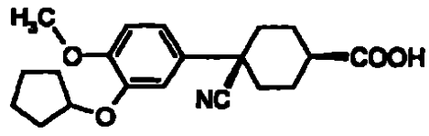
(0.0.8)

Se ha obtenido un mayor éxito relativo en la técnica con el descubrimiento y desarrollo de inhibidores de PDE4 más selectivos.

In vivo, los inhibidores de PDE4 reducen el influjo de eosinófilos a los pulmones de animales sometidos a pruebas de exposición a alérgenos reduciendo también la broncoconstricción y la respuesta bronquial elevada que ocurre después de la exposición

con alérgenos. Los inhibidores de PDE4 suprimen también la actividad de las células inmunitarias, incluyendo los linfocitos T $CD4^+$, monocitos, mastocitos, y basófilos; reducen el edema pulmonar; inhiben la neurotransmisión excitatoria no adrenérgica no colinérgica (eNANC); potencian la neurotransmisión inhibidora no adrenérgica no colinérgica (iNANC); reducen la mitogénesis del músculo liso de las vías respiratorias; e inducen la broncodilatación. Los inhibidores de PDE4 suprimen también la actividad de numerosas células inflamatorias asociadas a la patofisiología de la COPD, incluyendo monocitos/macrófagos, linfocitos T $CD8^+$, y neutrófilos. Los inhibidores de PDE4 reducen también la mitogénesis del músculo liso vascular, y potencialmente interfieren con la capacidad de las células epiteliales de las vías respiratorias de generar mediadores proinflamatorios. A través de la liberación de proteasas neutras e hidrolasas ácidas de sus gránulos, y la generación de especies de oxígeno reactivas, los neutrófilos contribuyen a la destrucción de tejidos asociada a la inflamación crónica, y están implicados además en la patología de trastornos tales como enfisema.

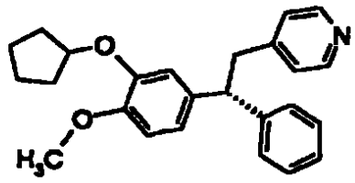
Los inhibidores selectivos de PDE4 que se han descubierto hasta la fecha proporcionan ventajas terapéuticas que incluyen SB-207.499, identificadas como ARIFLO®, que pueden representarse mediante la Fórmula (0.1.9):



SB-207,499 (0.1.9)

SB-207.499 administrado oralmente en dosis de 5, 10 y 15 mg *b.i.d.*, ha producido aumentos significativos de FEV_1 (volumen expiratorio máximo en 1 segundo) comparado con placebo en la semana 2 de un estudio que implica un gran

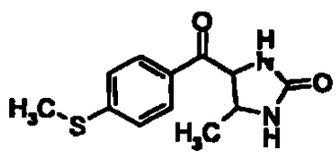
número de pacientes. Otro inhibidor potente, selectivo de PDE4, CDP840, ha demostrado la supresión de las reacciones tardías a un alérgeno inhalado después de 9,5 días de la administración oral con dosis de 15 y 30 mg en un grupo de pacientes con asma bronquial. CDP840 puede representarse mediante la Fórmula (0.0.9):



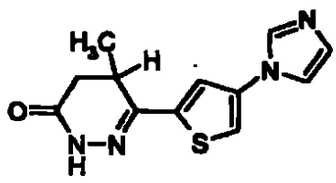
CDP840 (0.0.9)

Las PDE se han investigado también como terapia potencial para las enfermedades pulmonares obstructivas incluyendo COPD. En un amplio estudio de SB-207.499 en pacientes con COPD, el grupo de pacientes que recibían 15 mg *b.i.d.* ha experimentado una mejora progresiva en FEV_1, alcanzando una diferencia media máxima comparada con el placebo de 160 ml en la semana 6, lo que representa una mejora del 11%. Véase Compton y cols., "The efficacy of Ariflo (SB207499), a second generation, oral PDE4 inhibitor, in patients with COPD, "*Am. J. Respir. Crit. Care Med.* 159, 1999. Se ha observado que los pacientes con COPD grave presentan hipertensión pulmonar, y se ha logrado reducir la presión arterial pulmonar media en condiciones clínicas mediante la administración oral de los inhibidores selectivos de PDE3 milrinona y enoximona. Se ha demostrado también que la enoximona reduce la resistencia de las vías respiratorias en pacientes hospitalizados con COPD descompensada. Véase Leeman y cols., *Chest* 91 662-6, 1987. Usando la inhibición selectiva de PDE3 mediante motapizona y la inhibición selectiva de PDE5 mediante zaprinast, se ha demostrado que la inhibición combinada de PDE 3 y 5 ejerce una relajación de los anillos arteriales pulmonares que corresponde ampliamente con el

patrón de isozimas PDE hallado en el músculo liso de las arterias pulmonares. Véase Rabe y cols., *Am. J. Physiol.* 266 (LCMP 10): L536-L543, 1994. Las estructuras de milrinona y zaprinast se muestran anteriormente como las Fórmulas (0.0.4) y (0.0.8), respectivamente. Las estructuras de enoximona y motapizona pueden representarse mediante las Fórmulas (0.0.10) y (0.0.11) respectivamente:



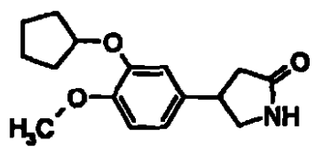
Enoximona
(0.0.10)



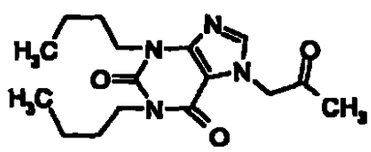
Motapizona (0.0.11)

Pueden usarse los efectos de los inhibidores de PDE4 sobre diversas respuestas inflamatorias celulares como base para la caracterización y selección de inhibidores para estudios adicionales. Estos efectos incluyen la elevación de AMPc y la inhibición de la producción de superóxido, desgranulación, quimiotactismo, y la liberación del factor necrosante tumoral alfa (TNFα) en los eosinófilos, neutrofilos y monocitos. Los inhibidores de PDE4 pueden inducir la emesis, es decir, las náuseas y vómitos que, como era de esperar, es un efecto adverso. El efecto adverso de emesis se hizo evidente cuando se investigaron los inhibidores de PDE4 por primera vez para analizar indicaciones del SNC tales como depresión, cuando se usaron rolipram y denbufilina en ensayos clínicos. Rolipram y denbufilina pueden representarse mediante las Fórmulas (0.0.12) y (0.0.13) respectivamente:

10



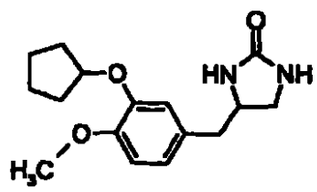
Rolipram
(0.0.12)



Denbufilina

(0.0.13)

El/Los mecanismo(s) mediante el/los cual(es) los inhibidores de PDE4 pueden potencialmente inducir emesis es/son inciertos, pero un estudio del inhibidor de PDE4 Ro-20-1724 sugiere que las nauseas y vómitos son mediados, al menos en parte, por los centros de emesis del cerebro. Los efectos adversos gastrointestinales pueden estar provocados por efectos locales, por ejemplo, rolipram es un estimulador muy potente de la secreción ácida de las células gástricas parietales, y el exceso de ácido resultante, al producir irritación local, puede exacerbar las alteraciones gastrointestinales. Ro-20-1724 puede representarse me liante la Fórmula (0.0.14):



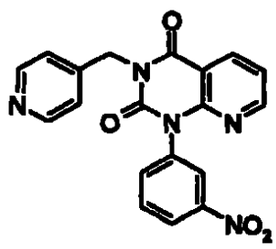
Ro-20-1724

(0.0.14)

Los esfuerzos para minimizar o eliminar los efectos adversos mencionados anteriormente asociados a veces a los inhibidores de PDE4 han incluido la creación de inhibidores que no penetran en el sistema nervioso central, y la administración de inhibidores de PDE4 mediante inhalación en lugar de oralmente.

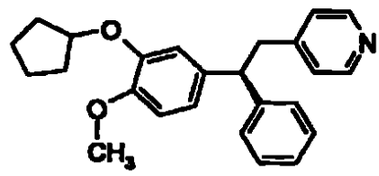
Con respecto a los subtipos de PDE4, A, B, C, y D, se ha observado que PDE4C es habitualmente menos sensible a todos los inhibidores; mientras que, con respecto a los subtipos A, B y D, no existen todavía pruebas claras de la especificidad inhibidora, que se define como una diferencia de 10 veces en los valores de CI_{50}. Aunque la mayoría de los inhibidores, especialmente RS-25.344, son más potentes contra PDE4D,

esto no equivale a selectividad. RS-25.344 puede representarse mediante la Fórmula (0.0.15):



RS-25,344 (0.0.15)

Por otra parte, hay un efecto estereoselectivo sobre la elevación de AMPc en una gama de tipos celulares, que se ha demostrado con los resultados de una investigación sobre CDP840, que se muestra anteriormente como la Fórmula (0.0.9), y su enantiómero menos activo CT-1731, que se representa mediante la Fórmula (0.0.16):



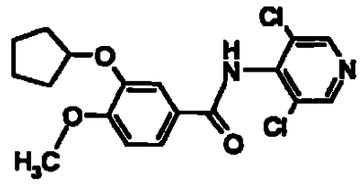
CT-1731 (0.0.16)

Se ha sabido durante algún tiempo que rolipram tenía la capacidad de interactuar con un sitio de unión de afinidad elevada en las membranas cerebrales, y se estableció posteriormente en la técnica que este sitio de unión de rolipram de afinidad elevada (S_r), que es diferente del sitio catalítico (S_c), existe en una PDE4A recombinante truncada y en un recombinante PDE4B de longitud completa. Más recientemente, se ha identificado S_r en los cuatro subtipos de PDE4. Véase Hughes y cols., *Drug Discovery Today* 2(3) 89-101, 1997. La presencia de S_r parece tener un efecto profundo sobre la

capacidad de ciertos inhibidores tales como rolipram RS-25.344 de inhibir la actividad catalítica de las isozimas PDE4.

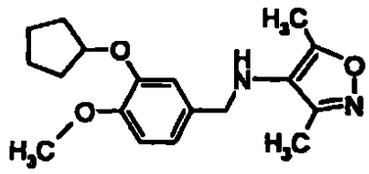
El impacto de los restos sobre la unión del inhibidor es también significativo. Se ha demostrado que la sustitución de un único aminoácido (aspartato por alanina) en la región catalítica de PDE4B es crítica para la inhibición con rolipram, y esto parece ser un efecto de clase porque los inhibidores relativos RP-73.401 y Ro-20-1724 también pierden potencia sobre la enzima mutante. Sin embargo, en el momento actual no se comprende completamente el papel de la unión de los inhibidores al S_c o al S_r, en términos de la elevación de AMPc y la inhibición de las respuestas celulares.

En estudios con cobayas, se ha observado que RP-73.401 es activo en (1) la inhibición de eosinofilia y peroxidasa eosinófila pulmonar inducida por antígenos (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) eosinofilia inducida por antígenos en el lavado broncoalveolar (BAL), Raeburn y cols., "Anti-inflammatory and bronchodilator properties of RP73401, a novel and selective phosphodiesterase Type IV inhibitor", *Br. J. Pharmacol.* 113 1423-1431, 1994; (3) eosinofilia de las vías respiratorias y factor activador de plaquetas (PAF)- inducidas por antígenos e hiperreactividad de las vías respiratorias inducida por ozono (AHR), Karlsson y cols., "Anti-inflammatory effects of the novel phosphodiesterase IV inhibitor RP73401" *Int. Arch. Allergy Immunol.* 107 425-426, 1995; y (4) eosinofilia pleural inducida por IL-5. El desarrollo de RP-73.401, piclamilast, ha sido interrumpido. Piclamilast puede representarse mediante la Fórmula (0.0.17):



Piclamilast (RP-73,401) (0.0.17)

Una serie relacionada de compuestos está representada por RPR-132294 y RRP-132703, que se ha demostrado en los estudios con ratas, que tienen actividad en la inhibición del broncoespasmo inducido por antígenos; Escott y cols., "Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic ratio in rats and dogs", *Br. J. Pharmacol.* 123 (Proc. Suppl.) 40 P, 1998, y Thurairatnam y cols., "Biological activity and side effect profile of RPR-132294 y RPR-132703 - novel PDE4 inhibitors", *XVth EFMC Int. Symp. Med. Chem.*, 1998. La estructura de RPR-132294 puede representarse mediante la Fórmula (0.0.18):

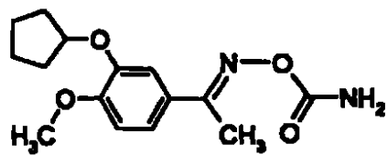


RPR-132294

(0.0.18)

Otro compuesto cuyo desarrollo ha sido interrumpido es WAY-PDA-641, filaminast que, en estudios en perros, se ha observado que es activo en la inhibición de la broncoconstricción inducida por seratonina. Filaminast puede representarse mediante la Fórmula (0.0.19):

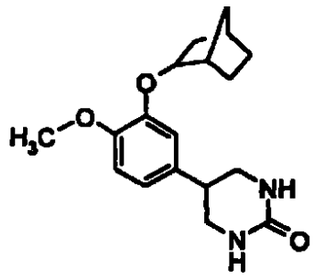
137



Filaminast (WAY-PDA-641)

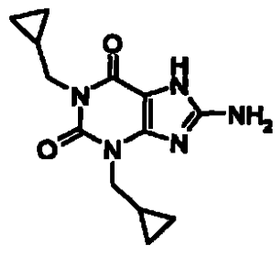
(0.0.19)

Se ha sugerido en la técnica que los inhibidores de PDE4 que tienen una afinidad elevada en S_r pueden correlacionarse con emesis y aumento de la secreción de ácido gástrico. RS-23.544, RP-73.401, y CP-80.633 producen emesis y tienen una afinidad elevada en el S_r. CDP840 y SB-207.499 tienen un afinidad comparativamente baja en el S_r, pero CDP840 tiene una potencia significativamente mayor en el S_e que la que tiene SB-207.499. Se ha demostrado que CDP840 proporciona una inhibición significativa de la respuesta tardía en el tratamiento del asma sin ningún efecto adverso de nauseas o cefalea. Otro inhibidor de PDE4 que se ha demostrado que tiene efectos adversos de nauseas y vómitos es BRL-61.063, también denominado cipamfilina, que se describe a continuación. El desarrollo de CDP840 ha sido interrumpido, mientras que CP-80.633, atizoram, ha continuado hasta los estudios clínicos. CP-80.633 y BRL-61.063 pueden representarse mediante las Fórmulas (0.0.20) y (0.1.12), respectivamente:



Atizoram (CP-80,633)

(0.0.20)

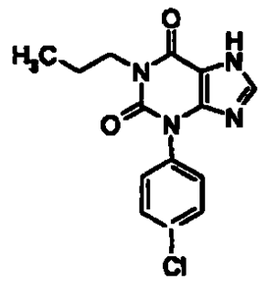


Cipamfilina (BRL-61,063)

(0.1.12)

Otro compuesto que está en desarrollo es LAS-31025, arofilina, que se ha

observado, en estudios en cobayas, que es activo en la inhibición de la broncoconstricción inducida por antígenos; Beleta, 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, Resumen 73. LAS-31205, arofilina, puede representarse mediante la Fórmula (0.0.21):



Arofilina LAS-31025)

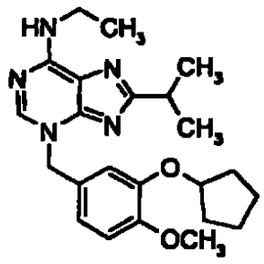
(0.0.21)

Un número de inhibidores de PDE4 han continuado en su desarrollo. Por ejemplo, se han determinado los efectos de V-11294A sobre la liberación de TNF *ex vivo* estimulada por LPS y la proliferación de linfocitos inducida por PHA en un estudio aleatorio, de doble ciego controlado por placebo que ha encontrado que una dosis oral de 300 mg es efectiva para reducir los niveles de TNF y la proliferación de linfocitos; Landells y cols., "Oral administration of the phosphodiesterase (PDE) 4 inhibitor, V11294A inhibits ex-vivo agonist-induced cell activation", *Eur. Resp. J.* 12 (Supl. 28) 362s, 1998; y Gale y cols., "Pharmacodynamic-pharmacokinetic (PD/PK) profile of the phosphodiesterase (PDE) 4 inhibitor, V11294A, in human volunteers", *Am. J. Respir. Crit. Care Med.* 159 A611, 1999.

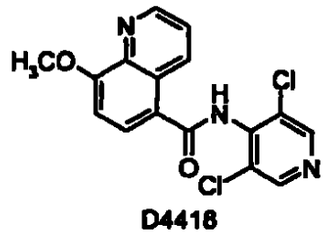
El compuesto D4418 ha sido administrado a voluntarios sanos en un estudio de Fase I de dosis aumentada única, aleatorio, controlado por placebo; Montana y cols., "Activity of D4418, a novel phosphodiesterase 4 (PDE4) inhibitor, effects in cellular and animal models of asthma and early clinical studies" *Am. J. Respir. Crit. Care Med.*

159 A108, 1999. D4418 es un inhibidor de PDE4 moderadamente potente con una CI_{50} de 200 nM. Tiene una absorción oral buena; una dosis de 200 mg proporciona una C_{max} en plasma de 1,4 μg/ml. Se ha interrumpido el desarrollo de D4418 debido a su potencia moderada, y se ha sustituido por el candidato D4396 en desarrollo preclínico.

V-11294A y D4418 pueden representarse mediante las Fórmulas (0.0.22) y (0.0.23), respectivamente:



V-11294A
(0.0.22)

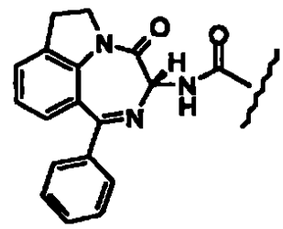


D4418

(0.0.23)

Se ha evaluado otro compuesto, CI-1018 en 54 sujetos y no se informó de afectos adversos en dosis de hasta 400 mg; Pruniaux y cols., "The novel phosphodiesterase inhibitor CI-1018 inhibits antigen-induced lung eosinophilia in sensitized brown-norway rats - comparison with rolipram," *Inflammation* S-04-6, 1999. Se ha demostrado que CI-1018 tiene una biodisponibilidad oral buena (57% en la rata) y buena potencia oral con un DE_{50} de 5 mg/kg en esa misma especie. CI-1018 es un inhibidor relativamente débil de PDE4 con una CI_{50} de 1,1 μM en células U937. Se ha identificado también CI-1018, o se asociado o se ha relacionado estrechamente en estructura a PD-168787, que en estudios en la rata se ha demostrado que posee actividad en la inhibición de la eosinofilia inducida por antígenos; Pascal y cols, "Synthesis and structure-activity relationships of 4-oxo-1-phenyl-3,4,6,7-tetrahydro-[1,4]-

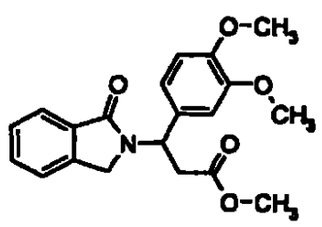
diazepino[6,7,1-hi]indolines: novel PDE4 inhibitors", 215th ACS, Dallas, USA, MEDI 50, 1998. Las estructuras inferidas para CI-1018 y PD-168787 pertenecen a una clase de diazepinona cuyo núcleo puede estar representado por la Fórmula (0.0.24):



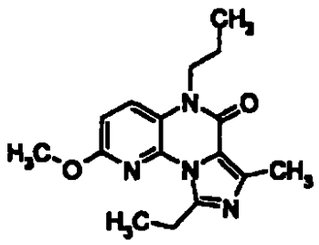
(0.0.24)

Los compuestos mencionados anteriormente han sido evaluados también en modelos animales que demuestran su actividad de inhibición de PDE4. Por ejemplo, en estudios en cobayas se ha observado que V-11294A es activo en la inhibición de la broncoconstricción inducida por antígenos; Cavalla y cols., "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. En estudios en cobayas se ha hallado que D4418 es activo en la inhibición de la broncoconstricción temprana y tardía inducida por antígenos y eosinofilia BAL; Montana y cols, referencia anterior. En estudios en ratas, se ha observado que CI-1018 es activo en la inhibición de la eosinofilia inducida por antígenos; Burnouf y cols., "Pharmacology of the novel phosphodiesterase Type 4 inhibitor, CI-1018", *215th ACS Nat. Meeting*, MEDI 008, 1998.

Otros compuestos que han continuado en su desarrollo incluyen CDC-3052, D-22888, YM-58997, y roflumilast, que pueden representarse mediante las Fórmulas (0.0.27), (0.0.28), (0.0.29), y (0.0.30), respectivamente:

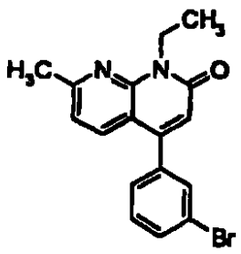


CDC-3052
(0.0.27)

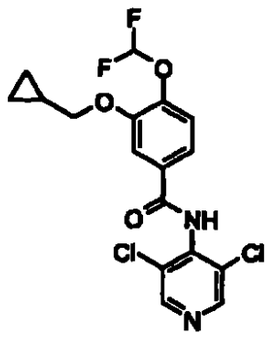


D-22888

(0.0.28)



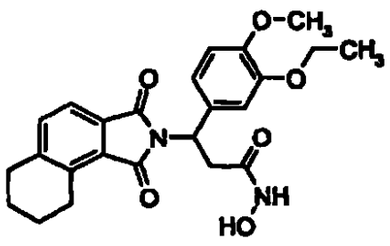
YM-58977
(0.0.29)



Roflumilast

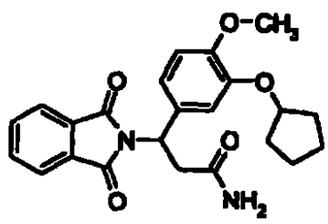
(0.0.30)

Se ha interrumpido el desarrollo de CDC-3052, pero ha sido sucedido por inhibidores muy potentes de PDE4 tales como el compuesto representado por la Fórmula (0.0.31), y por el compuesto antiinflamatorio CDC-801 representado mediante la Fórmula (0.0.32), respectivamente:



(0.0.31)

CDC-801

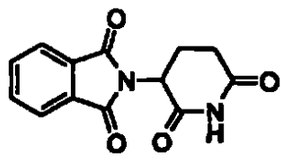


(0.0.32)

Se informa que el compuesto de Fórmula (0.0.32) tiene valores de CI_{50} de 42

pM y 130 nM como inhibidor de PDE4 y de la producción de TNF, respectivamente; Muller y cols., "N-Phthaloyl beta-aryl-beta-amino derivatives: Potent TNF-alpha and PDE4 inhibitors", *217th American Chemical Society*, Annheim, Alemania, MEDI 200, 1999; y Muller y cols., "Talidomide analogs and PDE4 inhibition", Bioorg. Med. Chem. Letts. 8 2669-2674, 1998.

CDC-801 es de una serie de compuestos basados en talidomida y ha sido desarrollado primordialmente para mejorar la actividad de la talidomida como inhibidor de TNF-α para el tratamiento de enfermedades autoinmunitarias. La talidomida puede representarse mediante la Fórmula (0.0.33):



Talidomida

(0.0.33)

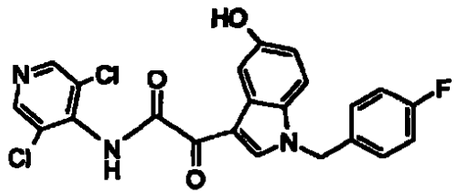
También se ha estudiado CDC-801 para el tratamiento de la enfermedad de Crohn, una enfermedad inflamatoria granulomatosa crónica de etiología desconocida que comúnmente implica al ileón terminal, con cicatrices y engrosamiento de la pared intestinal que frecuentemente lleva a la obstrucción intestinal y formación de fístulas y abscesos. La enfermedad de Crohn tiene una alta tasa de recurrencia después del tratamiento.

YM-58997 tiene un valor de CI_{50} de 1,2 nM contra PDE4; Takayama y cols., "Synthetic studies on selective Type IV phosphodiesterase (PDE IV) inhibitors ", 214th *American Chemical Society*, Las Vegas, USA, MEDI 245, 1997. YM-58997 tiene una estructura de 1,8-naftiridin-2-ona, al igual que YM-976.

Se ha estudiado el roflumilast para el tratamiento de COPD y asma, y tiene un

valor de CI_{50} de 3,5 nM en modelos estándar de asma *in vitro* en cobayas. También se ha descrito el uso de roflumilast y un tensioactivo para el tratamiento del síndrome disneico agudo del adulto (ARDS).

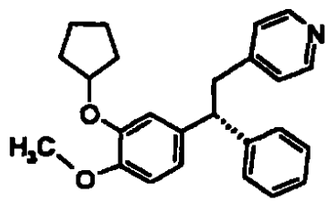
Se ha demostrado que AWD-12.281, que se denomina ahora loteprednol, es activo en un modelo de rinitis alérgica en rata, como se describe más adelante en una sección que trata de la rinitis alérgica y el uso de inhibidores de PDE4 para tratarla. AWD-12.281 puede representarse mediante la Fórmula (0.0.34):



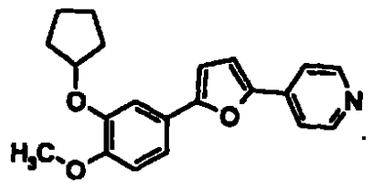
Loteprednol (AWD-12,281)

(0.0.34)

Los compuestos relacionados en estructura con CPD840, que se muestran anteriormente con la Fórmula (0.0.9), incluyen L-826.141, que se ha informado que son activos en un modelo de bronquitis en rata; Gordon y cols., "Anti-inflammatory effects of a PDE4 inhibitor in a rat model of chronic bronchitis", *Am. J. Respir. Crit. Care Med.* 159 A33, 1999. Otro compuesto similar está relacionado en estructura con los descritos por Perrier y cols., "Substituted furans as inhibitors of the PDE4 enzyme," *Bioorg. Med. Chem. Letts.* 9 323-326, 1999, y está representado por la Fórmula (0.0.35):

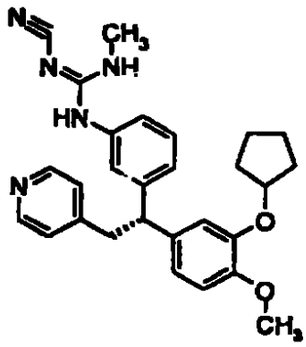


CDP840
(0.0.9)



(0.0.35)

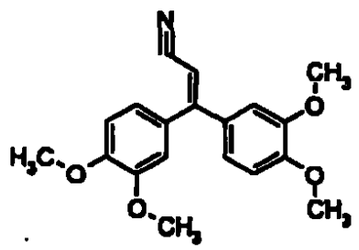
Otros compuestos que se ha observado que son inhibidores muy potentes de PDE4 son los representados por las Fórmulas (0.0.36), (0.0.37), y (0.0.38):



(0.0.36)

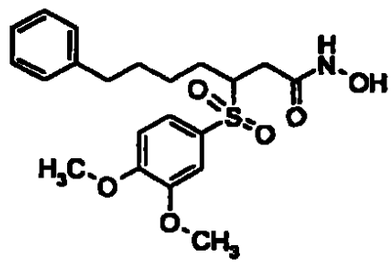


(0.0.37)

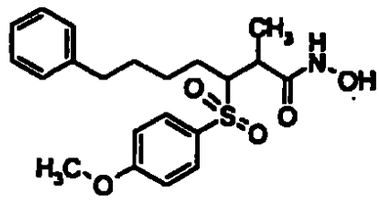


(0.0.38)

Se han creado compuestos que combinan la actividad de inhibición de PDE4 y de metaloproteinasa de matriz (MMP) en una única molécula; Groneberg y cols., "Dual inhibition of phosphodiesterase 4 and matrix metalloproteinases by an (arylsulfonyl)hydroxamic acid template", *J. Med. Chem.* 42(4) 541-544, 1999. Las siguientes Fórmulas (0.0.39) y (0.0.40) representan dos ejemplos de tales compuestos:



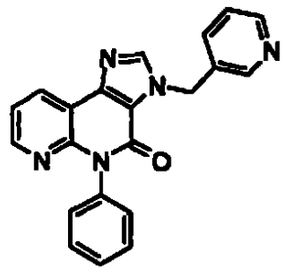
(0.0.39)



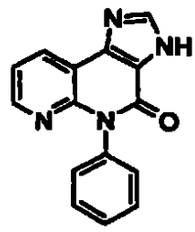
(0.0.40)

Los valores de CI_{50} respectivos de los compuestos de Fórmulas (0.1.36) y (0.1.37) usando un ensayo de PDE4 de macrófagos en cobayas fueron 1 nM y 30 nM.

En estudios en cobayas se ha demostrado que los compuestos que se identifican como KF19514 y KF17625 tienen actividad en la inhibición de los siguientes: broncoconstricción inducida por histamina e inducida por antígenos; eosinofilia pulmonar inducida por PAF y eosinofilia BAL inducida por antígenos; AHR inducida por acetilcolina (ACh); eosinofilia y neutrofilia BAL, y AHR inducidas por PAF; broncoespasmo inducido por antígenos; y broncoconstricción anafiláctica; Fujimura y cols., "Bronchoprotective effects of KF-19514 and cilostazol in guinea-pigs *in vivo*", *Eur. J. Pharmacol.* 327 57-63, 1997; Manabe y cols., referencia anterior; Manabe y cols., "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 y cols., "New bronchodilators. 3. Imidazo[4,5-c][1,8]naphthyridin-4(5H)-ones," *J. Med. Chem.* 35 4866-4874, 1992; Matsuura y cols., "Substituted 1,8-naphthyridin-2(1H)-ones as selective phosphodiesterase IV inhibitors," *Biol. Pharm. Bull* 17 (4) 498-503, 1994; y Manabe y cols., "Pharmacological properties of a new bronchodilator, KF17625," *Jpn. J. Pharmacol.* 58 (Supl. 1) 238P, 1992. KF19514 y KF17625 pueden representarse mediante las Fórmulas (0.0.41) y (0.0.42):



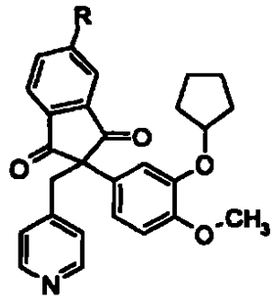
KF19514
(0.0.41)



KF17825

(0.0.42)

La potencia y la falta de tmesis reseñada en una serie de indandionas sugieren que la hipótesis que ha relacionado los efectos secundarios tales como la emesis con la relación de afinidad por la enzima PDE4 relativa a la del sitio de unión de afinidad elevada de rolipram (HARBS) es errónea. Tales indandionas pueden representarse mediante las Fórmulas (0.0.43) y (0.0.44):

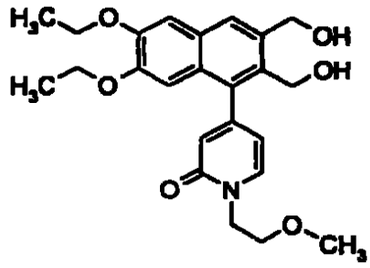


R = Benciloxi (0.0.43)

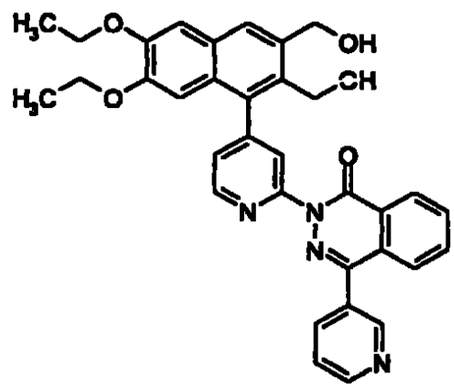
R = [1,4']-piperidinil-1'-carboniloxi (0.0.44)

Hasta ahora los inhibidores de PDE4 que se han creado entran en un número significativo de clases diferentes en lo que respecta a sus estructuras químicas. Tales clases han sido tan diversas como las fenantridinas y naftiridinas. Una clase de inhibidores de PDE4 son los lignanos tales como T-440, que se ha demostrado que tiene actividad en la inhibición de los siguientes: broncocostricción temprana inducida por antígenos, histamina, LTD4, U-46619, ACh, neuroquinina A, y endotelina-1;

bronconstricción temprana y tardía inducida por alérgenos y eosinofilia BAL; y AHR inducida por ozono y lesiones epiteliales de las vías respiratorias. La optimización de la potencia inhibidora sobre PDE4 de tales compuestos ha llevado al descubrimiento de T-2585, uno de los inhibidores más potentes de PDE4 descritos hasta la fecha con un valor de CI_{50} de 0,13 nM contra la PDE4 de pulmón en cobaya. T-440 y T-2585 pueden representarse mediante las Fórmulas (0.0.45) y (0.0.46):

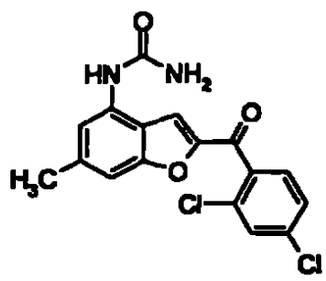


T-440
(0.0.45)



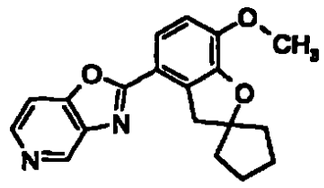
T-2585
(0.0.46)

Otra clase de inhibidores de PDE4 consiste en benzofuranos y benzotiofenos. En particular, se han utilizado anillos de furano y cromano como sucedáneos del ciclopentiléter del farmacóforo rolipram. Un ejemplo de un compuesto así es uno que está aparentemente relacionado en estructura a BAY 19-8004, y que puede representarse mediante la Fórmula (0.0.47):



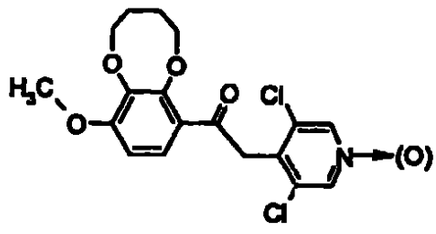
(0.0.47)

Se ha informado de otro compuesto tipo benzofurano que tiene un valor de CI_{50} de 2,5 nM, y puede representarse mediante la Fórmula (0.0.48):



(0.0.48)

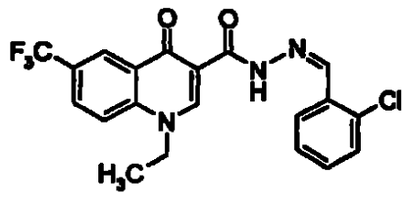
Un compuesto con una estructura relacionada, que no es, sin embargo, un benzofurano, se caracteriza por un anillo de dioxicina condensado y se informa de que produce casi una inhibición completa de la PDE4 de la tráquea canina a una concentración 100 nM. Este compuesto puede representarse mediante la Fórmula (0.0.49):



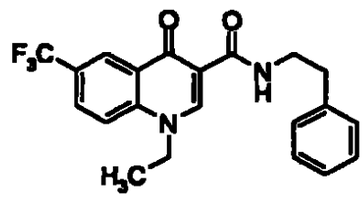
(0.0.49)

Las quinolinas y quinolonas son otra clase de estructuras inhibidoras de PDE4, y

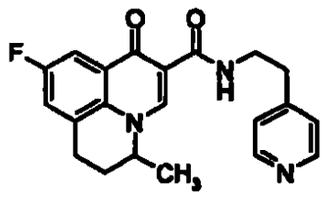
sirven como sucedáneo del resto catecol de rolipram. Este compuesto y dos compuestos de estructura similar pueden representarse mediante las Fórmulas (0.0.50), (0.0.51), y (0.0.52):



(0.0.50)

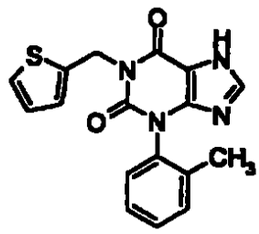


(0.0.51)



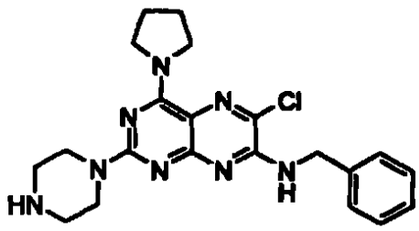
(0.0.52)

Las purinas, xantinas, y pteridinas representan otras clases adicionales de compuestos químicos a los que pertenecen los inhibidores de PDE4 descritos hasta ahora en la técnica. El compuesto V-11294A descrito anteriormente y representado por la Fórmula (0.0.22), es una purina. Se ha descrito en la técnica un inhibidor de PDE4 que es un compuesto de xantina, la clase de compuestos a los que pertenece la teofilina; Montana y cols., "PDE4 inhibitors, new xanthine analogues", *Bioorg. Med. Chem. Letts.* 8 2925-2930, 1998. El compuesto de xantina puede representarse mediante la Fórmula (0.0.54):



(0.0.54)

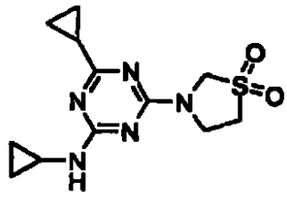
Se ha demostrado que un inhibidor potente de PDE4 que pertenece a la clase de compuestos de pteridina tiene un valor de CI_{50} de 16 nM contra una PDE4 derivada de células tumorales e inhibe el crecimiento de células tumorales en concentraciones micromolares; Merz y cols., "Synthesis of 7-Benzylamino-6-chloro-2-piperazino-4-pyrrolidinopteridina and novel derivatives tree of positional isomers. Potent inhibitors of cAMP-specific phosphodiesterase and of malignant tumor cell growth," *J. Med. Chem.* 41 (24) 4733-4743, 1998. El inhibidor de PDE4 de tipo pteridina puede representarse mediante la Fórmula (0.0.55):



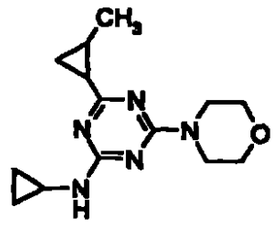
(0.0.55)

Las triazinas representan otra clase adicional más de compuestos químicos a los que pertenecen los inhibidores de PDE4 que han sido descritos en la técnica hasta ahora. Se han descrito dos triazinas así que presentan actividad broncodilatadora y son agentes relajantes potentes en un modelo de tráquea en cobaya. Estos compuestos, que pueden representarse mediante las Fórmulas (0.0.56) y (0.0.57) a continuación, son también

inhibidores de PDE4 moderadamente potentes con valores de CI_{50} de 150 y 140 nM, respectivamente:



(0.0.56)



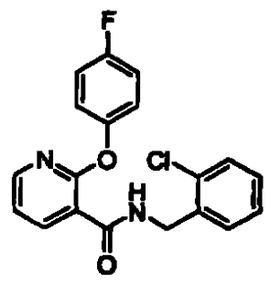
(0.0.57)

Una triazina que tiene una estructura que se asume que está íntimamente relacionada a la de los compuestos de Fórmulas (0.0.56) y (0.0.57) es UCB-29936, que se ha demostrado que tiene actividad en un modelo murino de choque séptico; Danhaive y cols, "UCB29936, a selective phosphodiesterase Type IV inhibitor: therapeutic potencial in endotoxic shock", *Am. J. Respir. Crit. Care. Med.* 159 A611, 1999.

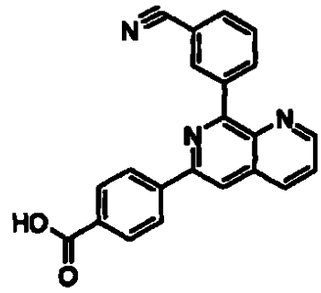
Se han realizado esfuerzos también en la técnica para mejorar la selectividad de los inhibidores de PDE4 con respecto a los subtipos A a D descritos más arriba. Actualmente hay cuatro isoformas (subtipos) conocidos de la isozima PDE4, que comprenden siete variantes de procesamiento, descritas también más arriba. El ARNm de la isoforma PDE4D se expresa en las células inflamatorias tales como neutrófilos y eosinófilos, y se ha sugerido en la técnica que los inhibidores selectivos de PDE4 D proporcionarán una buena eficacia clínica con efectos secundarios reducidos. Se ha descrito un derivado de nicotinamida que presenta selectividad en la inhibición de la isoforma PDE4D; documento WO 98/45268; así como un derivado de naftiridina que se informa que es un inhibidor selectivo de PDE4D; documento WO 98/18796. Estos compuestos pueden representarse mediante las Fórmulas (0.0.58) y (0.0.59),

152

respectivamente:

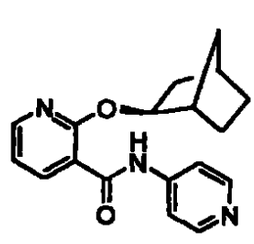


(0.0.58)

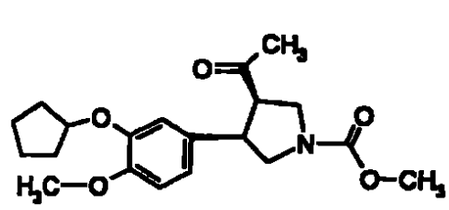


(0.0.59)

Se ha descrito otro compuesto de nicotinamida en la técnica que puede ser de utilidad en el tratamiento de enfermedades del SNC tales como la esclerosis múltiple; documento GB-2327675; y se ha descrito en la técnica un derivado de rolipram que es un inhibidor de PDE4 que se une con igual afinidad tanto a los sitios catalíticos como a los sitios HARB de la PDE4B2B humana; Tian y cols., "Dual inhibition of human Type 4 phosphodiesterase isostates by (*R,R*)-(+/-)-methyl-3-acetyl-4-[3-(ciclopentiloxi)-4-metoxyphenyl]-3-methyl-1-pyrrolidine carboxylate," *Biochemistry* 37(19) 6894-6904, 1998. El derivado de nicotinamida y el derivado de rolipram pueden representarse mediante las Fórmulas (0.0.60) y (0.0.61), respectivamente:



(0.0.60)



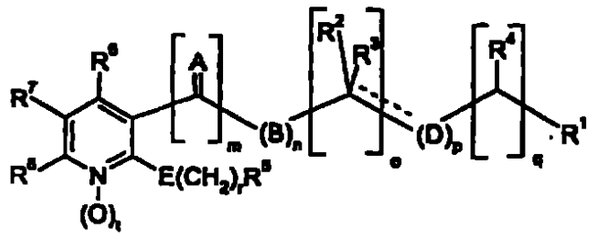
(0.0.61)

Puede encontrarse información adicional de los antecedentes relativa a las

isozimas PDE4 en publicaciones disponibles en la técnica, por ejemplo, Norman, "PDE4 inhibitors 1999," *Exp. Opin. Ther. Patents* 9(8) 1101-1118, 1999 (Ashley Publications Ltd.); y Dyke y Montana, "The therapeutic potencial of PDE4 inhibitors," *Exp. Opin. Invest. Drugs* 8(9) 1301-1325, 1999 (Ashley Publications Ltd.).

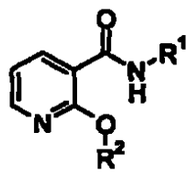
3.0 DESCRIPCIÓN DEL ESTADO DE LA TÉCNICA

El documento WO 98/45268 (Marfat y cols.), publicado el 15 de octubre de 1998, describe derivados de nicotinamida que tienen actividad como inhibidores selectivos de la isozima PDE4D. Estos inhibidores selectivos están representados por la Fórmula (0.1.1):



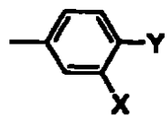
(0.1.1)

La patente de EE.UU. US 4.861.891 (Saccomano y cols.), expedida el 29 de agosto de 1989, describe derivados de nicotinamida que funcionan como inhibidores independientes de calcio de c-AMP fosfodiesterasa de utilidad como antidepresivos, de Fórmula (0.1.2):



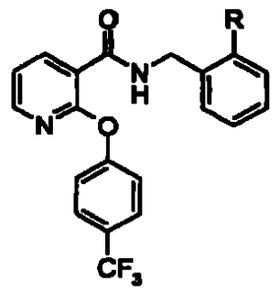
(0.1.2)

El núcleo de nicotinamida de un compuesto típico descrito en esta patente está unido directamente al grupo R^1, que se define como 1-piperidilo, 1-(3-indolil)etilo, alquilo C_1-C_4, fenilo, 1-(1-feniletilo), o bencilo opcionalmente monosustituido con metilo, metoxi, cloro o fluoro. El sustituyente R^2 es biciclo[2.2.1]hept-2-ilo o



donde Y es H, F, o Cl; y X es H, F, Cl, OCH_3, CF_3, CN, COOH, -C(=O)alcoxi C_1-C_4, $NH(CH_3)C(=O)$-(metilcarbamoilo) o $N(CH_3)_2C(=O)$-(dimetilcarbamoílo).

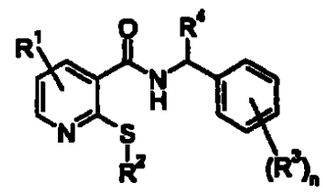
El documento US 4.692.185 (Michaely y cols.) describe herbicidas tales como los de Fórmula (0.1.3):



(0.1.3)

donde R es alquilo C_1-C_4, haloalquilo C_1-C_4, o halo.

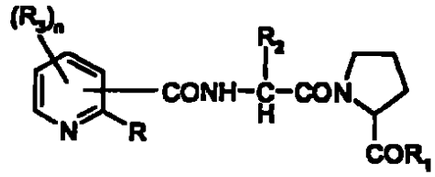
El documento EP 550 900 (Jesche y cols.) describe herbicidas y nematicidas vegetales de Fórmula (0.1.4):



(0.1.4)

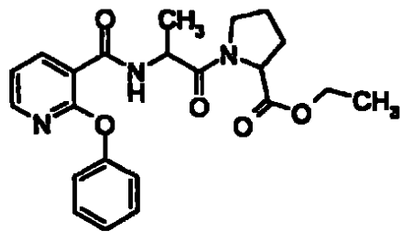
donde n es 0-3; R^1 se selecciona de numerosos grupos, pero habitualmente es H, 6-CH_3, o 5-Cl; R^2 es alquilo, alquenilo, alquinilo, cicloalquilo, arilo o aralquilo; R1 y R2 son halo, CN, NO_2, alquilo, haloalquilo, alcoxi, haloalcoxi, alquiltio, haloalquiltio, alquilsulfonilo, haloalquilsulfonilo, arilo, ariloxi, o ariltio; y R^4 es alquilo.

El documento EP 500 989 (Mol y cols) describe inhibidores Fórmula (0.1.5):



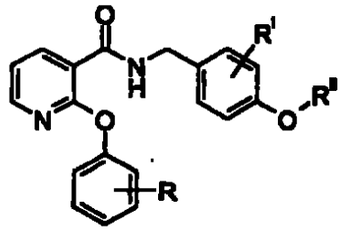
(0.1.5)

donde n es 0-3; R es OH, SH, COOH, NH_2, halo, OR_4, SR_4, $COOR_4$, NHR_4 o $N(R_4)_2$, donde R_4 es alquilo inferior, arilo opcionalmente sustituido, o acilo; R_1 es OH, alcoxi inferior, arilalcoxiinferior opcionalmente sustituido, ariloxi, o amino disustituido; R_2 es alquilo inferior, aminoalquilo inferior; R1 y R2 son halo, NO_2, alquilo inferior, halo alquilo inferior, arilalquilo inferior, o arilo. Las realizaciones específicas descritas incluyen compuestos tales como el de Fórmula (0.1.6):



(0.1.6)

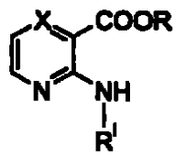
El documento FR 2.140.772 (Aries) describe compuestos que se afirma tienen utilidad como analgésicos, tranquilizantes, antipiréticos, antiinflamatorios, y antirreumáticos, de Fórmula (0.1.7):



(0.1.7)

donde R es 1 o 2 sustituyentes elegidos de alquilo inferior, trihalometilo, alcoxi, y halo; R' es H o alquilo; y R'' es hidrógeno o alquilo.

El documento JP 07 304775 (Otsuka y cols.) describe derivados de naftiridina y piridopirazina que tienen acción antiinflamatoria, inmunomoduladora, analgésica, antipirética, antialérgica, y antidepresiva. Se describen también intermedios de Fórmula (0.1.8):

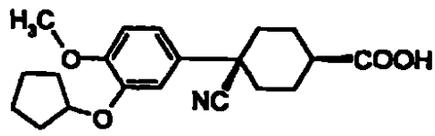


(0.1.8)

donde X puede ser CH, y R y R' son cada uno alquilo inferior.

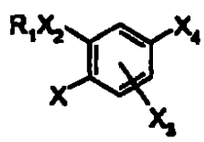
Con respecto a las descripciones de las patentes y solicitudes de patente publicadas identificadas anteriormente, se apreciará que únicamente la descripción del documento WO 98/45268 (Marfat y cols.) trata de la inhibición de isozimas PDE4. El estado de la técnica contiene también información que se refiere a compuestos totalmente diferentes en estructura química a los de Fórmula (1.0.0) de la presente invención, pero que, por otra parte, poseen una actividad biológica similar a la de los compuestos de Fórmula (1.0.0). Las patentes y solicitudes de patente publicadas representativas que describen dicha información se ilustran más adelante.

Los documentos US 5.552.438; US 5.602.157; y US 5.614.540 (todos de Christensen), que comparten la misma fecha de prioridad, 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 a continuación:



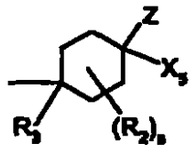
ARIFLO®
Ácido cis-[4-ciano-4-(3-ciclopentil-oxi-4-metoxifenil)ciclohexano-1-carboxílico (0.1.9)

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)

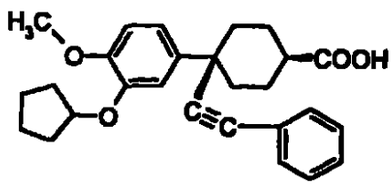
donde R_1 = -$(CR_4R_5)_rR_6$ donde r = 0 y R_6 = cicloalquilo C_{3-6}; X = YR_2 donde Y = O y R_2 = -CH_3; X_2 = O; X_3 = H; y X_4 = un resto de Fórmula parcial (0.1.10.1)



(0.1.10.1)

donde X_5 = H; s = 0; R_1 y R_2 = CN; y Z = $C(O)OR_{14}$ donde R_{14} = H. Las descripciones de los documentos US 5.602.157 y US 5.614.540 difieren de las del documento US 5.552.438 y entre sí en lo que se refiere a la definición del grupo R_3, que en el caso del compuesto ARIFLO®, es CN. Se describe una forma salina preferida del compuesto ARIFLO® que es la sal tris(hidroximetil)amoniometano.

El documento US 5.863.926 (Christensen y cols.) describe análogos del compuesto ARIFLO®, por ejemplo el de Fórmula (0.1.11):

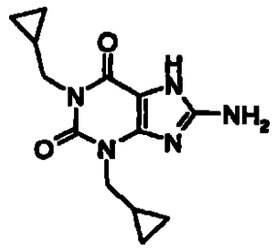


(0.1.11)

El documento WO 99/18793 (Webb y cols.) describe un proceso para hacer ARIFLO® y compuestos relacionados. El documento WO 95/00139 (Barnette y cols) reivindica un compuesto que tiene una relación de CI_{50} para aproximadamente 0,1 o superior comparando con la CI_{50} para la forma catalítica PDE IV que se une a rolipram con afinidad elevada, dividida entre la CI_{50} de la forma que se une a rolipram con una afinidad baja; pero en una reivindicación dependiente restringe el alcance del mismo a un compuesto que no se sabía que es un inhibidor de PDE4 antes del 21 de junio de

1993.

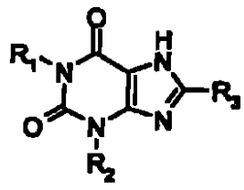
El documento WO 99/20625 (Eggleston) describe formas cristalinas polimórficas de cipamfilina para el tratamiento de enfermedades mediadas por PDE_4 y TNF, de Fórmula (0.1.12):



Cipamfifilina

(0.1.12)

El documento WO 99/20280 (Griswold y cols.) describe un procedimiento para tratar prurito mediante la administración de una cantidad efectiva de un inhibidor de PDE4, por ejemplo un compuesto de Fórmula (0.1.13):



(0.1.13)

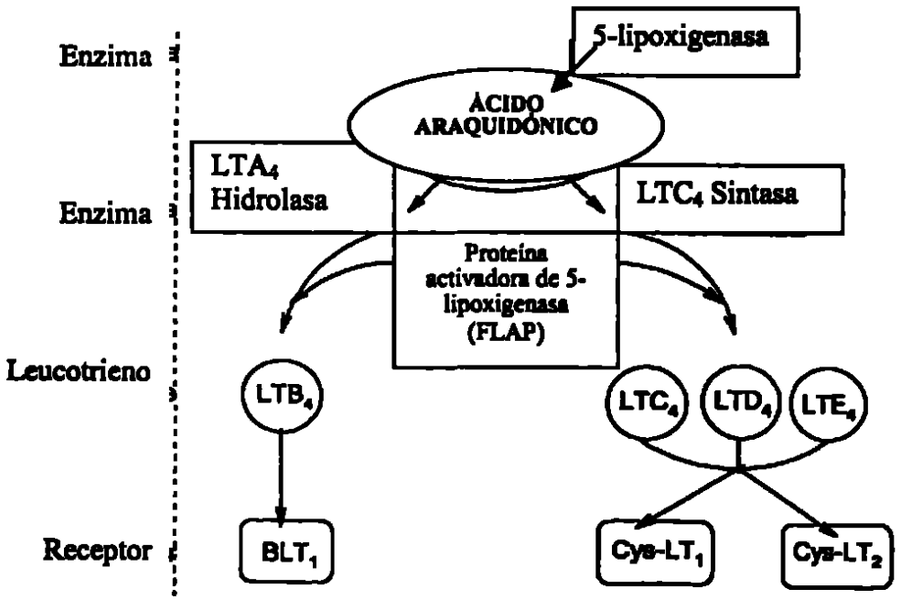
El documento US 5.922.557 (Pon) describe una línea celular CHO-K1 que expresa de forma estable niveles elevados de una enzima PDE4A completa de Km baja específica para cAMP, que se ha usado, a su vez, para examinar potentes inhibidores de la enzima PDE4 y comparar el orden de rango de sus potencias para elevar cAMP en una preparación de células enteras con su capacidad de inhibir la actividad fosfodiesterasa en una preparación de células lisadas. Se dice además que se ha

encontrado que el ensayo de inhibición de enzima soluble descrito en la técnica anterior no refleja el comportamiento de los inhibidores que actúan *in vivo*. Después se describe un ensayo mejorado de enzima soluble para células enteras que se dice que refleja el comportamiento de los inhibidores que actúan *in vivo*. Se describe adicionalmente que existen al menos cuatro isoformas o subtipos diferentes de PDE4, y se ha demostrado que cada subtipo da lugar a un número de variantes de procesamiento, que pueden exhibir diferentes localizaciones celulares y afinidades por inhibidores.

Con respecto a las descripciones de las patentes identificadas anteriormente y las solicitudes de patente publicadas, se apreciará que los compuestos implicados poseen la misma actividad biológica que los compuestos de Fórmula (1.0.0.). Al mismo tiempo, sin embargo, los expertos en la técnica observarán que las estructuras químicas de dichos compuestos descritos en la técnica anterior no son únicamente diferentes entre sí, sino también diferentes a las de los compuestos novedosos de la presente invención. El estado de la técnica contiene todavía información adicional que se refiere a compuestos que son diferentes en estructura química a los de Fórmula (1.0.0.), y que además, no poseen una actividad de inhibición de PDE4 similar a la de los compuestos de Fórmula (1.0.0.). Tales compuestos descritos en la técnica anterior a menudo, sin embargo, tienen una utilidad terapéutica similar a la que poseen los compuestos de Fórmula (1.0.0.), es decir en el tratamiento de enfermedades y afecciones inflamatorias, respiratorias y alérgicas. En particular esto es aplicable a ciertos inhibidores de enzimas y antagonistas de receptores en la denominada ruta de los leucotrienos. Este es especialmente el caso con respecto a los leucotrienos LTB_4 y LTD_4. En consecuencia, se describen a continuación patentes y solicitudes de patente publicadas representativas que describen información adicional de este tipo.

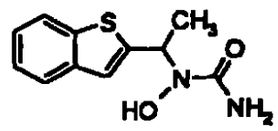
El ácido araquidónico es metabolizado por ciclooxigenasa-1 y 5-lipoxigenasa.

La ruta de 5-lipoxigenasa lleva a la producción de leucotrienos (LTs) que contribuyen a la respuesta inflamatoria a través de su efecto sobre la agregación, desgranulación y quimiotactismo de los neutrófilos; la permeabilidad vascular; la contractilidad del músculo liso; y sobre los linfocitos. Los leucotrienos cisteinílicos, LTC_4, LTD_4, y LTE_4, desempeñan un papel importante en la patogénesis del asma. En el siguiente diagrama se ilustran los componentes de la ruta de los leucotrienos que suponen dianas para la intervención terapéutica:



En consecuencia, los agentes que son capaces de intervenir en cualquiera de las etapas de la ruta de la 5-lipoxigenasa ofrecen una oportunidad de tratamiento terapéutico. Un ejemplo de un agente así es el inhibidor de la 5-lipoxigenasa, zileuton,

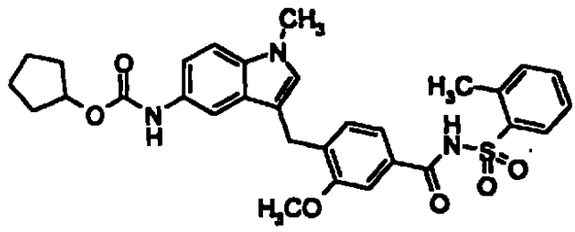
un agente terapéutico identificado como ZYFLO® que puede representarse mediante la Fórmula (0.1.14):



ZYFLO®

Zileuton (0.1.14)

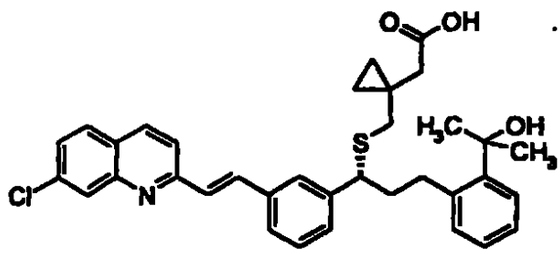
Otro agentes así es el antagonista del receptor de LTD_4 zafirlukast, un agente terapéutico identificado como ACCOLATE® que puede representarse mediante la Fórmula (0.1.15):



ACCOLATE®

Zafirlukast (0.1.15)

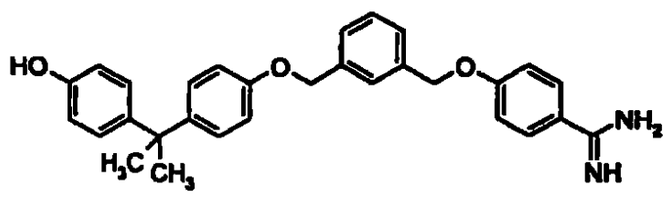
Un antagonista adicional del receptor de LTD_4 es montelukast, un agente terapéutico identificado como SINGULAIR® que puede representarse mediante la Fórmula (0.1.16):



SINGULAIR®

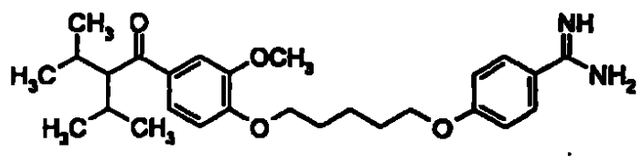
Montelukast (0.1.16)

Otro tipo de las dianas terapéuticas mencionadas anteriormente es el receptor de LTB_4, y un ejemplo de un antagonista para dicho receptor es BIIL-260, un agente terapéutico que puede representarse mediante la Fórmula (0.1.17):



BIIL-260 (0.1.17)

Otro ejemplo de un agente terapéutico que es un antagonista del receptor de LTB_4 es CGS-25019c que puede representarse mediante la Fórmula (0.1.18):



CGS-25019c (0.1.18)

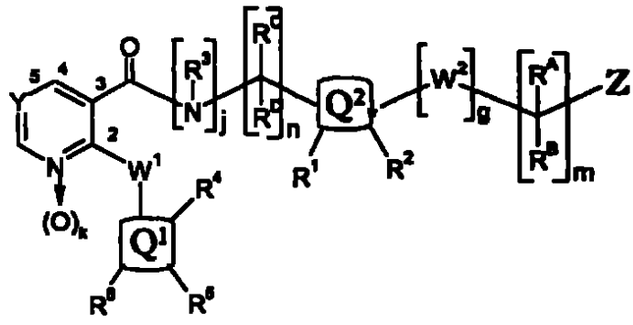
Nada en el estado de la técnica descrito anteriormente describe o sugeriría a los

expertos en la técnica los compuestos novedosos de la presente invención o su actividad de inhibición de PDE4 y la mejora significativa resultante en la utilidad terapéutica e índice terapéutico en el tratamiento de enfermedades y trastornos inflamatorios, respiratorios y alérgicos.

4.0 SUMARIO DE LA INVENCIÓN

La presente invención concierne compuestos novedosos que tienen actividad biológica como inhibidores de la fosfodiesterasa denominada isoenzima "Tipo IV" ("isozima PDE4"). Las realizaciones de los compuestos novedosos de la presente invención son activas como inhibidores no selectivos de la isozima PDE4. Otras realizaciones de dichos compuestos novedosos tienen especificidad de sustrato por la isozima PDE4, especialmente por el subtipo D. Dichos compuestos novedosos que tienen actividad inhibidora de PDE4 no selectiva o selectiva para D son generalmente de utilidad en el tratamiento terapéutico de diversas enfermedades y afecciones inflamatorias, alérgicas, y respiratorias, y ofrecen en particular una mejora significativa del tratamiento terapéutico de las enfermedades respiratorias obstructivas, especialmente el asma y la enfermedad pulmonar obstructiva crónica (COPD).

La presente invención se refiere a un compuesto de Fórmula (1.0.0):



(1.0.0)

en el que

- g es 0 ó 1;

- 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 0, 1, ó 2;

- n es 1 ó 2;

- W^1 es -O-; $-S(=O)_t-$, donde t es 0, 1, ó 2; o $-N(R^3)-$ donde R^3 tiene el mismo significado que se define más adelante:

- W^2 es -O-; $-S(=O)_t-$, donde t es 0, 1, ó 2; o $-N(R^3)-$ donde R^3 tiene el mismo significado que se define más adelante, o $-CR^{29}R^{30}-$;

donde

- R^{29} y R^{30} son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -F; $-CF_3$; -alquilo C_1-C_3; -cicloalquilo C_3-C_6; fenilo; bencilo; y piridilo; en el que dichos restos alquilo, cicloalquilo, fenilo, bencilo y piridilo están cada uno sustituidos independientemente con 0 a 3 sustituyentes R^{10}, donde R^{10} tiene el mismo significado que se define más adelante;

- Y es $=C(R^1{}_a)-$, donde $R^1{}_a$ tiene el mismo significado que se define más adelante; o $-[N\rightarrow(O)_k]-$ donde k es 0 ó 1;

donde

- $R^1{}_a$ es un miembro seleccionado del grupo constituido por -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; $-OR^{16}$; y $-C(=O)NR^{22}{}_aR^{22}{}_b$;

donde

$-R^{22}{}_a$ y $R^{22}{}_b$ son cada uno 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;

- R^A y R^B son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -F; -CF_3; -alquilo C_1-C_4; cicloalquilo C_3-C_7; fenilo; y bencilo; en el que dichos restos alquilo, cicloalquilo, fenilo, y bencilo están cada uno sustituido independientemente con 0 a 3 sustituyentes R^{10};

donde

- R^{10} es un miembro seleccionado del grupo constituido por fenilo; piridilo; -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}; -$NR^{16}S(=O)_2R^{17}$; y -$S(=O)_2NR^{16}R^{17}$; donde dicho fenilo o piridilo está sustituido con 0 a 3 R^{11};

donde

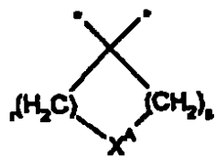
- R^{11} es -F; -Cl; -CF_3; -CN; -NO_2; -OH; -alcoxi C_1-C_3; alquilo C_1-C_3; o -$NR^{16}R^{17}$;

y

-R^{16} y R^{17} son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -alquilo C_1-C_4; -alquenilo C_2-C_4; -cicloalquilo C_3-C_6; fenilo; bencilo; y piridilo; en el que dicho alquilo, alquenilo, cicloalquilo, fenilo, bencilo, o piridilo está sustituido por 0 a 3 sustituyentes seleccionados del grupo constituido por -F, -Cl, -CF_3, -CN, y -alquilo C_1-C_3;

o

- R^A y R^B se toman conjuntamente, pero únicamente en el caso en que m es 1, para formar un resto espiro de Fórmula (1.2.0):



(1.2.0)

donde

r y s son independientemente 0 a 4 siempre que la suma de r + s sea al menos 1 pero no mayor que 5;

y

X^A se selecciona de $-CH_2-$, $-CH(R^{11})-$, o $C(R^{11})_2-$, donde cada R^{11} se selecciona independientemente de los otros y cada uno tiene el mismo significado que se define anteriormente; $-NR^{15}-$, donde R^{15} tiene el mismo significado que se define más adelante; -O-; y $-S(=O)_t-$, donde t es 0, 1, ó 2;

y

dicho resto espiro de Fórmula parcial (1.2.0) está sustituido en lo que se refiere a uno cualquiera o más de sus átomos de carbono, excepto el que define a X^A, con 0 a 3 sustituyentes R^{14}, donde R^{14} tiene el mismo significado que se define más adelante; en lo que se refiere a un átomo de nitrógeno del mismo con 0 ó 1 sustituyente R^{15}, donde R^{15} tiene el mismo significado que se define más adelante; y en lo que se refiere a un átomo de azufre del mismo con 0 o 2 átomos de oxígeno;

- R^C y R^D tienen el mismo significado definido anteriormente para R^A y R^B pero uno de ellos debe ser -H, y se seleccionan independientemente el uno del otro y de R^A y R^B;

- R^1 y R^2 pueden aparecer de forma individual o juntos en cualquier anillo o anillos que comprenden un significado del resto Q^2 como se define más adelante; y R^1 y R^2 son cada uno un miembro seleccionado independientemente del grupo constituido por -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 $-C(=O)NR^{22}{}_aR^{22}{}_b$; donde R^{16}, $R^{22}{}_a$, y $R^{22}{}_b$ tienen los mismos significados que se definen anteriormente;

- R^3 es -H; -alquilo C_1-C_3; fenilo; bencilo; o $-OR^{16}$, donde R^{16} tiene el mismo

significado definido anteriormente;

- R^4, R^5 y R^6 pueden aparecer individualmente o juntos en cualquier anillo o anillos que comprenden un significado del resto Q^1 como se define más adelante; y R^4, R^5 y R^6 son cada uno un miembro seleccionado independientemente del grupo constituido por

los siguientes:

- *(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 -$CH_2C(=NR^{22}a)NR^{16}R^{17}$;

donde

- p es 0, 1, ó 2; y $R^{22}{}_a$, R^{16}, y R^{17} tienen los mismos significados definidos anteriormente;

- *(b)* -alquilo C_1-C_4; y -alcoxi C_1-C_4 en el caso en que uno o más de R^4, R^5, o R^6 tiene el significado de -OR^{16} en *(a)* anteriormente y R^{16} se define como -alquilo C_1-C_4; donde dicho alquilo y alcoxi se sustituyen cada uno independientemente con 0 a 3 sustituyentes -F o -Cl; o 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 del grupo constituido por 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-dihidrobenzofuranilo; 2-*H*-cromenilo; cromanilo; benzotienilo; 1-*H*-indazolilo; bencimidazolilo; benzoxazolilo; benzoisoxazolilo; benzotiazolilo; quinolinilo; isoquinolinilo; ftalazinilo; quinazolinilo; quinoxalinilo; y purinilo; donde dichos restos arilo y heterociclilo están cada uno sustituido independientemente con 0 a 2 sustituyentes R^{14}.

donde

– R^{14} es un miembro seleccionado del grupo constituido por -alquilo C_1-C_4; -cicloalquilo C_3-C_7; fenilo; bencilo; piridilo; y quinolinilo; donde 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, o -$NR^{16}R^{17}$; y dicho grupo R^{14} está constituido adicionalmente por -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-$C(=O)NR^{16}R^{17}$; -$NR^{16}R^{17}$; -$NR^{16}C(=O)R^{17}$; -$NR^{16}C(=O)OR^{17}$; -$NR^{16}S(=O)_2R^{17}$; o -$S(=O)_2NR^{16}R^{17}$; donde R^{16} y R^{17} tienen los mismos significados definidos anteriormente;

y además donde

—R^{15} es un miembro seleccionado independientemente del grupo constituido por -H; -$NR^{16}R^{17}$; -$C(=O)R^{16}$; -OR^{16}; -alquilo (C_1-C_4)-OR^{16}; -$C(=O)OR^{16}$; -alquilo (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 donde u es 0, 1, ó 2; fenilo; bencilo; piridilo; y quinolinilo; donde dicho alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, bencilo, piridilo o quinolinilo está sustituido con 0 a 3 sustituyentes R^{12}; donde R^{16} y R^{17} tienen los mismos significados definidos anteriormente; y

donde

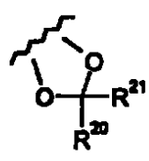
—R^{12} es un miembro seleccionado independientemente del grupo constituido por -F; -Cl; -CO_2R^{18}; -OR^{16}; -CN; -$C(=O)NR^{18}R^{19}$; -$NR^{18}R^{19}$; -$NR^{18}C(=O)R^{19}$; -$NR^{18}C(=O)OR^{19}$; -$NR^{18}S(=O)_pR^{19}$; -$S(=O)_pNR^{18}R^{19}$, donde p es 1 ó 2; -alquilo C_1-C_4; y -alcoxi C_1-C_4 en el caso en que R^{12} tiene el significado de -OR^{16} anterior y R^{16} se define como -alquilo C_1-C_4; donde dicho alquilo y alcoxi están cada uno independientemente sustituidos con 0 a 3 sustituyentes seleccionados independientemente de -F; -Cl; -alcoxi (C_1-C_2)carbonilo; -alquil (C_1-C_2)carbonilo; y alquil (C_1-C_2)carboniloxi; donde R^{16} tiene el mismo significado definido anteriormente; y

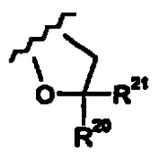
donde

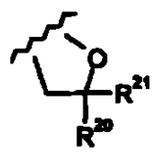
—R^{18} y R^{19} se seleccionan independientemente del grupo constituido por -H; -alquilo C_1-C_4; y fenilo; donde dicho alquilo o fenilo está sustituido por 0-3 de -F; o -Cl;

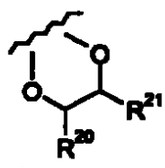
o en el caso en que Q^1 es fenilo

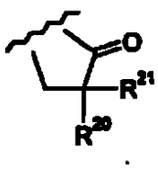
- *(d)* R^5 y R^6 se toman conjuntamente para formar un resto que es un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.3.1) a (1.3.15):

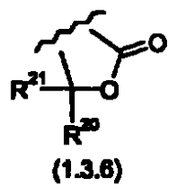

(1.3.1)

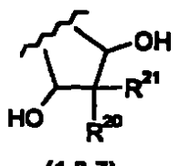

(1.3.2)

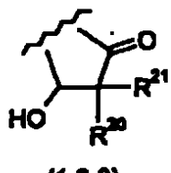

(1.3.3)

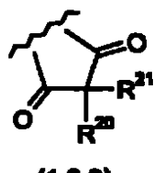

(1.3.4)

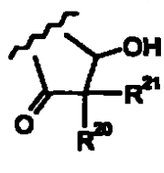

(1.3.5)

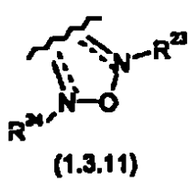

(1.3.6)

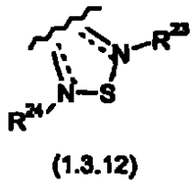

(1.3.7)

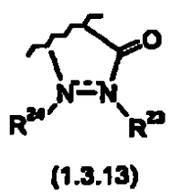

(1.3.8)

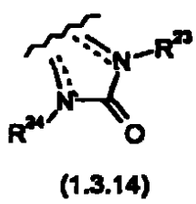

(1.3.9)

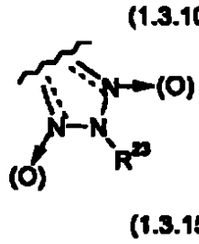

(1.3.10)


(1.3.11)


(1.3.12)


(1.3.13)


(1.3.14)


(1.3.15)

en los que

-- R^{20} y R^{21} son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -F; -Cl; $-CH_3$; $-CH_2F$; $-CHF_2$; $-CF_3$; $-OCH_3$; y $-OCF_3$;

-- R^{23} y R^{24} son cada uno 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 discontinua --- representa un enlace doble;

- Q^1 es un resto que comprende un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3 a 7 miembros, o que es un policiclo condensado de 7 a 12 miembros; siempre que Q^1 no sea un resto biarilo discontinuo o restringido como se define en Q^2 más adelante; y en el que opcionalmente un átomo de carbono de dicho sistema de anillos de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo

pueden reemplazarse por N;

en el que

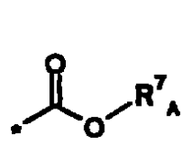
dicho resto que define Q^1 está sustituido en cualquier anillo o anillos del mismo con R^4, R^5, y R^6, que tienen los mismos significados definidos anteriormente;

- Q^2 es un resto biarilo discontinuo o restringido que consiste en un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3- a 7- miembros, o que es un policiclo condensado de 7 a 12 miembros; en el que opcionalmente un átomo de carbono de dicho sistema de anillos de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo pueden reemplazarse por N;

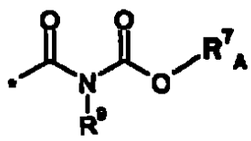
- Z es un miembro seleccionado independientemente del grupo constituido por

los siguientes

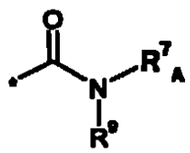
-*(a)* el grupo constituido por las Fórmulas parciales (1.1.1) a (1.1.15):



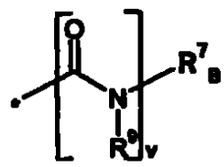
(1.1.1)



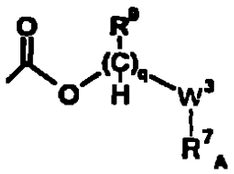
(1.1.2)



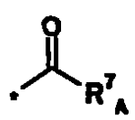
(1.1.3)



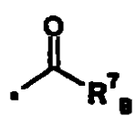
(1.1.4)



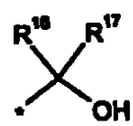
(1.1.5)



(1.1.6)



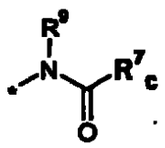
(1.1.7)



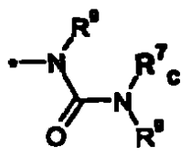
(1.1.8)



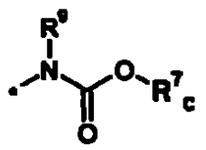
(1.1.9)



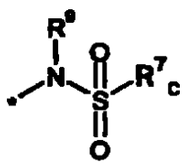
(1.1.10)



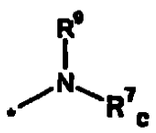
(1.1.11)



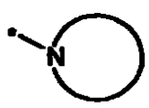
(1.1.12)



(1.1.13)



(1.1.14)



(1.1.15)

en las que

donde R^{16} y R^{17} tienen los mismos significados definidos anteriormente; y R^9 tiene el mismo significado definido más adelante;

– "*" indica el punto de unión de cada Fórmula parcial (1.1.1) a (1.1.15) a la porción restante de la Fórmula (1.0.0);

– q es 1, 2, ó 3, siempre que cuando q es 2 ó 3, R^9 tiene el significado de -H al menos en un caso, o en dos casos, respectivamente;

– v 0 ó 1;

– W^3 es -O-; -N(R^9)-, donde R^9 tiene el mismo significado definido más adelante; o -OC(=O)-;

- R^7_A es un miembro seleccionado independientemente del grupo constituido por los siguientes:

– *(1)* -H;

– *(2)* -alquilo C_1-C_6; -alquenilo C_2-C_6; o -alquinilo C_2-C_6; donde dicho alquilo, alquenilo o alquinilo está sustituido con 0 a 3 sustituyentes R^{10}, donde R^{10} tiene el mismo significado definido anteriormente;

– *(3)* -$(CH_2)_u$-cicloalquilo C_3-C_7 donde u es 0, 1, ó 2; y adicionalmente donde dicho cicloalquilo C_3-C_7 está sustituido con 0 a 3 sustituyentes R^{10} donde R^{10} tiene el mismo significado definido anteriormente;

y

– *(4)* fenilo o bencilo, donde dicho fenilo o bencilo está sustituido independientemente con 0 a 3 sustituyentes R^{10} donde R^{10} tiene el mismo significado definido anteriormente;

– R^7_B es un miembro seleccionado independientemente del grupo constituido por

los siguientes:

– *(1)* 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; pirrolidonilo; 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; 1*H*-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;

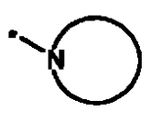
donde

cualquier resto referido en *(1)* o *(2)* anteriormente está opcionalmente sustituido con respecto a *(i)* cualesquiera uno o más átomos de carbono del mismo opcionalmente con un sustituyente R^{14} donde R^{14} tiene el mismo significado definido anteriormente; *(ii)* cualesquiera uno o más átomos de nitrógeno del mismo que no es un punto de unión de dicho resto, opcionalmente con un sustituyente R^{15} donde R^{15} tiene el mismo significado definido anteriormente, y todas las formas tautómeras del mismo; y *(iii)* cualquier átomo de azufre del mismo que no es un punto de unión de dicho resto, con 0, 1, ó 2 átomos de oxígeno;

– R^9 es un miembro seleccionado del grupo constituido por -H; -alquilo C_1-C_4; cicloalquilo C_3-C_7; fenilo; bencilo; piridilo; -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}; donde R^{16} tiene el mismo significado definido anteriormente;

-- $R^7{}_C$ es un miembro seleccionado independientemente del grupo constituido por los significados de $R^7{}_A$ y los significados de $R^7{}_B$ definidos anteriormente;

y adicionalmente en el que



(1.1.15)

– comprende un sistema de anillos carbocíclico saturado o insaturado monocíclico de 4 a 8 miembros, o bicíclico condensado o abierto, de 5 a 10 miembros que contiene un heteroátomo de nitrógeno como se muestra en la Fórmula parcial (1.1.15); en el que opcionalmente de 1 a 3 átomos de carbono de dicho sistema de anillos carbocíclico puede ser reemplazado individualmente por un heteroátomo de nitrógeno; u opcionalmente 1 átomo de carbono del mismo puede ser reemplazado por un heteroátomo de oxígeno o por un heteroátomo de azufre; u opcionalmente 2 átomos de carbono del mismo pueden ser reemplazados individualmente por un heteroátomo de nitrógeno y un heteroátomo de oxígeno, o por un heteroátomo de nitrógeno y un heteroátomo de azufre;

donde

cualquier resto de Fórmula parcial (1.1.15) mencionado anteriormente está opcionalmente sustituido con respecto a *(1)* cualesquiera uno o más átomos de carbono del mismo, con un sustituyente R^{14} donde R^{14} tiene el mismo significado definido anteriormente; *(2)* cualesquiera uno o más átomos de nitrógeno del mismo, con un sustituyente R^{15} donde R^{15} tiene el mismo significado definido anteriormente, y todas las formas tautómeras, y opcionalmente formas de N-óxido del mismo; o *(3)* cualquier átomo de azufre del mismo con 0, 1, ó 2 átomos de oxígeno;

y **Z** se selecciona adicionalmente de

- *(b)* un resto que comprende un miembro seleccionado del grupo constituido por -O-P(=O)$(OH)_2$ (fosfórico); -PH(=O)OH (fosfínico); -P(=O)$(OH)_2$ (fosfónico); -[P(=O)(OH)-O-alquilo (C_1-C_4)] (alquilfosfono); -P(=O)(OH)-O-alquilo (C_1-C_4) (alquilfosfinilo); -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)$_2NHR^{26}$ o -NHS(=O)$_2R^{26}$ (sulfonamido) donde R^{26} es $-CH_3$, $-CF_3$, u

o-tolilo; y acilsulfonamido seleccionado del grupo consituido por -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)NHalquilo 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};

donde

– R^{25} es -H; -alquilo C_1-C_4; fenilo; u -OR^{18}, donde R^{18} tiene el mismo significado definido anteriormente;

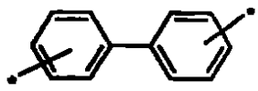
o

una sal farmacéuticamente aceptable del mismo.

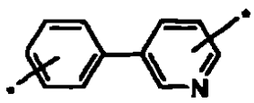
La presente invención concierne en particular un compuesto de Fórmula (1.0.0) como se refiere anteriormente en el que el grupo Q^2 comprende un miembro seleccionado del grupo constituido por

los siguientes

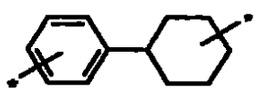
restos representados por las Fórmulas parciales (1.2.1) a (1.2.32):



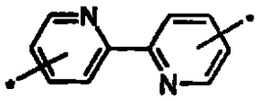
(1.2.1)



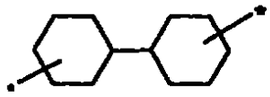
(1.2.2)



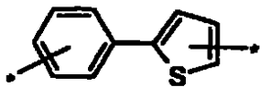
(1.2.3)



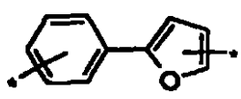
(1.2.4)



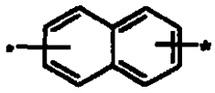
(1.2.5)



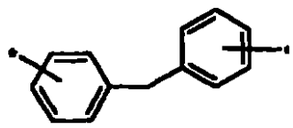
(1.2.6)



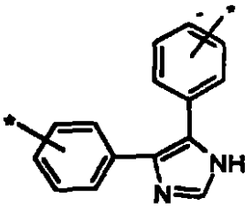
(1.2.7)



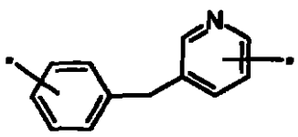
(1.2.8)



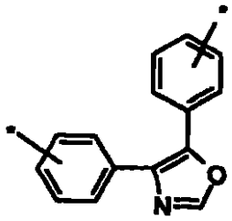
(1.2.9)



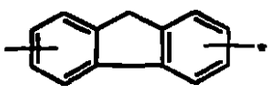
(1.2.10)



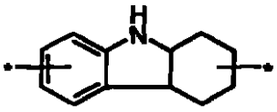
(1.2.11)



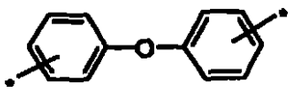
(1.2.12)



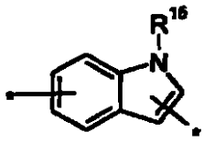
(1.2.13)



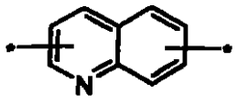
(1.2.14)



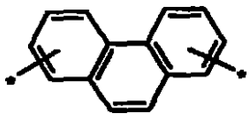
(1.2.15)



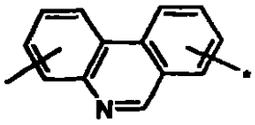
(1.2.16)



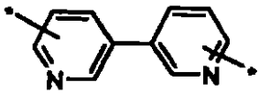
(1.2.17)



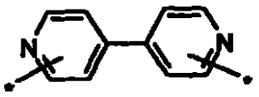
(1.2.18)



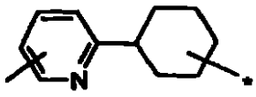
(1.2.19)



(1.2.20)



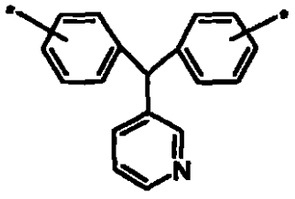
(1.2.21)



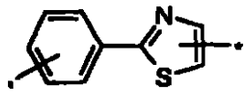
(1.2.22)



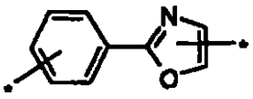
(1.2.23)



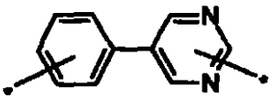
(1.2.24)



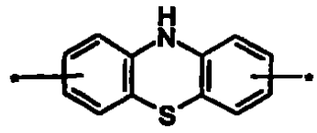
(1.2.25)



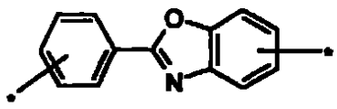
(1.2.26)



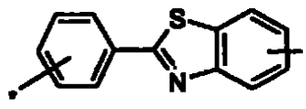
(1.2.27)



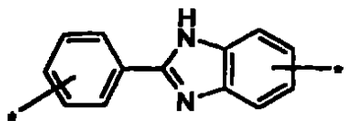
(1.2.28)



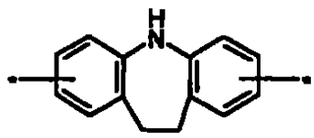
(1.2.29)



(1.2.30)



(1.2.31)

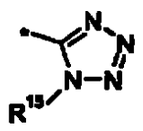


(1.2.32)

donde "*" es un símbolo que indica los dos puntos de unión de dicho grupo Q^2 a los componentes restantes de la Fórmula (1.0.0).

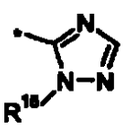
La presente invención concierne en particular un compuesto de Fórmula (1.0.0) como se refiere anteriormente en el que el grupo terminal Z comprende un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.1.1) a (1.1.3), (1.1.5), (1.1.6), y (1.1.10) a (1.1.14), en el que un significado preferido de R^7_A o R^7_C es el significado de hidrógeno, metilo, trifluorometilo, *iso*-propilo, fenilo, ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo ilustrado en las Fórmulas parciales (1.4.24) a (1.4.28) a continuación.

La presente invención concierne además un compuesto de Fórmula (1.0.0) en el que Z comprende las Fórmulas parciales (1.1.4) y (1.1.10) a (1.1.14). Un significado preferido de R^7_B de Fórmula parcial (1.1.4) donde v es 0 ó 1, o R^7_C de Fórmulas parciales (1.1.10) a (1.1.14) es el significado de un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.4.1) a (1.4.28) ilustradas a continuación:



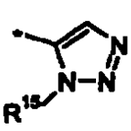
tetrazol-5-ilo

(1.4.1)



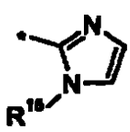
1,2,4-triazol-3-ilo

(1.4.2)



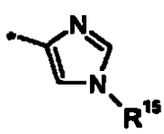
1,2,3-triazol-5-ilo

(1.4.3)



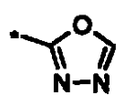
imidazol-2-ilo

(1.4.4)



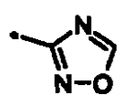
imidazol-4-ilo

(1.4.5)



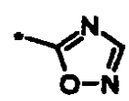
1,3,4-oxadiazolilo

(1.4.6)



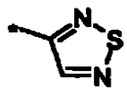
1,2,4-oxadiazol-3-ilo

(1.4.7)



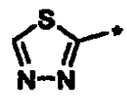
1,2,4-oxadiazol-5-ilo

(1.4.8)



1,2,5-tiadiazol-2-ilo

(1.4.9)



1,3,4-tiadiazolilo

(1.4.10)



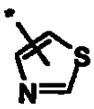
oxazolilo

(1.4.11)



isoxazolilo

(1.4.12)



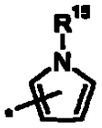
tiazolilo

(1.4.13)



isotiazolilo

(1.4.14)



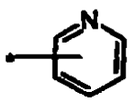
pirrolilo

(1.4.15)



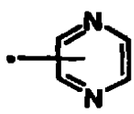
pirazolilo

(1.4.16)



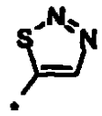
piridilo

(1.4.17)



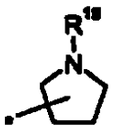
pirazinilo

(1.4.18)



1,2,3-tiadiazol-5-ilo

(1.4.19)



pirrolidinilo

(1.4.20)



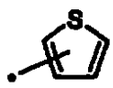
furanilo

(1.4.21)



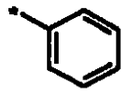
tetrahidrofuranilo

(1.4.22)



tienilo

(1.4.23)



fenilo

(1.4.24)



ciclopropilo

(1.4.25)



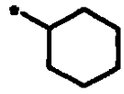
ciclobutilo

(1.4.26)



ciclopentilo

(1.4.27)



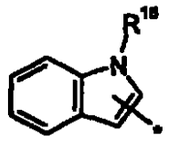
ciclohexilo

(1.4.28)

donde "*" indica el punto de unión a la porción restante de la Fórmula (1.0.0); y donde cada átomo de carbono está sustituido opcionalmente con un sustituyente R^{14}; y donde R^{14} y R^{15} tienen el mismo significado definido anteriormente; y todas las formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

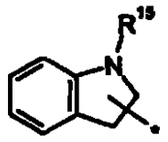
La presente invención concierne además en particular un compuesto de Fórmula (1.0.0) como se refiere anteriormente en el que el grupo terminal Z comprende las

Fórmulas parciales (1.1.4) y (1.1.10) a (1.1.14), y donde los significados preferidos de R^7_B y R^7_C en dichas Fórmulas parciales (1.1.4) y (1.1.10) a (1.1.14) son cada uno, independientemente, un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.5.1) a (1.5.29):



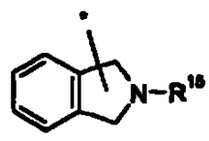
indolilo

(1.5.1)



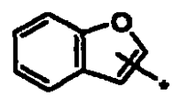
indolinilo

(1.5.2)



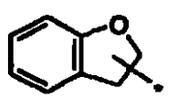
isoindolinilo

(1.5.3)



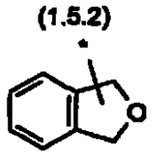
benzo[*b*]furanilo

(1.5.4)



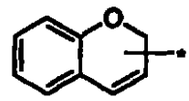
2,3-dihidrobenzo-furanilo

(1.5.5)



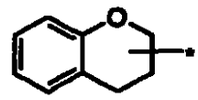
1,3-dihidroisobenzo-furanilo; ftalanilo

(1.5.6)



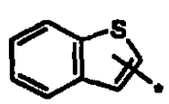
2*H*-1-benzopiranilo

(1.5.7)



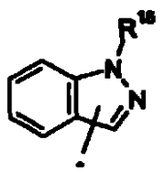
cromanilo

(1.5.8)



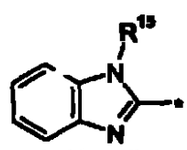
benzotienilo

(1.5.9)



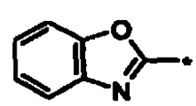
1*H*-indazolilo

(1.5.10)



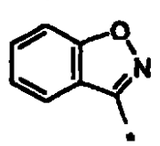
bencimidazolilo

(1.5.11)



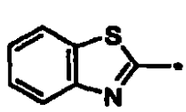
benzoxazolilo

(1.5.12)



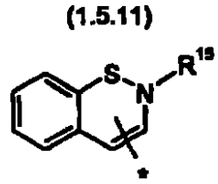
benzisoxazolilo

(1.5.13)



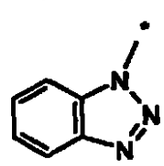
benzotiazolilo

(1.5.14)



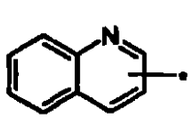
2*H*-1,2-benzotiazinilo

(1.5.15)



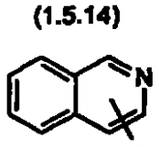
benzotriazolilo

(1.5.16)



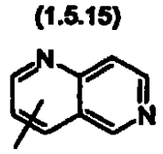
quinolinilo

(1.5.17)



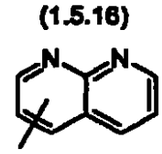
isoquinolinilo

(1.5.18)



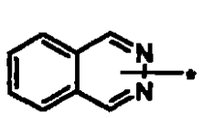
1,6-naftiridinilo

(1.5.19)



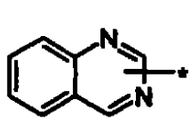
1,8-naftiridinilo

(1.5.20)



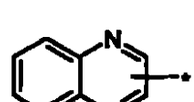
ftalazinilo

(1.5.21)



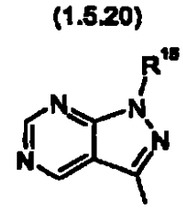
quinazolinilo

(1.5.22)



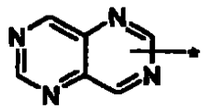
quinoxalinilo

(1.5.23)



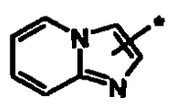
1*H*-pirazolo[3,4-*d*]-pirimidinilo

(1.5.24)



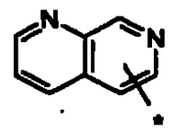
pirimido [5,4-*d*]-pirimidinilo

(1.5.25)



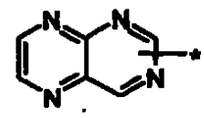
imidazo- [1,2-*a*]-piridinilo

(1.5.26)



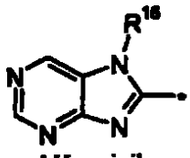
1,7-naftiridinilo

(1.5.27)



pteridinilo

(1.5.28)

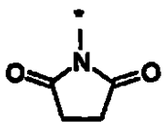


1*H*-purinilo

(1.5.29)

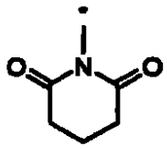
donde "*" indica el punto de unión a la porción restante de la Fórmula (1.0.0); y donde cada átomo de carbono está sustituido opcionalmente con un sustituyente R^{14}; y donde R^{14} y R^{15} tienen el mismo significado definido anteriormente, y todas las formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

La presente invención concierne además un compuesto de Fórmula (1.0.0) en el que el grupo terminal Z tiene el significado de un resto de Fórmula parcial (1.1.15) donde el número y posición de los átomos de carbono y el reemplazo de los mismos por uno o más heteroátomos, así como la sustitución de uno o más de dichos átomos de carbono del mismo por R^{14} donde R^{14} es oxo(=O), se seleccionan de tal forma que Z comprende un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.7.1) a (1.7.46):



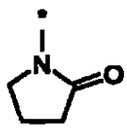
succinimid-1-ilo

(1.7.1)



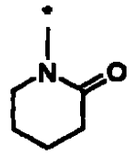
glutarimid-1-ilo

(1.7.2)



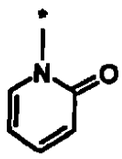
pirrolidin-2-on-1-ilo

(1.7.3)



piperid-2-on-1-ilo

(1.7.4)



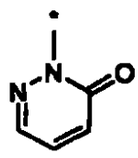
pirid-2-on-1-ilo

(1.7.5)



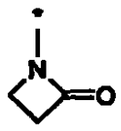
pirid-4-on-1-ilo

(1.7.6)



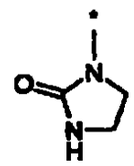
piridazin-3-on-2-ilo

(1.7.7)



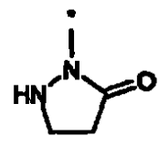
azetidin-2-on-1-ilo

(1.7.8)



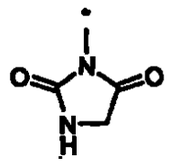
imidazolidin-2-on-1-ilo

(1.7.9)



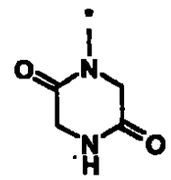
pirazol-5-on-1-ilo

(1.7.10)



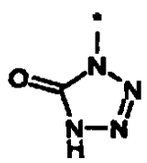
imidazolidin-2,4-dion-1-ilo

(1.7.11)



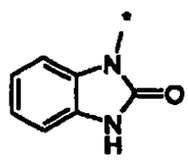
piperazin-2,5-dion-1-ilo

(1.7.12)



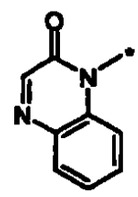
4,5-dihidro-5-oxo 1*H*-tetrazol-1-ilo

(1.7.13)



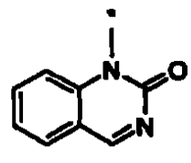
bencimidazolin-2-on-1-ilo

(1.7.14)



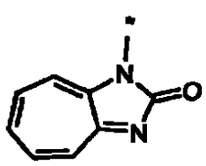
1*H*-quinoxalin-2-on-1-ilo

(1.7.15)



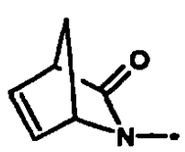
1*H*-quinazolin-2-on-1-ilo

(1.7.16)



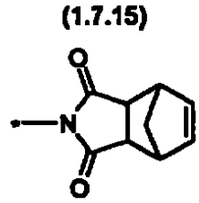
1*H*-cicloheptimidazol-2-on-1-ilo

(1.7.17)



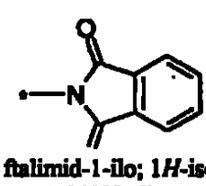
2-azabiciclo[2.2.1]-hept-5-en-3-on-1-ilo

(1.7.18)



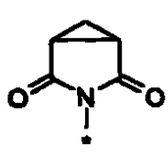
norborn-5-en-2,3-dicarboximid-1-ilo 1*H*-tetrazol-1-ilo

(1.7.19)



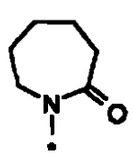
ftalimid-1-ilo; 1*H*-isoindol-1,3(2*H*)-dion-1-ilo

(1.7.20)



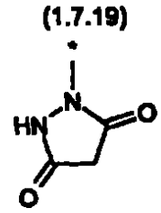
3-azabiciclo[3,1,0]-hexano-2,4-dion-3-ilo 1*H*-tetrazol-1-ilo

(1.7.21)



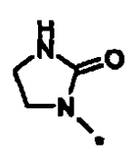
2*H*-azepin- 2-on-1-ilo

(1.7.22)



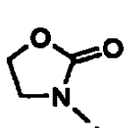
pirazolidin-3,5-dion-1-ilo

(1.7.23)



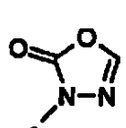
imidazolidin-2-on-1-ilo

(1.7.24)



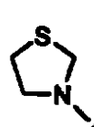
oxazolidin- 2-on-1-ilo

(1.7.25)



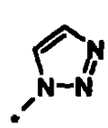
1,3,4-oxadiazol-2(3*H*)-on-3-ilo

(1.7.26)



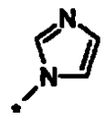
tiazolidin-3-ilo

(1.7.27)



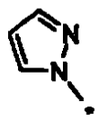
1*H*-1,2,3-triazol-1-ilo

(1.7.28)



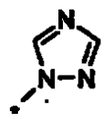
imidazol-1-ilo

(1.7.29)



pirazol-1-ilo

(1.7.30)



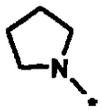
1*H*-1,2,4-triazol-1-ilo

(1.7.31)



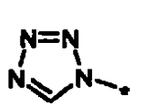
azetidin-1-ilo

(1.7.32)



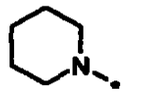
pirrolidin-1-ilo

(1.7.33)



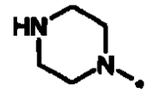
tetrazol -1-ilo

(1.7.34)



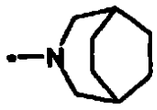
piperidin-1-ilo

(1.7.35)



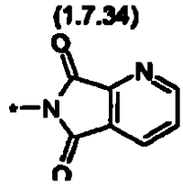
piperazin-1-ilo

(1.7.36)



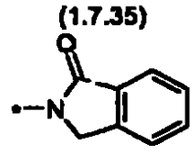
3-azabiciclo[3,2,2]-non-3-ilo

(1.7.37)



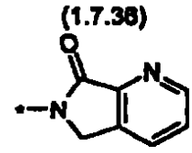
pirrolo[3,4-*b*]piridin-5,7-dion-6-ilo

(1.7.38)



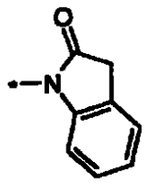
2,3-dihidro-*iso*-indol-1-on-2-ilo

(1.7.39)



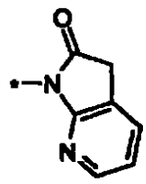
pirrolo[3,4-*b*]piridin-7-on-6-ilo

(1.7.40)



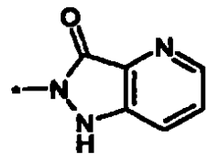
1,3-dihidroindol-2-on-1-ilo

(1.7.41)



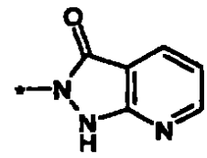
pirrolo[4,5-*b*]piridin-3-on-2-ilo

(1.7.42)



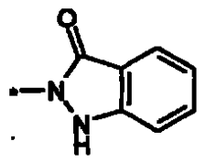
1*H*-pirazolo[4,5-*e*]piridin-7-on-2-ilo

(1.7.43)



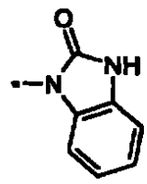
1*H*-pirazolo[4,5-*b*]piridin-4-on-2-ilo

(1.7.44)



1*H*-indazol-3-on-2-ilo

(1.7.45)



1*H*-bencimidazol-2-on-3-ilo

(1.7.46)

Cualquier resto que es un miembro seleccionado del grupo constituido por las

Fórmulas parciales (1.7.1) a (1.7.46) representadas arriba, incluye la sustitución opcional del mismo con respecto a *(1)* cualesquiera uno o más átomos de carbono del mismo, con un sustituyente R^{14} donde R^{14} tiene el mismo significado definido anteriormente; *(2)* cualesquiera uno o más átomos de nitrógeno del mismo, con un sustituyente R^{15} donde R^{15} tiene el mismo significado definido anteriormente, y todas las formas tautómeras, y opcionalmente formas de N-óxido del mismo; o *(3)* cualquier átomo de azufre del mismo con 0, 1, ó 2 átomos de oxígeno.

La presente invención concierne además un procedimiento para tratar un sujeto que sufre una enfermedad o afección mediada por la isozima PDE4, especialmente el subtipo D de la misma, en su papel de reguladora de la activación y desgranulación de eosinófilos humanos, que comprende administrar a dicho sujeto que necesita dicho tratamiento una cantidad terapéuticamente efectiva de un compuesto de Fórmula (1.0.0) como se describe anteriormente. De forma similar, la presente invención concierne además una composición farmacéutica para usarse en tal tratamiento terapéutico, que comprende un compuesto de Fórmula (1.0.0) como se describe anteriormente junto con un vehículo farmacéuticamente aceptable.

La presente invención se refiere a los inhibidores de la isozima PDE4, especialmente el subtipo D, que comprenden un compuesto de Fórmula (1.0.0) como se describe anteriormente que es de utilidad en el tratamiento o prevención de uno de los miembros seleccionados de los grupos de enfermedades, trastornos, y afecciones constituidos por:

- asma de cualquier tipo, etiología, o patogénesis; o asma que es un miembro seleccionado del grupo constituido por asma atópica; asma no atópica; asma alérgica; asma atópica, bronquial, mediada por IgE; asma bronquial; asma idiopática; asma verdadera; asma intrínseca provocada por alteraciones patofisiológicas; asma extrínseca

provocada por factores medioambientales; asma idiopática de causa desconocida o no evidente; asma no atópica; asma bronquítica; asma enfisematosa; asma inducida por el ejercicio; asma ocupacional; asma infecciosa provocada por infección bacteriana, fúngica, protozóica, o viral; asma no alérgica; asma incipiente; síndrome de sibilancias en el niño;

- broncoconstricción crónica o agua; bronquitis crónica; obstrucción de las vías respiratorias menores; y enfisema;

- enfermedades obstructivas o inflamatorias de las vías respiratorias de cualquier tipo, etiología, o patogénesis; o una enfermedad obstructiva o inflamatoria de las vías respiratorias que es un miembro seleccionado del grupo constituido por asma; neumoconiosis; neumonía eosinófila crónica; enfermedad pulmonar obstructiva crónica (COPD); COPD que incluye bronquitis crónica, enfisema pulmonar o disnea asociada a los mismos; COPD caracterizada por la obstrucción irreversible, progresiva de las vías respiratorias; síndrome disneico agudo del adulto (ARDS), y exacerbación de la hiperreactividad de las vías respiratorias como consecuencia de otras farmacoterapias;

- neumoconiosis de cualquier tipo, etiología, o patogénesis; o neumoconiosis que es un miembro seleccionado del grupo constituido por aluminosis o enfermedad de los trabajadores de la bauxita; antracosis o asma de los mineros; asbestosis o asma de los montadores de calderas; calicosis o enfermedad del sílex; ptilosis provocada por la inhalación del polvo de las plumas de avestruz; siderosis provocada por la inhalación de partículas de hierro; silicosis o enfermedad de los amoladores; bisinosis o asma del polvo del algodón; y neumoconiosis del talco;

- bronquitis de cualquier tipo, etiología o patogénesis; o bronquitis que es un miembro seleccionado del grupo constituido por bronquitis aguda; bronquitis laringotraqueal aguda; bronquitis araquídica; bronquitis catarral; bronquitis

pseudomembranosa; bronquitis seca; bronquitis asmática infecciosa; bronquitis productiva; bronquitis por estafilococos o estreptococos; y bronquitis vesicular;

- bronquiectasia de cualquier tipo, etiología o patogénesis; o bronquiectasia que es un miembro seleccionado del grupo constituido por bronquiectasia cilíndrica; bronquiectasia saculada; bronquiectasia fusiforme; bronquiectasia capilar; bronquiectasia cística; bronquiectasia seca; y bronquiectasia folicular;

- rinitis alérgica estacional; o rinitis alérgica perenne; o sinusitis de cualquier tipo, etiología o patogénesis; o sinusitis que es un miembro seleccionado del grupo constituido por sinusitis purulenta o no purulenta; sinusitis aguda o crónica; y sinusitis etmoide, frontal, maxilar, o esfenoidal;

- artritis reumatoide de cualquier tipo, etiología o patogénesis; o artritis reumatoide que es un miembro seleccionado del grupo constituido por artritis aguda; artritis gotosa aguda; artritis inflamatoria crónica; artritis degenerativa; artritis infecciosa; artritis de Lyme; artritis proliferativa; artritis psoriásica; y artritis vertebral;

- gota, y fiebre y dolor asociados a la inflamación;

- un trastorno relacionado con la eosinofilia de cualquier tipo, etiología o patogénesis; o un trastorno relacionado con la eosinofilia que es un miembro seleccionado del grupo constituido por eosinofilia; eosinofilia en infiltración pulmonar; síndrome de Loffler; neumonía eosinófila crónica; eosinofilia pulmonar tropical; aspergilosis bronconeumónica; aspergiloma; granulomas que contienen eosinófilos; angitis granulomatosa alérgica o síndrome de Churg-Strauss; poliarteritis nodosa (PAN); y vasculitis necrosante sistémica;

- dermatitis atópica; o dermatitis alérgica; o eczema alérgico o atópico;

- urticaria de cualquier tipo, etiología o patogénesis; o urticaria que es un miembro seleccionado del grupo constituido por urticaria inmunomediada; urticaria

mediada por complemento; urticaria inducida por materiales urticantes; urticaria inducida por agentes físicos; urticaria inducida por estrés; urticaria idiopática; urticaria aguda; urticaria crónica; angioedema; urticaria colinérgica; criourticaria de la forma de autosoma dominante o de la forma adquirida; urticaria de contacto; megaurticaria; y urticaria papular;

- conjuntivitis de cualquier tipo, etiología o patogénesis; o conjuntivitis que es un miembro seleccionado del grupo constituido por conjuntivitis actínica; conjuntivitis catarral aguda; conjuntivitis contagiosa aguda; conjuntivitis alérgica; conjuntivitis atópica; conjuntivitis catarral crónica; conjuntivitis purulenta; y conjuntivitis primaveral;

- uveítis de cualquier tipo, etiología o patogénesis; o uveítis que es un miembro seleccionado del grupo constituido por inflamación de toda o parte de la úvea; uveítis anterior; iritis; ciclitis; iridociclitis; uveítis granulomatosa; uveítis no granulomatosa; uveítis facoantígena; uveítis posterior; coroiditis; y corioretinitis;

- soriasis;

- esclerosis múltiple de cualquier tipo, etiología o patogénesis; o esclerosis múltiple que es un miembro seleccionado del grupo constituido por esclerosis múltiple progresiva primaria; y esclerosis múltiple recidivante remitente;

- enfermedades autoinmunitarias/inflamatorias de cualquier tipo, etiología o patogénesis; o una enfermedad autoinmunitaria/inflamatoria que es un miembro seleccionado del grupo constituido por trastornos hematológicos autoinmunitarios; anemia hemolítica; anemia aplásica; eritrocitopenia pura; púrpura trombocitopénica idiopática; lupus eritematoso sistémico; policondritis; escleroderma; granulomatosis de Wegner; dermatomiositis; hepatitis activa crónica; miastenia grave; síndrome de Stevens-Johnson; esprue idiopática; enfermedades inflamatorias del intestino

autoinmunitarias; colitis ulcerosa; enfermedad de Crohn; oftalmopatía endocrina; enfermedad de Grave; sarcoidosis; alveolitis; neumonitis por hipersensibilidad crónica; cirrosis biliar primaria; diabetes juvenil o diabetes melitus tipo I; uveítis anterior; uveítis granulomatosa o posterior; queratoconjuntivitis seca; queratoconjuntivitis epidémica; fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial; fibrosis pulmonar idiopática; fibrosis quística; artritis soriásica; glomerulonefritis con y sin síndrome nefrótico; glomerulonefritis aguda; síndrome nefrótico idiopático; nefropatía de cambio mínimo; enfermedades cutáneas inflamatorias/hiperproliferativas; soriasis; dermatitis atópica; dermatitis de contacto; dermatitis alérgica de contacto; pénfigo familiar benigno; pénfigo eritematoso; pénfigo foliáceo; y pénfigo vulgar;

- prevención del rechazo de aloinjertos tras el trasplante de órganos;

-. enfermedad inflamatoria del intestino (IBD) de cualquier tipo, etiología, o patogénesis; o enfermedad inflamatoria del intestino que es un miembro seleccionado del grupo constituido por colitis ulcerosa (UC); colitis colágena; colitis poliposa; colitis transparietal; y enfermedad de Crohn (CD);

- choque séptico de cualquier tipo, etiología, o patogénesis; o choque séptico que es un miembro seleccionado del grupo constituido por insuficiencia renal; insuficiencia renal aguda; caquexia; caquexia por malaria; caquexia hipofisiaria; caquexia urémica; caquexia cardiaca; caquexia suprarrenal o enfermedad de Addison; caquexia cancerosa; y caquexia como consecuencia de infección por el virus de inmunodeficiencia humano (VIH);

- lesión hepática;

- hipertensión pulmonar; e hipertensión pulmonar inducida por hipoxia;

- enfermedades de pérdida ósea; 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 del grupo constituido por depresión; enfermedad de Parkinson; deterioro del aprendizaje y memoria; disquinesia tardía; drogodependencia; demencia ateriosclerótica; y demencias que acompañan el corea de Huntington, enfermedad de Wilson, parálisis agitante, y atrofias talámicas;

- infección, especialmente infección por virus en las que tales virus aumentan la producción de TNF-α en su huésped, o en las que tales virus son sensibles a la regulación por aumento de TNF-α en su huésped de forma que su replicación u otras actividades vitales sufren un impacto adverso, incluyendo un virus que es un miembro seleccionado del grupo constituido por VIH-1, VIH-2, y VIH-3; citomegalovirus, CMV; gripe; adenovirus; y virus del Herpes, incluyendo *Herpes zoster* y *Herpes simplex*;

- infecciones por levaduras y hongos en las que dichas levaduras y hongos son sensibles a regulación por aumento mediante TNF-α o provocan la producción de TNF-α en su huésped, por ejemplo meningitis fúngica; particularmente cuando se administra en junto con otros fármacos de elección para el tratamiento de infecciones sistémicas de levaduras y hongos, incluyendo pero sin limitación, polimixinas; por ejemplo, Polimicina B; imidazoles, por ejemplo, clotrimazol, econazol, miconazol, y cetoconazol; triazoles, por ejemplo, fluconazol e itranazol; y anfotericinas, por ejemplo, Amfotericina B y Anfotericina B liposómica.

- lesión por isquemia - reperfusión; diabetes autoinmunitaria; autoinmunidad retiniana; leucemia linfocítica crónica; infecciones por VIH; lupus eritematoso; enfermedad renal y ureteral; trastornos urogenitales y gastrointestinales; y enfermedades de próstata.

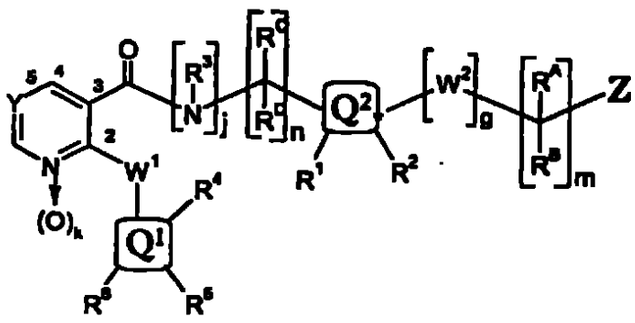
En particular, los compuestos de Fórmula (1.0.0) son de utilidad en el

tratamiento de (1) enfermedades y afecciones inflamatorias que comprenden: inflamación articular, artritis reumatoide, espondilitis reumatoide, osteoartritis, enfermedad inflamatoria del intestino, colitis ulcerosa, glomerulonefritis crónica, dermatitis, y enfermedad de Crohn; (2) enfermedades y afecciones respiratorias que comprenden: asma, síndrome disnéico agudo, enfermedad inflamatoria pulmonar crónica, bronquitis, enfermedad obstructiva de las vías respiratorias crónica, y silicosis; (3) enfermedades y afecciones infecciosas que comprenden: sepsis, choque séptico, choque endotóxico, sepsis por bacterias gram negativas, síndrome de choque tóxico, fiebre y mialgias debidas a infección bacteriana, viral o fúngica, y gripe; (4) enfermedades y afecciones inmunitarias que comprenden: diabetes autoinmunitaria, lupus eritematoso sistémico, reacción de injerto contra huésped, rechazos de aloinjertos, esclerosis múltiple, soriasis, y rinitis alérgica; y (5) otras enfermedades y afecciones que comprenden: enfermedades de resorción ósea; lesión por reperfusión; caquexia secundaria a infección o enfermedad; caquexia secundaria al síndrome de inmunodeficiencia adquirida (SIDA), infección por el virus de inmunodeficiencia humano (VIH), o complejo relacionado con el SIDA (ARC); formación queloide; formación de tejido cicatricial; diabetes melitus tipo 1; y leucemia.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

5.0 Compuestos

La presente invención concierne compuestos novedosos que pueden representarse mediante la Fórmula (1.0.0) siguiente:

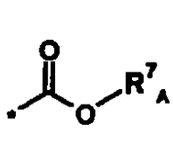


(1.0.0)

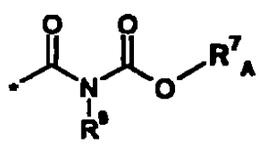
El alcance más amplio de los compuestos de la presente invención se circunscribe anteriormente en la Sección 4.0 relativa al Sumario de la invención. A continuación se proporciona una descripción adicional de tales compuestos en términos de una gama de diferentes tipos y grupos de realizaciones, así como realizaciones específicas que caracterizan y ejemplifican los compuestos de Fórmula (1.0.0). También se describen realizaciones preferidas y más preferidas de dichos compuestos, pero se entenderá que la referencia a tales preferencias no pretende, en modo alguno, limitar y no limita el alcance de la presente invención en relación a dichos compuestos.

El significado del resto terminal Z descrito en detalle anteriormente es el de un miembro seleccionado independientemente del grupo constituido por las fórmulas parciales (1.1.1) a (1.1.15):

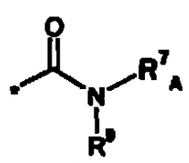
196



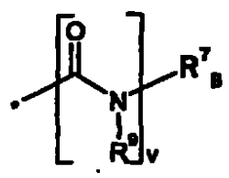
(1.1.1)



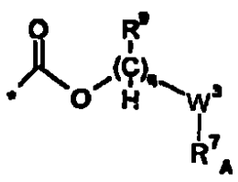
(1.1.2)



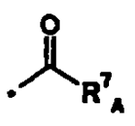
(1.1.3)



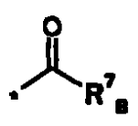
(1.1.4)



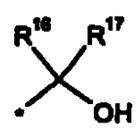
(1.1.5)



(1.1.6)



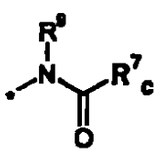
(1.1.7)



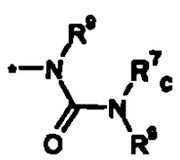
(1.1.8)



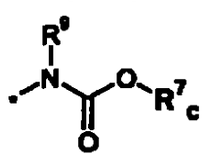
(1.1.9)



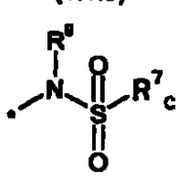
(1.1.10)



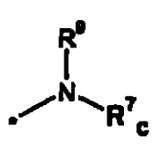
(1.1.11)



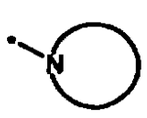
(1.1.12)



(1.1.13)



(1.1.14)



(1.1.15)

Los sustituyentes R^7_A, R^7_B y R^7_C, así como R^9, R^{16}, y R^{17} de las Fórmulas parciales enumeradas anteriormente, así como sus sub-sustituyentes R^{10}, R^{11}, R^{12}, R^{14}, R^{15}, R^{18}, y R^{19}, se definen anteriormente y proporcionan una delineación clara del alcance pretendido de los compuestos de la presente invención. Las realizaciones particulares dentro de dicho alcance comprenden los significados particulares de los sustituyentes R^7_A, R^7_B y R^7_C, y R^9, así como de los otros sustituyentes que forman parte

de la Fórmula (1.0.0). Tales realizaciones incluyen, pero sin limitación las descritas en los párrafos (i) a (vi) más adelante.

Para ayudar a los expertos en la técnica a considerar el alcance y extensión de la descripción de la presente invención descrita a continuación en el presente documento, se definen ciertos términos y expresiones usados en el presente documento en los párrafos inmediatamente posteriores.

Según se usan en el presente documento, las expresiones "-alquilo C_1-C_3", "-alquilo C_1-C_4", y "-alquilo C_1-C_6", se pretende que incluyan conformaciones de cadena ramificadas así como lineales de estos grupos alifáticos. Así, las expresiones referidas anteriormente 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-metilbutano), 2-metilpentano, 3-metilpentano, 1-etilpropano, y 1-etilbutano. Los significados de las expresiones referidas anteriormente se pretende también sean de aplicación a dichas expresiones independientemente de que estén sustituidas o no. Por lo tanto, la expresión "alquilo C_1-C_3 fluorado" se pretende que englobe las diversas especies fluoradas de los grupos alifáticos *n*-propilo e *iso*-propilo.

Tanto Q^1 como Q^2 se definen en el presente documento como que comprenden un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3 a 7 miembros, o que es un policiclo condensado de 7 a 12 miembros; donde opcionalmente un átomo de carbono de dicho sistema de anillos de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo pueden reemplazarse por N. Estas definiciones se pretende que signifiquen primero, un sistema de anillos de carbono que tiene dos o más anillos, especialmente

biciclos y triciclos, más especialmente biciclos, en los que los anillos están condensados, es decir, hay presentes al menos un par de átomos de carbono que constituyen el enlace puente. Estos sistemas de anillos policíclicos pueden ser saturados o insaturados. Segundo, la definición referida anteriormente se pretende que signifique también un sistema de anillos de carbono que tiene dos o más anillos en el que dichos anillos son discontinuos, es decir, están unidos entre sí mediante un enlace covalente sencillo o doble y no hay presentes átomos de carbono que constituyen el enlace puente. Estos sistemas de anillos policíclicos pueden ser también saturados o insaturados.

Con respecto a la situación en la que se ha seleccionado un sistema de anillos de carbono que es discontinuo, al contrario que uno que está condensado, debe observarse que no se permite que el resto Q^1 sea un sistema de anillos de carbono discontinuo así. Por el contrario, se requiere que el resto Q^2 sea discontinuo en esta situación. Se proporciona adicionalmente en el presente documento que el resto Q^2 debe tener el significado de un sistema de anillos de carbono que es discontinuo, o debe tener el significado de un sistema de anillos de carbono "biarilo restringido". En consecuencia, estos dos requisitos esenciales se han unido en la expresión "biarilo discontinuo o restringido", que según se usa en el presente documento se pretende que signifique un sistema de anillos discontinuos o un sistema de anillos policíclicos condensados como se define anteriormente en el que (1) los átomos de carbono constituyentes del enlace puente están unidos mediante un enlace, es decir, no hay átomos de carbono adicionales entre dichos átomos de carbono constituyentes del enlace tipo puente; y (2) los heteroátomos, si están presentes, sólo están contenidos en un sistema policíclico de anillos condensados tricíclico o superior.

En consecuencia, los tipos de sistemas de anillos biarilo restringidos y

discontinuos que pueden comprender un significado de Q^2, pero que no pueden comprender un significado de Q^1 incluyen, entre otros, los siguientes, en los que los números detrás de los nombres se refieren a las Fórmulas parciales para ellos mencionadas en el presente documento en cualquier otra parte: bifenilo (1.2.1); 3-fenilpiridina (1.2.2); ciclohexilbenceno (1.2.3); [2,2']bipiridinilo (1.2.4.); biciclohexilo (1.2.5); 2-feniltiofeno (1.2.6); 2-fenilfurano (1.2.7); naftaleno (1.2.8); difenilmetano (1.2.9); 4,5-difenil-1H-imidazol (1.2.10); 3-bencilpiridina (1.2.11); 4,5-difeniloxazol (1.2.12); fluoreno (1.2.13); 9*H*-carbazol (1.2.14); feniléter (1.2.15); 1*H*-indol (1.2.16); quinolina (1.2.17); fenantreno (1.2.18); fenantridina (1.2.19); [3,3']bipiridinilo (1.2.20); [4,4']bipiridinilo (1.2.21); 2-ciclohexilpiridina (1.2.22); bifenileno (1.2.23); 3-benzhidrilpiridina (1.2.24); 2-feniltiazol (1.2.25); 2-feniloxazol (1.2.26); 5-fenilpirimidina (1.2.27); 10*H*-fenotiazina (1.2.28); 2-fenil-benzooxazol (1.2.29); 2-fenilbenzotiazol (1.2.30); 2-fenil-1*H*-benzoimidazol (1.2.31); y 10,11-dihidro-5*H*-dibenzo[b,f]azepina (1.2.32).

Como ilustración adicional se entenderá que, por ejemplo, un resto naftilo es un resto biarilo restringido como se define en el presente documento, dado que es un biciclo condensado con un enlace entre los átomos de carbono que constituyen el enlace tipo puente, y no hay heteroátomos presentes. Un resto quinolinilo, por otra parte, aunque es también un biciclo condensado con un enlace entre los átomos de carbono que constituyen el enlace puente, no es un resto biarilo restringido según se usa en el presente documento, ya que hay también presente un heteroátomo de nitrógeno, y la definición de biarilo restringido según se usa en el presente documento requiere que el sistema de anillos condensados sea tricíclico o policíclico superior cuando haya un heteroátomo presente. El resto bifenilo es un ejemplo de un sistema de anillos discontinuo, en consecuencia, puede ser un significado de Q^2 pero no puede ser un

significado de Q^1.

Según se usa en el presente documento, la expresión "sistema de anillos de carbono saturados o insaturados que es... policiclo de 7 a 12 miembros, condensado o discontinuo" se pretende que incluya dichos sistemas de anillos de carbono condensados bi- y tricíclicos 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. La expresión referida anteriormente se pretende también que incluya sistemas de anillos de carbono bi y tricíclicos monoinsaturados tales como biciclo[2,2,2]oct-5-enilo, y biciclo[2.2.2]oct-7-enilo; así como tales sistemas de anillos de carbono aromáticos bi- y tricíclicos tales como naftileno y bifenileno. La expresión referida anteriormente se pretende que incluya además dichos sistemas de anillos de carbono biciclos aromáticos discontinuos tales como bifenileno.

Los sistemas de anillos de carbono incluidos dentro del alcance de la expresión referida anteriormente y descrita anteriormente incluyen también restos en los que opcionalmente un átomo de carbono del mismo puede sustituirse con un heteroátomo seleccionado de N, O, o S, y cuando se selecciona N, opcionalmente un segundo átomo de carbono del mismo puede reemplazarse por un heteroátomo seleccionado de N, O, y S. Los restos resultantes incluyen pirrolilo; pirrolidinilo; furanilo, tienilo; piridilo; pirimidinilo; piperidinilo; piperazinilo; imidazolilo; imidazolidinilo; oxazolilo; isoxazolilo; tiazolilo; indolilo; quinolinilo; isoquinolinilo; bencimidazolilo; benzoxazolilo; morfolinilo; quinuclidinilo; y azabiciclo[3,3,0]octanilo.

Según se usa en el presente documento con respecto a los compuestos de Fórmula (1.0.0), así como otras fórmulas y fórmulas parciales que se refieren a los mismos, cuando uno o más átomos de nitrógeno componentes de los mismos está o están representados como [N⇒(O)], comprende o comprenden una forma de óxido de

nitrógeno opcional de dicho(s) átomo(s) de nitrógeno. Cuando hay más de una de esas formas de óxido de nitrógeno, se seleccionan independientemente la una de la otra. Además, se apreciará que dicha(s) forma(s) de óxido de nitrógeno pueden representarse también como "[N=>(O)$_u$]" donde u es 0 ó 1.

(i) Las realizaciones de la presente invención incluyen aquellas que son un compuesto de Fórmula (1.0.0) en el que Q^1 es fenilo o piridilo; ◊ ◊ Q^2 es bifenilo, 3-fenilpiridina, ciclohexilbenceno, [2,2']bipiridinilo, biciclohexilo, naftaleno, o bifenileno; ◊ ◊ j es 1; ◊ ◊ m es 0 ó 1; ◊ ◊ n es 1; ◊ ◊ Z es un resto seleccionado de las Fórmulas parciales (1.1.1) a (1.1.3), (1.1.5), (1.1.6), y (1.1.10) a (1.1.14) donde R^7_A es (a) -H, o -CH_3 sustituido con 0-3 R^{10} donde R^{10} es -F; o es -CH_3 sustituido con 0 ó 1 R^{10} donde R^{10} es - CN, -OR^{16} donde R^{16} es -CH_3 o -CH_2CH_3, o -$NR^{16}R^{17}$ o -$NR^{16}C(=O)R^{17}$ donde R^{16} y R^{17} son -H o -CH_3; (b) ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo; o (c) fenilo o bencilo sustituido con 0-2 R^{10} donde R^{10} es -F, -Cl, -CF_3, -CH_3, o -CH_2OH, -SCH_3, -CN, -NO_2, -OR^{16}, o -$NR^{16}R^{17}$ donde R^{16} y R^{17} son -H, -CH_3, o -CH_2CH_3; ◊ ◊ R^9 es -H o -CH_3; ◊ ◊ W^1 es -O-; ◊ ◊ g es 1 y W^2 es -O- o -$CR^{29}R^{30}$- donde R^{29} y R^{30} son ambos -H, o g es 0 y W^2 está por tanto ausente, ◊ ◊ Y es =C(R^1_a)-; ◊ ◊ R^1_a es -H o -F; ◊ ◊ R^A y R^B son independientemente -H o -CH_3; o R^A y R^B se toman conjuntamente para formar un resto cicloalquil (C_3-C_7)-espiro; ◊ ◊ uno de R^C y R^D es -H y el otro es -H o -CH_3; ◊ ◊ R^1 y R^2 son -H, -F, o -OCH_3; ◊ ◊ R^3 es -H o -CH_3; y ◊ ◊ R^4, R^5 y R^6 son -H siempre que R^5 y R^6 no son ambos -H al mismo tiempo, -F, -Cl, -OCH_3, -CN; -NO_2, -C(=O)R^3 O-C(=O)O R^3 donde R^3 es -CH_3; o R^5 y R^6 se toman conjuntamente para formar un resto de Fórmula parcial (1.3.1), (1.3.2), (1.3.3), (1.3.4), (1.3.11), (1.3.12), o (1.3.15).

(ii) Las realizaciones preferidas del tipo descrito en el párrafo inmediatamente anterior son aquellas en las que Z es un resto de Fórmula parcial (1.1.1), (1.1.3), (1.1.6),

o (1.1.10); R^9 es -H; R^A y R^B son ambos -H; R^C y R^D son ambos -H; R^3 es -H; R^4 es -H; R^5 es -H, -F, -Cl, -CN, $-OCH_3$, o $-C(=O)CH_3$, o $-NO_2$; R^6 es -H siempre que R^5 y R^6 no sean ambos -H al mismo tiempo, o -F; o R^5 y R^6 se toman conjuntamente para formar un resto de Fórmula parcial (1.3.1) o Fórmula parcial (1.3.11) donde R^{23} y R^{24} están ambos ausentes.

(iii) Realizaciones adicionales de la presente invención comprenden un compuesto de Fórmula (1.0.0) en el que Q^1 es fenilo o piridilo; ◊ ◊ Q^2 es bifenilo, 3-fenilpiridina, ciclohexilbenceno, [2,2']bipiridinilo, biciclohexilo, naftaleno, o bifenileno; j es 1; ◊ ◊ m es 0 ó 1; ◊ ◊ n es 1; ◊ ◊ Z es un resto seleccionado de las Fórmulas parciales (1.1.4) y (1.1.7) donde $R^7{}_B$ es tetrazol-5-ilo, 1,2,4,-triazol-3-ilo, 1,2,4-triazol-3-on-5-ilo, imidazol-2-ilo, imidazol-4-ilo, 1,3,4-oxadiazolilo, 1,2,4-oxadiazol-3-ilo, 1,3,4-oxadiazol-5-ilo, oxazolilo, isoxazolilo, pirrolilo, pirazolilo, succinimidilo, pirrolidonilo, tiazolilo, isotiazolilo, 1,2,3-tiadiazolilo, 1,3,4-tiadiazolilo, piridilo, pirazinilo, furanilo, tetrahidrofuranilo, tienilo, indolilo, 2,3-dihidrobenzofuranilo, benzotienilo, 1*H*-indazolilo, bencimidazolilo, benzoxazolilo, benzotriazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, 1,6-naftiridinilo, o 1,8-naftiridinilo, todos los cuales están sustituidos independientemente con 0 ó 1 R^{14} donde R^{14} es $-CH_3$, $-OR^{16}$ donde R^{16} es -H, o $-CH_3$, oxo (=O), $-C(=O)OR^{16}$ donde R^{16} es -H o $-CH_3$; ◊ ◊ R^9 es -H o $-CH_3$; ◊ ◊ W^1 es -O-; ◊ ◊ g es 1 y W^2 es -O- o $-CR^{29}R^{30}$- donde R^{29} y R^{30} son ambos -H, o g es 0 y W^2 está por tanto ausente; ◊ ◊ Y es $=C(R^1{}_a)$-; ◊ ◊ $R^1{}_a$ es -H; o -F; ◊ ◊ R^A y R^B son independientemente -H o $-CH_3$; o R^A y R^B se toman conjuntamente para formar un resto cicloalquil (C_3-C_7)-espiro; ◊ ◊ uno de R^C y R^D es -H y el otro es -H o $-CH_3$; ◊ ◊ R^1 y R^2 son -H, -F, o $-OCH_3$; ◊ ◊ R^3 es -H o $-CH_3$; y ◊ ◊ R^4, R^5 y R^6 son -H siempre que R^5 y R^6 no sean ambos -H al mismo tiempo, -F, -Cl, $-OCH_3$, -CN; $-NO_2$, o –C (=O) R^3 o $-C(=O)OR^3$

donde R^3 es $-CH_3$; o R^5 y R^6 se toman conjuntamente para formar un resto de Fórmula parcial (1.3.1), (1.3.2), (1.3.3), (1.3.4), (1.3.11), (1.3.12), o (1.3.15).

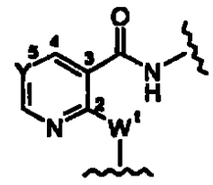
(iv) Las realizaciones preferidas del tipo descrito en el párrafo inmediatamente anterior son aquellas en las que R^9 es -H; R^A y R^B sean ambos -H; R^C y R^D son ambos -H; R^3 es -H; R^4 es -H; R^5 es -H, -F, -Cl, -CN, $-OCH_3$, $-C(=O)CH_3$, o $-NO_2$; R^6 es -H siempre que R^5 y R^6 no son ambos -H al mismo tiempo, o -F; o R^5 y R^6 se toman conjuntamente para formar un resto de Fórmula parcial (1.3.1) o Fórmula parcial (1.3.11) donde R^{23} y R^{24} están ambos ausentes.

(v) Las realizaciones adicionales de la presente invención incluyen un compuesto de Fórmula (1.0.0) en el que Q^1 es fenilo o piridilo; ◊ ◊ Q^2 es bifenilo, 3-fenilpiridina, ciclohexilbenceno, [2,2']bipiridinilo, biciclohexilo, naftaleno, o bifenileno; ◊ ◊ j es 1; ◊ ◊ m es 0 ó 1; ◊ ◊ n es 1; ◊ ◊ Z es un resto de Fórmula parcial (1.1.15) que comprende ftalimid-1-ilo, succinimid-1-ilo, pirrolid-2-on-1-ilo, glutarimid-1-ilo, piperid-2-on-1-ilo, pirid-2-on-1-ilo, imidazolidin-2,4-dion-1-ilo, 4,5-dihidro-5-oxo-1*H*-tetrazol-1-ilo, bencimidazolin-2-on-1-ilo, norborn-5-on-2,3-dicarboximid-1-ilo, imidazolidin-2-on-1-ilo, tiazolidin-3-ilo, 1*H*-1,2,3-triazol-1-ilo, 1*H*-1,2,4-triazol-1-ilo, pirrolidin-1-ilo, tetrazol-1-ilo, piperidin-1-ilo, piperazin-1-ilo, 1*H*-pirazolo[4,5-*e*]piridin-7-on-2-ilo, 1*H*-indazol-3-on-2-ilo, 1*H*-bencimidazol-2-on-3-ilo, o pirrolo[3,4-*b*]piridin-5,7-dion-6-ilo; ◊ ◊ W^1 es -O-; ◊ ◊ g es 1 y W^2 es -O- o $-CR^{29}R^{30}-$ donde R^{29} y R^{30} son ambos -H, o g es 0 y W^2 está por tanto ausente; ◊ ◊ Y es $=C(R^1_a)-$; ◊ ◊ R^1_a es -H; o -F; ◊ ◊ R^A y R^B son independientemente -H o $-CH_3$; o R^A y R^B se toman conjuntamente para formar un resto cicloalquil (C_3-C_7)-espiro; ◊ ◊ uno de R^C y R^D es -H y el otro es -H o $-CH_3$; ◊ ◊ R^1 y R^2 son -H, -F, o $-OCH_3$; ◊ ◊ R^3 es -H o $-CH_3$; y ◊ ◊ R^4, R^5 y R^6 son -H siempre que R^5 y R^6 no sean ambos -H al mismo tiempo, -F, -Cl, $-OCH_3$, -CN; $-NO_2$, o $-C(=O)OR^3$ donde R^3 es $-CH_3$; o R^5 y R^6 se toman conjuntamente para

formar un resto de Fórmula parcial (1.3.1), (1.3.2), (1.3.3), (1.3.4), (1.3.11), (1.3.12), o (1.3.15), donde para las Fórmulas parciales (1.3.11) y (1.3.12) R^{23} y R^{24} están ambos ausentes.

(vi) Las realizaciones preferidas del tipo descrito en el párrafo inmediatamente anterior son aquellas en las que R^9 es -H; R^A y R^B son ambos -H; R^C y R^D son ambos -H; R^3 es -H; R^4 y R^5 son ambas -H, y R^6 es -F; o R^5 y R^6 se toman conjuntamente para formar un resto de Fórmula parcial (1.3.1) o (1.3.11).

Una parte del núcleo central de los compuestos de Fórmula (1.0.0) es el de una nicotinamida de Fórmula (1.0.1):



(1.0.1)

derivada del ácido nicotínico. Esta parte del núcleo central se elabora después definiendo el resto Y como = $C(R^1_B)$-, o $[N\rightarrow(O)_k]$- donde k es 0 ó 1, y donde el símbolo $\rightarrow(O)$ indica un heteroátomo de nitrógeno en forma de su N-óxido cuando k es 1. Los restos heterocíclicos que contienen N que definen R^7_B y R^7_C, opcionalmente uno o más de los N-heteroátomos que comprenden dichos restos heterocíclicos pueden estar en forma del N-óxido de dichos N-heteroátomos. En consecuencia, las consideraciones que conciernen los N-óxidos que se acaban de describir son de aplicación también a tales restos que contienen N-óxidos que definen R^7_B y R^7_C.

Cuando Y tiene el significado de -[N=) $(O)_k$]- los compuestos de la presente invención son pirimidinas. El grupo pirimidina de los compuestos de Fórmula (1.0.0) es una parte significativa del alcance de la presente invención. Se prefiere, sin embargo, que los compuestos de Fórmula (1.0.0) tengan el resto Y definido como $=C(R^1_a)$- donde el sustituyente R^1_a se selecciona independientemente de los otros sustituyentes que forman los compuestos de Fórmula (1.0.0).

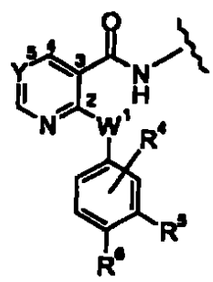
Además de -H, el R^1_a del resto $=C(R^1_a)$- se define como un miembro seleccionado del grupo constituido por: -F; -Cl; -CN; $-NO_2$; -alquilo C_1-C_4; -alquinilo C_2-C_4; -alquilo C_1-C_3 fluorado; -alcoxi C_1-C_3 fluorado; $-OR^{16}$; y $-C(=O)NR^{12}_aR^{12}_b$; donde R^{12}_a y R^{12}_b son cada uno 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.

Se prefiere que el sustituyente R^1_a del resto $=C(R^1_a)$- signifique -H; -F; -Cl; $-CH_3$; $-OCH_3$; o -alquinilo C_2-C_4; más preferiblemente R^1_a es -F o -H.

<u>5.1 Unión (W^1) y el resto Q^1 sustituido con R^4, R^5, y R^6</u>

El núcleo central de nicotinamida de los compuestos de Fórmula (1.0.0) se caracteriza por la formación en el átomo de carbono en la posición 2 del anillo piridilo o pirimidinilo de un enlace a un anillo que comprende el resto Q^1. En realizaciones preferidas, el resto Q^1 tiene el significado de un anillo fenilo que está sustituido en *para* con un resto R^6, sustituido en *meta* con un resto R^5, o sustituido en una cualquiera de las posiciones restantes con un resto R^4, dando como resultado un resto de Fórmula parcial (1.0.3):

206



(1.0.3)

donde W^1 tiene el significado de -O-; -S(=O)$_t$-, donde t es 0, 1, ó 2; o -N(R^3)- es -H; -alquilo C_1-C_3; fenilo; bencilo; o -OR^{16}, donde R^{16} tiene el mismo significado definido anteriormente.

En otras realizaciones de la presente invención, W^1 tiene el significado de -S(=O)$_t$, donde t es 0, 1, ó 2; y preferiblemente tiene el significado -S- mediante el cual se forma un enlace tioéter. Cuando el átomo de azufre del enlace tioéter está oxigenado, da como resultado un enlace sulfinilo o sulfonilo. En otras realizaciones adicionales, cuando W^1 tiene el significado de -N(R^3)-, se forma un enlace amino, que preferiblemente será -NH-. Sin embargo, el átomo de nitrógeno puede estar sustituido y cuando este es el caso, se prefiere que dicho sustituyente sea -CH_3.

Los significados de los sustituyentes R^4, R^5, y R^6 se seleccionan del mismo grupo de definiciones, pero se entenderá que dichos significados se seleccionan de forma independiente entre sí. R^5 y R^6 pueden ser también -H siempre que no sean ambos -H al mismo tiempo. En consecuencia, cuando el resto Q^1 tiene el significado de un anillo fenilo, puede estar sustituida la posición *para* (R^6), *meta* (R^5), u *orto* (R^4), del anillo fenilo, o pueden estar sustituidas las tres posiciones, o puede estar sustituida cualquier combinación de dichas posiciones. Se prefiere sin embargo, en los compuestos de Fórmula (1.0.0) que estén sustituidas las posiciones *para* y/o *meta*, mejor que la posición *orto*.

Cuando el resto Q^1 tiene el significado preferido de un anillo fenilo, R^5 y R^6

pueden tomarse conjuntamente también para formar un miembro seleccionado de un grupo de fórmulas parciales descritas en más detalle más adelante. Algunos de estos significados de R^5 y R^6 tomados conjuntamente constituyen también realizaciones preferidas de los compuestos de Fórmula (1.0.0).

R^5 y R^6 pueden ser -H siempre que los dos no sean -H al mismo tiempo; en consecuencia, siempre habrá un sustituyente en una o ambas posiciones ocupadas por R^5 y R^6. Además de -H; R^5 y R^6 pueden, entre otros ser -F; -Cl; -CN; $-NO_2$; $-C(=O)R^{16}$; $-OR^{16}$; $-C(=O)OR^{16}$; o $-NR^{16}R^{17}$. Cuando R^5 es -H y R^6 es -F, dan como resultado las realizaciones preferidas de la presente invención. En una realización preferida adicional de la presente invención, R^5 y R^6 pueden ser también $-OR^{16}$, donde R^{16} es hidrógeno; alquilo C_1-C_4; o cicloalquilo C_3-C_6; en los que dicho alquilo y cicloalquilo están sustituidos por 0 a 3 sustituyentes seleccionados del grupo constituido por -F y -Cl. Otras realizaciones preferidas son aquellas en las que R^{16} es metilo; difluorometilo; etilo; o ciclopentilo.

El químico médico apreciará que la elección de sustituyentes entre los descritos anteriormente estará influenciada por el efecto que dichos sustituyentes tienen a su vez sobre las propiedades fisicoquímicas de las moléculas globales resultantes. El presente estado de la técnica proporciona la capacidad de sintetizar rápida y fácilmente un gran número de compuestos químicamente muy similares basándose en la elección de sustituyentes descrita anteriormente, y a partir de ahí experimentar la eficiencia relativa de las moléculas resultantes con procedimientos rápidos de experimentación *in vitro*. La síntesis química de combinación y los métodos de experimentación disponibles en la actualidad en la técnica han expandido incluso considerablemente más el número de combinaciones de sustituyentes que pueden evaluarse de forma rápida. La información que se ha producido así a través del uso de estas técnicas permite una predicción

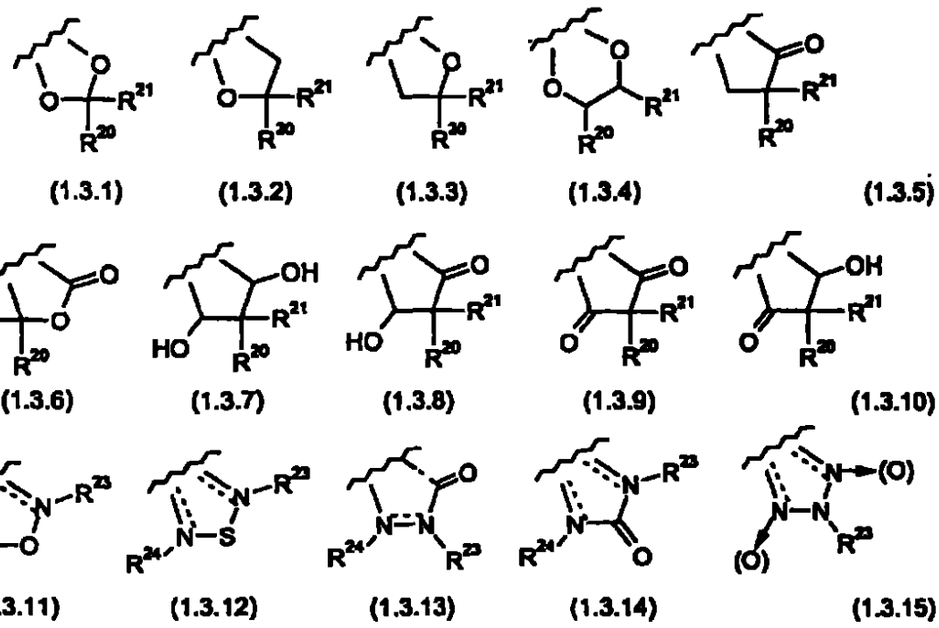
razonable en el presente documento de ciertas preferencias que existen en lo que se refiere a los diversos métodos de la presente invención. Tales realizaciones preferidas se describen en detalle en el presente documento.

Las realizaciones preferidas de la presente invención incluyen además aquellas en las que tanto R^5 como R^6 son -F; en las que R^5 es -H y R^6 es -F; y en las que R^6 es -H y R^5 es -F; $-OR^{16}$, por ejemplo, $-OCH_3$, $-OCH_2F$, $-OCHF_2$, o $-OCF_3$; -CH; -COOH; $-COOCH_3$; $-CONH_2$; $-OCOCH_3$; o NH_2. Las realizaciones más preferidas son aquellas 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 $-NO_2$, -CN, $-OCH_3$, o $-C(=O)CH_3$, y R^6 es -H.

R^5 y R^6 pueden seleccionarse también de sustituyentes que comprenden -alquilo C_1-C_4 y -alcoxi C_1-C_4 en los que dicho alquilo y alcoxi están sustituidos con 0 a 3 sustituyentes -F o -Cl; ó 0 ó 1 sustituyentes alcoxi (C_1-C_2)-carbonilo-; alquil (C_1-C_2)carbonilo-; o alquil (C_1-C_4)carboniloxi-.

5.2.0 Q^1 es fenilo y R^5, y R^6 se toman conjuntamente

Cuando el resto Q^1 tiene el significado preferido de un anillo fenilo, R^5 y R^6 pueden tomarse también conjuntamente para formar un resto que es un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.3.1) a (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)

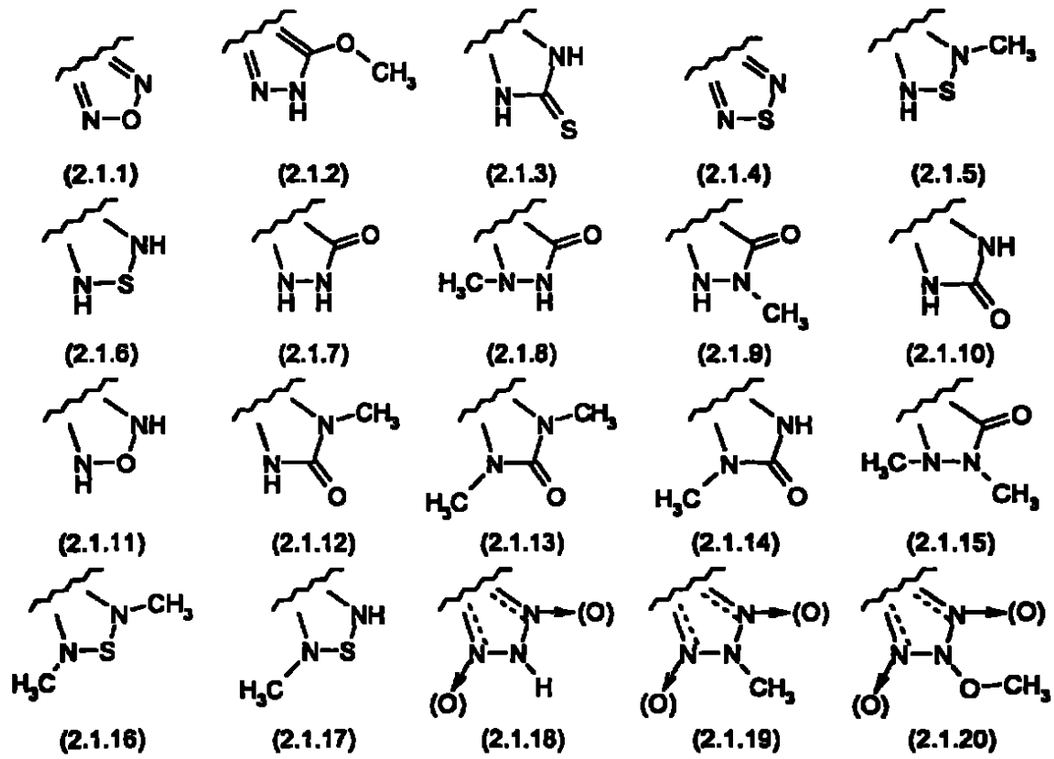
(1.3.11) (1.3.12) (1.3.13) (1.3.14) (1.3.15)

en las que R^{20} y R^{21} son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -F; -Cl; $-CH_3$; $-CH_2F$; $-CHF_2$; $-CF_3$; $-OCH_3$; y $-OCF_3$; y R^{23} y R^{24} son cada uno 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 discontinua ---- representa un enlace doble. Para el resto de Fórmula parcial (1.3.13) los componentes del átomo de nitrógeno se representan como - [N(⇨O)]- y por lo tanto comprenden formas de óxido de nitrógeno opcionales de dichos átomos de nitrógeno, seleccionados independientemente entre sí. Se apreciará que dicha forma de óxido de nitrógeno puede representarse también como -N (⇨O)$_j$] donde j es 0 ó 1, como en la Fórmula (1.0.0).

Cuando el resto Q^1 tiene el significado preferido de un anillo 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, junto con el grupo fenilo al que están unidos se forma un grupo

1,3-benzodioxol. De forma análoga, la estructura de Fórmula parcial (1.3.2) forma un grupo 1,4-benzodioxano.

Cuando el resto Q^1 tiene el significado preferido de un anillo fenilo, y cuando R^5 y R^6 se toman conjuntamente para formar los restos de Fórmulas parciales (1.3.9) a (1.3.13) y R^{23} y R^{24} son como se ha definido, se forman benzofurazano, benzotiofurazano, triazol, y otros grupos análogos, así como derivados sustituidos de los mismos, incluyendo, entre otros, los siguientes restos de Fórmulas parciales (2.1.1) a (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)

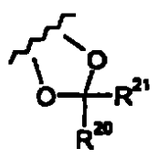
(2.1.16) (2.1.17) (2.1.18) (2.1.19) (2.1.20)

en las que la línea discontinua ---- en las Fórmulas parciales (2.1.18), (2.1.19), y (2.1.20) representa un enlace doble cuando ningún átomo de oxígeno se une al átomo de

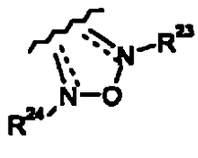
nitrógeno correspondiente, y representa un enlace sencillo cuando un átomo de oxígeno se une a dicho átomo de nitrógeno correspondiente.

Los expertos en la técnica en la preparación de moléculas orgánicas apreciarán que los compuestos de Fórmula (1.0.0) en los que R^5 y R^6 se toman conjuntamente para formar restos de Fórmulas parciales (2.1.2), (2.1.3), (2.1.7), (2.1.8), (2.1.10), (2.1.12), y (2.1.14) ilustradas anteriormente existen en formas tautómeras, 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 tautómero contrario. Estos tautómeros están relacionados por el desplazamiento de un hidrógeno y uno o más enlaces π, y cuando sea necesario, los expertos en la técnica podrán fácilmente discernir o determinar qué forma tautómera está presente o es la más estable.

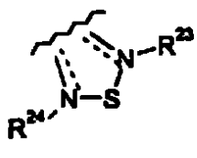
Las realizaciones preferidas de la presente invención resultan directamente de la definición de R^5 y R^6 cuando se toman conjuntamente para formar un resto que es un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.3.1), (1.3.11), (1.3.12), (1.3.15):



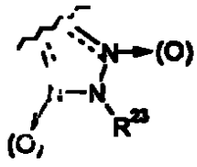
(1.3.1)



(1.3.11)

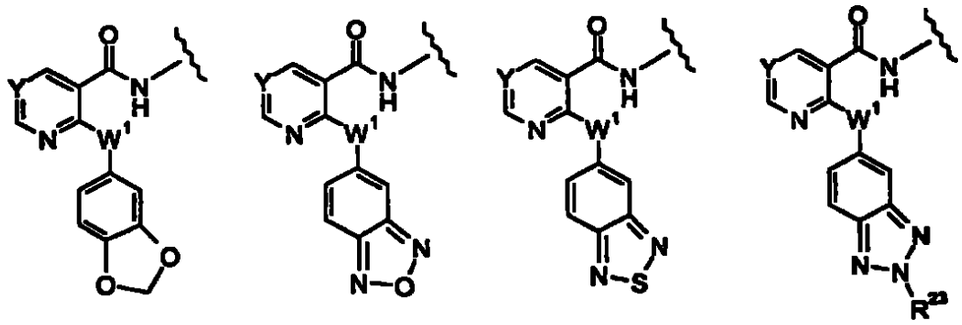


(1.3.12)



(1.3.15)

En consecuencia, adicionalmente resultan restos de Fórmulas parciales (1.0.15) a (1.0.18):



(1.0.15) (1.0.16) (1.0.17) (1.0.18)

donde R^{23} es -H o $-CH_3$; y W^1 tiene el significado de -O-; $-S(=O)_t-$, donde t es 0, 1, ó 2; o $-N(R^3)-$ donde R^3 es como se define en el presente documento y es preferiblemente -H o $-CH_3$. En compuestos preferidos de Fórmula (1.0.0), W tiene el significado de -O- mediante el cual se crea un enlace éter para unir el heterociclo bicíclico benzocondensado 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 los compuestos del tipo ilustrado por la Fórmula parcial (1.3.11), donde únicamente uno de R^{23} o R^{24} puede estar presente. Se reconocerá que cuando R^{23} o R^{24} están ambos ausentes, y las líneas discontinuas: --- en consecuencia representan enlaces dobles, la porción fenilo de los heterociclos bicíclicos benzocondensados resultantes representados no pueden tener todos los enlaces dobles representados en dichas Fórmulas parciales, dado que el resultado sería átomos de carbono pentavalentes en dicha porción fenilo que no son posibles

En consecuencia, cuando R^{23} y R^{24} están ambos ausentes, los compuestos resultantes se caracterizan por estructuras tales como las que se muestran 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} de los heterociclos bicíclicos benzocondensados representados por la Fórmula

parcial (1.3.1) son -H, -F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$ o $-CF_3$. Preferiblemente, R^{20} y R^{21} son ambos -H o -F, en cuyo caso, los compuestos resultantes se caracterizan por la estructura que se muestra en la Fórmula parcial (1.0.15) anteriormente, o por su análogo difluoro correspondiente (no se muestra). Los sustituyentes R^{23} y R^{24} de los heterociclos bicíclicos benzocondensados representados por los restos de Fórmulas parciales (1.3.9) a (1.3.13) son cada uno independientemente -H; $-CH_3$; $-OCH_3$; o está ausente en cuyo caso, la línea discontinua ---- representa un enlace doble. Se entenderá, por supuesto, que cuando R^{23} y R^{24} están ausentes no hay átomos de carbono pentavalentes en la porción fenilo de dichos heterociclos bicíclicos benzocondensados con benzo. Las estructuras heterocíclicas bicíclicas benzocondensadas resultantes se muestran en las Fórmulas parciales (1.0.15) a (1.0.18) anteriores.

5.2.1 Q^1 es distinto de fenilo

Además de aquellas realizaciones de la presente invención en las que Q^1 tiene el significado preferido de fenilo, la presente invención se ha definido también anteriormente como que concierne a un compuesto de Fórmula (1.0.0) en el que Q^1 tiene el significado definido anteriormente como un resto que comprende un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3 a 7 miembros, o que es un policiclo condensado de 7 a 12 miembros; en los que opcionalmente un átomo de carbono de dicho sistema de anillos de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo pueden reemplazarse por N. La presente invención concierne además un compuesto de Fórmula (1.0.0) en el que Q^1 comprende especialmente un miembro seleccionado del grupo constituido por pirrolilo; pirrolidinilo; furanilo; tienilo; piridilo; pirimidinilo; piperidinilo; piperazinilo; imidazolilo; imidazolidinilo; oxazolilo;

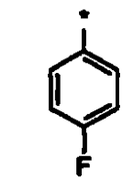
214

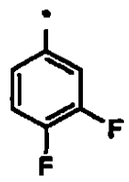
isoxazolilo; morfolinilo; tiazolilo; indolilo; quinolinilo; isoquinolilo; bencimidazolilo; benzoxazolilo; quinuclidinilo; y azabiciclo[3.3.0]octanilo; un resto -cicloalquilo C_3-C_7 monocíclico; un resto cicloalquenilo C_5-C_7 monocíclico, que es un miembro seleccionado del grupo constituido por ciclopentenilo, ciclohexenilo, y ciloheptenilo; y un resto cicloalquilo C_7-C_{10} o cicloalquenilo C_7-C_{10} bicíclicos que es un miembro seleccionado del grupo constituido por norbornilo, 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.

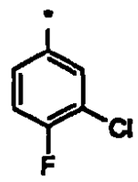
5.2.2 Restos Q^1 subgenéricos representativos

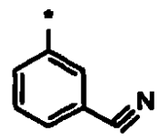
Adicionalmente la presente invención concierne todavía especialmente un compuesto de Fórmula (1.0.0) en el que particularmente Q^1 y los sustituyentes R^4, R^5 y R^6 se seleccionan de forma tal que el término a mano izquierda de dicho compuesto de Fórmula (1.0.0) está representado por las siguientes Fórmulas parciales (2.0.1) a (2.0.72):

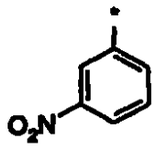
215

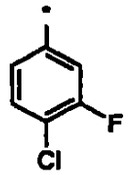

(2.0.1)

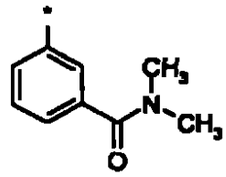

(2.0.2)

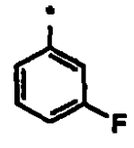

(2.0.3)

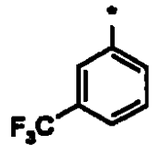

(2.0.4)

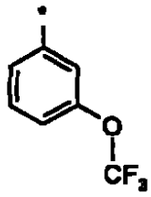

(2.0.5)

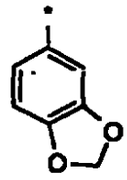

(2.0.6)

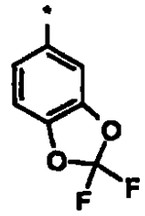

(2.0.7)

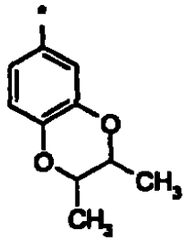

(2.0.8)

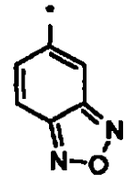

(2.0.9)

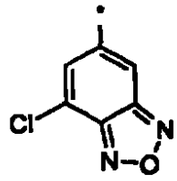

(2.0.10)

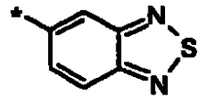

(2.0.11)

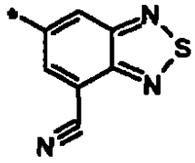

(2.0.12)

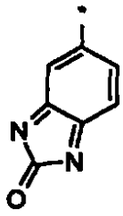

(2.0.13)

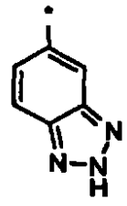

(2.0.14)

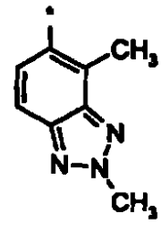

(2.0.15)

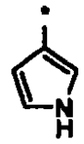

(2.0.16)

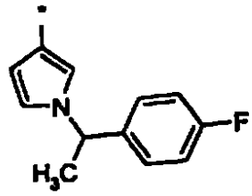

(2.0.17)

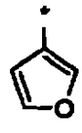

(2.0.18)

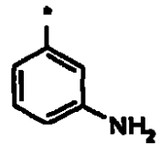

(2.0.19)

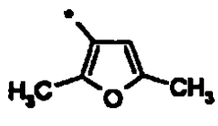

(2.0.20)


(2.0.21)

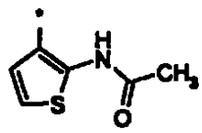

(2.0.22)


(2.0.23)

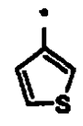

(2.0.24)



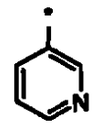
(2.0.25)



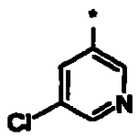
(2.0.26)



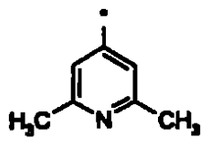
(2.0.27)



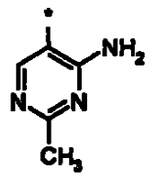
(2.0.28)



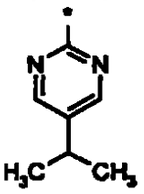
(2.0.29)



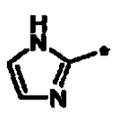
(2.0.30)



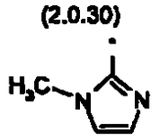
(2.0.31)



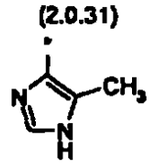
(2.0.32)



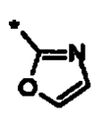
(2.0.33)



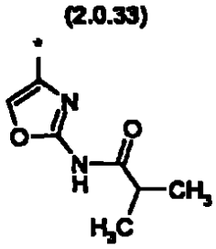
(2.0.34)



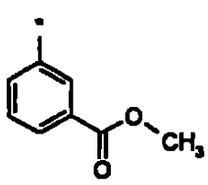
(2.0.35)



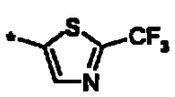
(2.0.36)



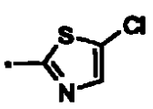
(2.0.37)



(2.0.38)



(2.0.39)



(2.0.40)



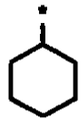
(2.0.41)



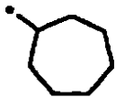
(2.0.42)



(2.0.43)



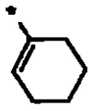
(2.0.44)



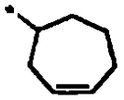
(2.0.45)



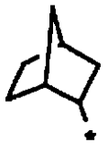
(2.0.46)



(2.0.47)



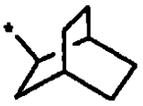
(2.0.48)



(2.0.49)



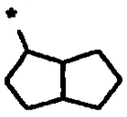
(2.0.50)



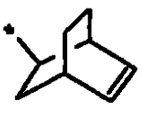
(2.0.51)



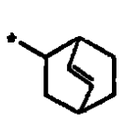
(2.0.52)



(2.0.53)



(2.0.54)

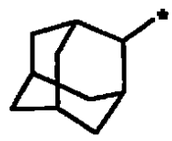


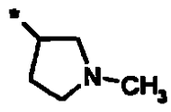
(2.0.55)

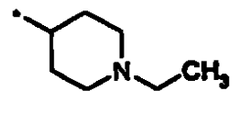


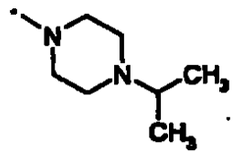
(2.0.56)

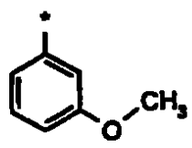
217

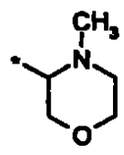

(2.0.57)

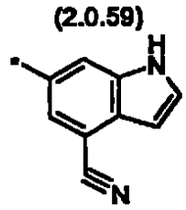

(2.0.58)

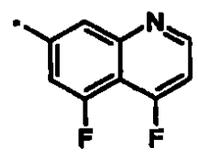

(2.0.59)

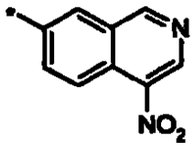

(2.0.60)

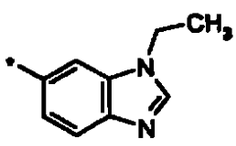

(2.0.61)

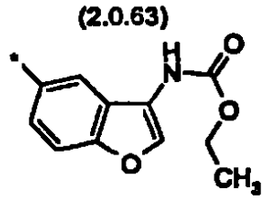

(2.0.62)

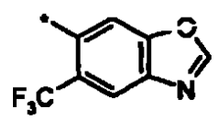

(2.0.63)

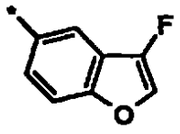

(2.0.64)

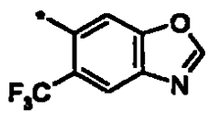

(2.0.65)

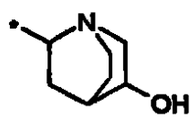

(2.0.66)

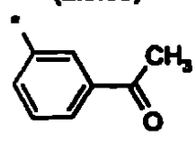

(2.0.67)


(2.0.68)


(2.0.69)


(2.0.70)

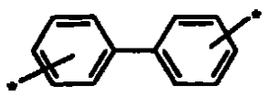

(2.0.71)


(2.0.72)

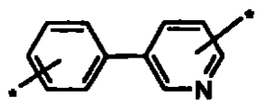
5.3.0 El resto Q^2

El resto Q^2 es una de las características clave de los compuestos de Fórmula (1.0.0) y se denomina en el presente documento resto biarilo. Según se usa en el presente documento, el término "biarilo" incluye no sólo los grupos biarilos convencionales tales como bifenilo, sino variantes condensadas de los mismos, variantes que contienen naftilo y variantes que contienen heteroátomos de los mismos, y variantes benzhidrilo de los mismos. Por lo tanto, los grupos biarilo que definen el resto Q^2 comprenden, entre otros, bifenilo (1.2.1); 3-fenilpiridina (1.2.2); ciclohexilbenceno (1.2.3); [2,2']bipiridinilo (1.2.4); biciclohexilo (1.2.5); 2-feniltiofeno (1.2.6); 2-fenilfurano (1.2.7); naftaleno (1.2.8); difenilmetano (1.2.9); 4,5-difenil-1H-imidazol

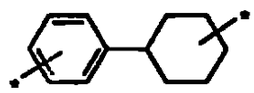
(1.2.10); 3-bencilpiridina (1.2.11); 4,5-difeniloxazol (1.2.12); fl... reno (1.2.3); 9*H*-carbazol (1.2.14); feniléter (1.2.15); 1*H*-indol (1.2.16); quinolina (1.2.17); fenantreno (1.2.18); fenantridina (1.2.19); [3,3']bipiridinilo (1.2.20); [4,4']bipiridinilo (1.2.21); 2-ciclohexilpiridina (1.2.22); bifenileno (1.2.23); 3-benzhidrilpiridina (1.2.24); 2-feniltiazol (1.2.25); 2-feniloxazol (1.2.26); 5-fenilpirimidina (1.2.27); 10*H*-fenotiazina (1.2.28); 2-fenilbenzooxazol (1.2.29); 2-fenilbenzotiazol (1.2.30); 2-fenil-1*H*-benzoimidazol (1.2.31); y 10,11-dihidro-5*H*-dibenzo[b,f]azepina (1.2.32). Las referencias numéricas entre paréntesis con los significados referidos anteriormente del resto Q^2 corresponden a las fórmulas estructurales, que pueden representarse mediante las Fórmulas parciales (1.2.1) a (1.2.32) a continuación. Debe tenerse en cuenta que los puntos de unión en cualquiera de los dos lados del resto bivalente se han ilustrado como que no son específicos de forma que dichas Fórmulas parciales pueden englobar variaciones dentro de cada resto que se considera que están dentro del alcance de la presente invención:



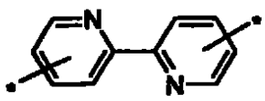
(1.2.1)



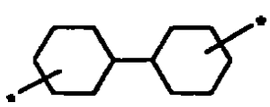
(1.2.2)



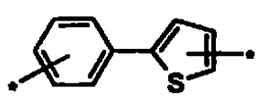
(1.2.3)



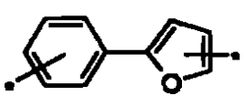
(1.2.4)



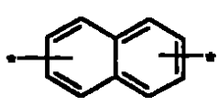
(1.2.5)



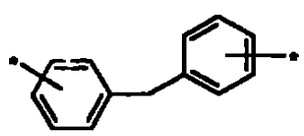
(1.2.6)



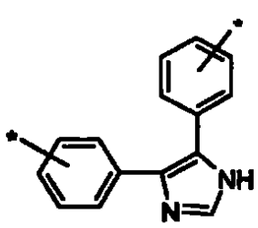
(1.2.7)



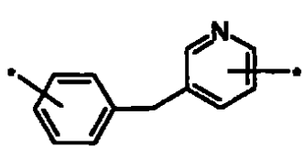
(1.2.8)



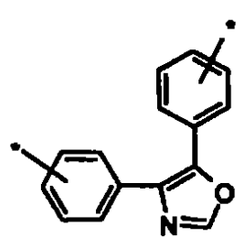
(1.2.9)



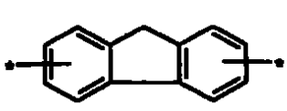
(1.2.10)



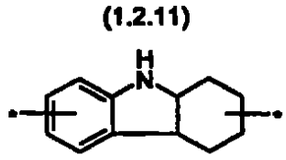
(1.2.11)



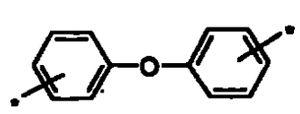
(1.2.12)



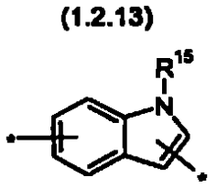
(1.2.13)



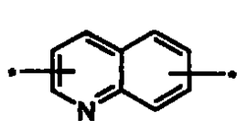
(1.2.14)



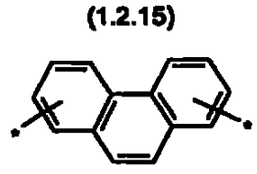
(1.2.15)



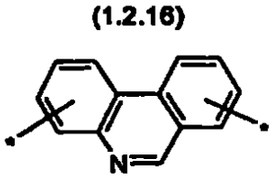
(1.2.16)



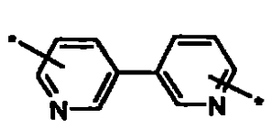
(1.2.17)



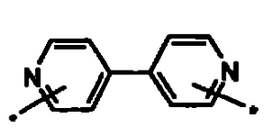
(1.2.18)



(1.2.19)

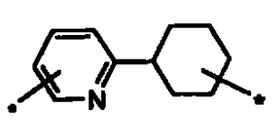


(1.2.20)



(1.2.21)

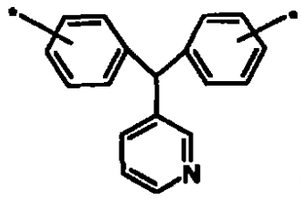
220



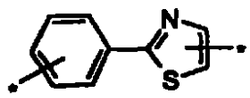
(1.2.22)



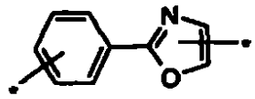
(1.2.23)



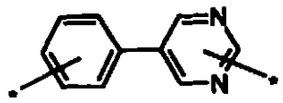
(1.2.24)



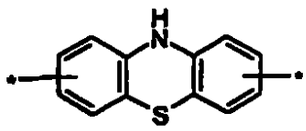
(1.2.25)



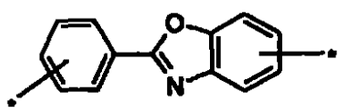
(1.2.26)



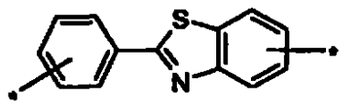
(1.2.27)



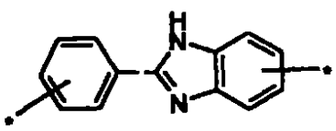
(1.2.28)



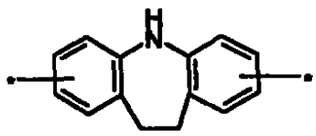
(1.2.29)



(1.2.30)



(1.2.31)



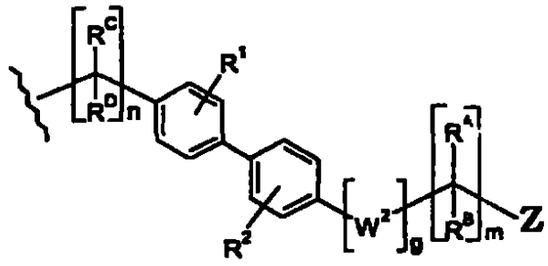
(1.2.32)

Los grupos ilustrados anteriormente de Fórmulas parciales (1.2.1) a (1.2.32) que definen el resto Q^2 están sustituidos opcionalmente con R^1 y R^2, donde R^1 y R^2 pueden aparecer de forma individual o conjunta en cualquier anillo o anillos que comprenden un resto o parte componente de las Fórmulas parciales (1.2.1) a (1.2.32) que definen Q^2. R^1 y R^2 son cada uno un miembro seleccionado de forma independiente del grupo constituido por -H; -F; -Cl; $-R^{12}$; $-OR^{12}$; $-S(=O)_pR^{12}$; $-C(=O)OR^{12}$; $-OC(=O)R^{12}$; =O (oxo), -CN; $-NO_2$; $-C(=O)NR^{12}R^{13}$; $-OC(=O)NR^{15}R^{12}$; $-NR^{14}C(=O)NR^{15}R^{12}$; $-NR^{14}C(=NR^{14})NR^{15}R^{12}$; $-NR^{14}C(=NCN)NR^{15}R^{12}$; $-NR^{14}C(=N\text{-}NO_2)NR^{15}R^{12}$; $-C(=NR^{14})NR^{15}R^{12}$; $-OC(=NR^{14})NR^{15}R^{12}$; $-OC(=N\text{-}NO_2)NR^{15}R^{12}$; $-NR^{15}R^{12}$; $-CH_2NR^{15}R^{12}$; $-NR^{14}C(=O)R^{12}$; $-NR^{14}C(=O)OR^{12}$; $=NOR^{12}$; $-NR^{14}S(=O)_pR^{13}$; y $-S(=O)_pNR^{12}R^{13}$; donde R^{12}, R^{13}, R^{14}, y R^{15} tienen los significados definidos

anteriormente.

5.3.1. Q^2 es bifenilo sustituido con R^1 y R^2

El lado izquierdo de un compuesto de Fórmula (1.0.0) tiene un núcleo de nicotinamida con un enlace éter, tioéter o sulfonilo a un grupo fenilo sustituido; mientras que el lado derecho de un compuesto de Fórmula (1.0.0) comprende realizaciones preferidas en las que Q^2 tiene el significado preferido de un bifenilo que está sustituido con los sustituyentes R^1 y R^2. Preferiblemente, solo un único sustituyente, R^1 o R^2 está presente en cada anillo, y el grupo bifenilo está sustituido en la posición 4 por el resto que contiene los sustituyentes R^A, R^B, y Z. Este lado derecho preferido del compuesto de Fórmula (1.0.0) puede representarse mediante la Fórmula (1.0.4):



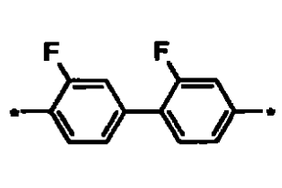
(1.0.4)

Donde R^1 y/o R^2 es -H, preferiblemente no habrá sustituyente en ninguna posición unida al resto del lado izquierdo de la molécula de Fórmula (1.0.0). Otras realizaciones que son preferidas son aquellos compuestos de la presente invención que tienen un sustituyente, especialmente un sustituyente en la posición 2 de cualquiera o ambos grupos fenilo que comprenden el resto bifenilo. Así, en algunas realizaciones preferidas de los compuestos de la presente invención, el significado de R^1 y R^2 se

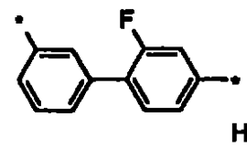
define como -H; -Cl; -F; alquilo C_1-C_3 clorado y/o fluorado; alcoxi C_1-C_3 clorado y/o fluorado; o alquinilo C_2-C_4.

Se prefiere tener un grupo halógeno en el punto de la molécula ocupado por el sustituyente R^1 o R^2, dado que habitualmente da como resultado una actividad inhibidora mejorada. Se contempla que está dentro del alcance de la presente invención que R^1 o R^2 es un grupo lipófilo pequeño que comprende -Cl o -F; alquilo C_1-C_3 clorado y/o fluorado; o alcoxi C_1-C_3 clorado y/o fluorado.

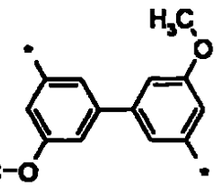
En consecuencia, las realizaciones de la presente invención en las que el resto Q^2 está sustituido con R^1 y opcionalmente con R^2 incluye los representados por las Fórmulas parciales (2.6.1) a (2.6.12):



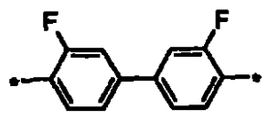
(2.6.1)



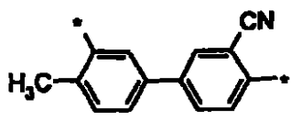
(2.6.2)



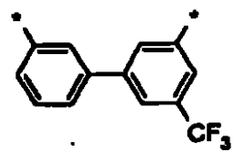
(2.6.3)



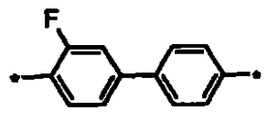
(2.6.4)



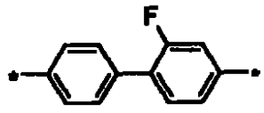
(2.6.5)



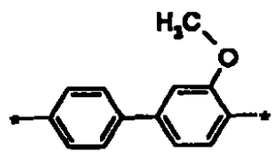
(2.6.6)



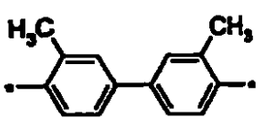
(2.6.7)



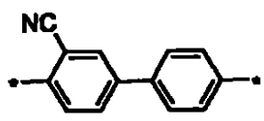
(2.6.8)



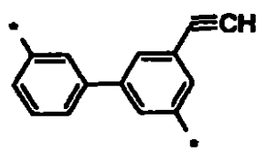
(2.6.9)



(2.6.10)



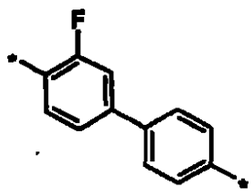
(2.6.11)



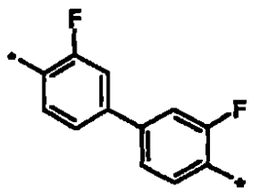
(2.6.12)

5.3.2. Q^2 en realizaciones específicas

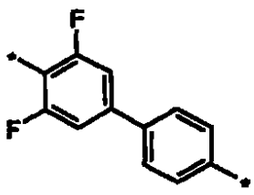
La presente invención concierne también adicionalmente de forma especial un compuesto de Fórmula (1.0.0) en el que particularmente Q^2 y los sustituyentes R^1 y R^2 se seleccionan de tal forma que esta parte del término del lado derecho de dicho compuesto de Fórmula (1.0.0) está representado por las Fórmulas parciales siguientes (3.0.1) a (3.0.29) expuestas a continuación.



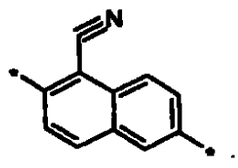
(3.0.1)



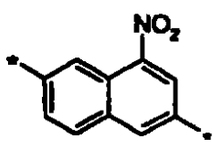
(3.0.2)



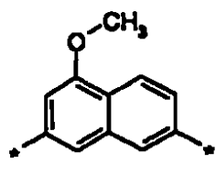
(3.0.3)



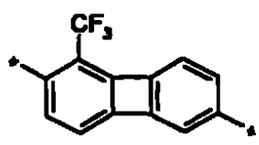
(3.0.4)



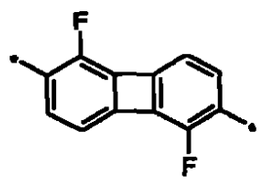
(3.0.5)



(3.0.6)

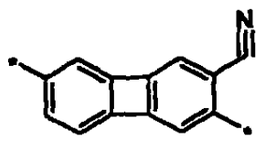


(3.0.7)

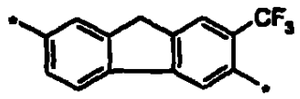


(3.0.8)

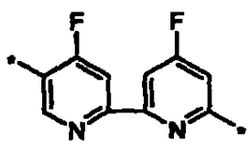
225



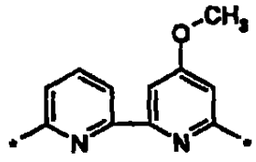
(3.0.9)



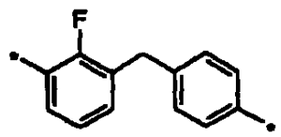
(3.0.10)



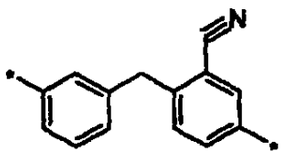
(3.0.11)



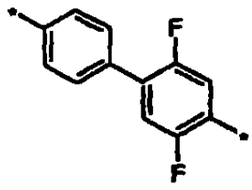
(3.0.12)



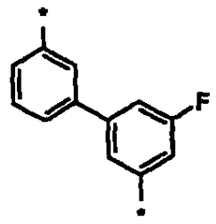
(3.0.13)



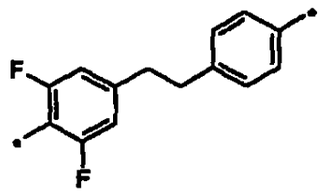
(3.0.14)



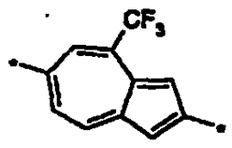
(3.0.15)



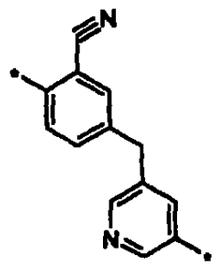
(3.0.16)



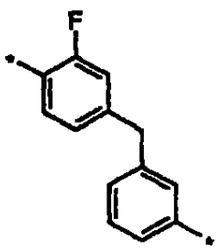
(3.0.17)



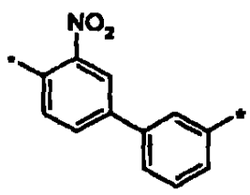
(3.0.18)



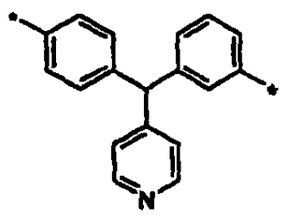
(3.0.19)



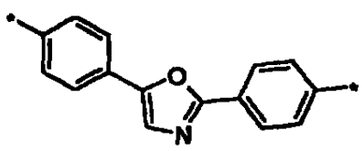
(3.0.20)



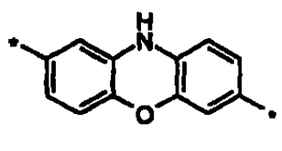
(3.0.21)



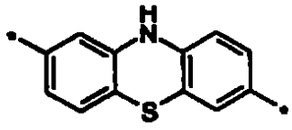
(3.0.22)



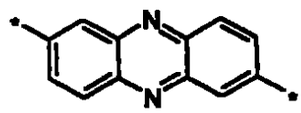
(3.0.23)



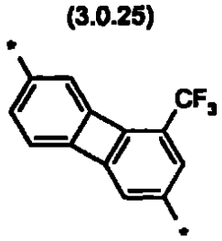
(3.0.24)



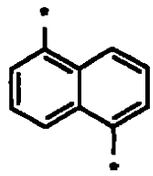
(3.0.25)



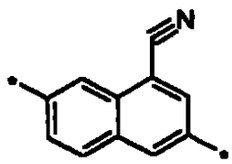
(3.0.26)



(3.0.27)



(3.0.28)



(3.0.29)

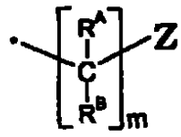
5.4.0. El resto $[W^2]_g$

El resto $[W^2]_g$ en la Fórmula (1.0.0) proporciona la posibilidad de derivados con enlaces éter, tioéter, amina y carbono de los compuestos de la presente invención. Así, en el caso en que g es 1, W^2 es –O- $S(=O)_t$-, donde t es 0, 1, ó 2; o -$N(R^3)$- donde R^3 tiene el mismo significado que se define en el presente documento, o –$CR^{29}R^{30}$. Cuando W^2 tiene el significado de -$N(R^3)$-, R^3 es preferiblemente -H y da como resultado un enlace amino simple. Cuando W^2 tiene el significado de -$S(=O)_t$-, t es preferiblemente 0 y da como resultado un enlace tioéter simple. En el caso en que g es 1, se prefiere más que W^2 tenga el significado de -O-, por el que da como resultado un enlace éter simple. En el caso en que g es 1, es también un significado de W^2 que es un resto carbono -$CR^{29}R^{30}$- donde R^{29} y R^{30} se seleccionan cada uno de -H; -F; -CF_3; -alquilo C_1-C_3; -cicloalquilo C_3-C_6; fenilo; bencilo; y piridilo; en el que dichos restos alquilo, cicloalquilo, fenilo, bencilo y piridilo están cada uno sustituidos independientemente con 0 a 3 sustituyentes R^{10}, donde R^{10} tiene el mismo significado que se define en el presente documento. En el caso en que W^2 tenga el significado de -$CR^{29}R^{30}$-, es

preferible que R^{29} y R^{30} tengan ambos el significado de -H, por el que da como resultado un enlace metileno simple.

5.4.1 Los sustituyentes R^A y R^B

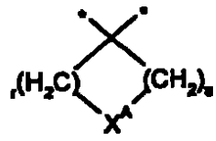
El grupo de Fórmula parcial (1.0.4) anterior se sustituye en la posición 4 con un resto que contiene los sustituyentes Z, R^A y R^B, que pueden representarse mediante la Fórmula parcial (1.1.15):



(1.1.15)

donde m es 0, 1 ó 2. En las realizaciones más preferidas de los compuestos de la presente invención, m tiene el significado de 0 ó 1. Cuando m es 1 está presente el resto -[R^A-C- R^B]-, y R^A y R^B son preferiblemente cada uno un miembro seleccionado independientemente del grupo constituido por -H; y alquilo C_1-C_4.

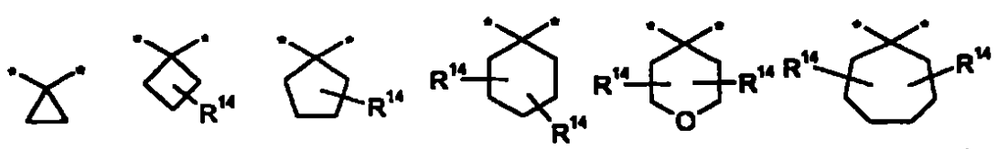
En otras realizaciones preferidas de la presente invención R^A y R^B pueden tomarse conjuntamente, pero únicamente en el caso en que m es 1, para formar un resto espiro de Fórmula (1.2.0):



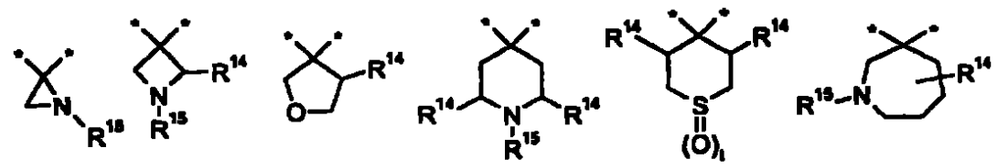
(1.2.0)

donde r y s son independientemente de 0 a 4 siempre que la suma de r + s es al menos 1, pero no superior a 5; X^A es $-CH_2$, $-CHR^{11}$, o $-C(R^{11})_2$- donde cada R^{11} se selecciona independientemente de los otros y cada R^{12} tiene el mismo significado

definido en el presente documento; -NR^{15}- donde R^{15} tiene el tiene el mismo significado definido en el presente documento; -O-; o -$S(=O)_t$, donde t es 0, 1, ó 2; y dicho resto espiro está sustituido en cualesquiera uno o más átomos de carbono del mismo con 0 a 3 sustituyentes R^{14}, en un átomo de nitrógeno del mismo con 0 ó 1 sustituyente R^{15}, y en un átomo de azufre del mismo en 0 ó 2 átomos de oxígeno. En consecuencia, esto da como resultado, entre otros, los restos ilustrados por las Fórmulas parciales (1.5.1) a (1.5.12):



(1.5.1) (1.5.2) (1.5.3) (1.5.4) (1.5.5) (1.5.6)



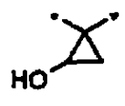
(1.5.7) (1.5.8) (1.5.9) (1.5.10) (1.5.11) (1.5.12)

donde t es 0, 1, ó 2; y R^{14} y R^{15} tienen el mismo significado definido en el presente documento.

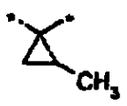
Los significados preferidos del sustituyente R^{14} incluyen -F; -Cl; =O; -OH; -CH_3; -CH_2OH; -$CH(CH_3)OH$;-$C(CH_3)_2OH$ -OCH_3; -C(=O)OH; -$C(=O)NH_2$; -NH_2; -$NHCH(CH_3)_2$; -$NHC(=O)CH_3$; -$NHC(=O)OCH_2CH_3$; -$NHS(=O)_2CH_3$; y -$S(=O)_2NH_2$, que da como resultado restos tales como los de Fórmulas parciales (3.1.1) a (3.1.34):



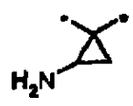
(3.1.1)



(3.1.2)



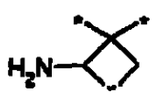
(3.1.3)



(3.1.4)



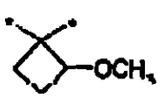
(3.1.5)



(3.1.6)



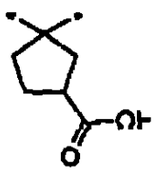
(3.1.7)



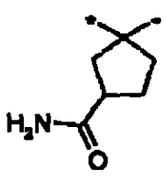
(3.1.8)



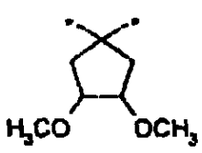
(3.1.9)



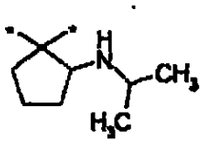
(3.1.10)



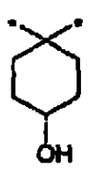
(3.1.11)



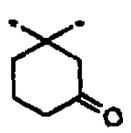
(3.1.12)



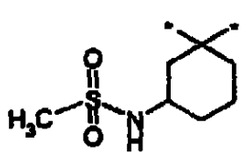
(3.1.13)



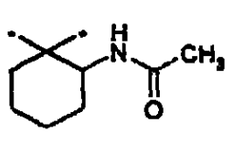
(3.1.14)



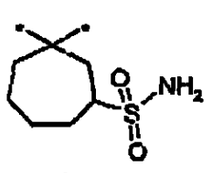
(3.1.15)



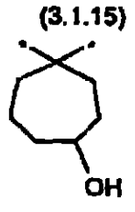
(3.1.16)



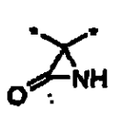
(3.1.17)



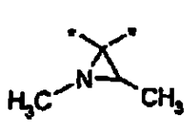
(3.1.18)



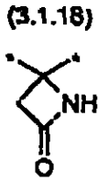
(3.1.19)



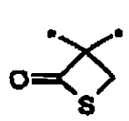
(3.1.20)



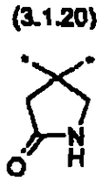
(3.1.21)



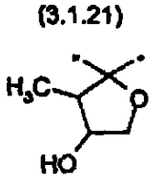
(3.1.22)



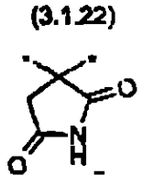
(3.1.23)



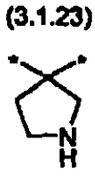
(3.1.20)



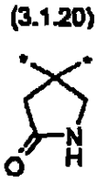
(3.1.21)



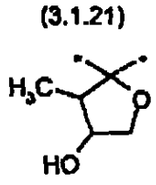
(3.1.22)



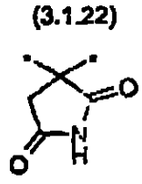
(3.1.23)



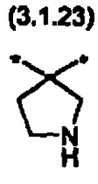
(3.1.24)



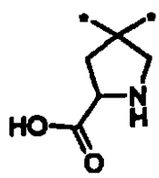
(3.1.25)

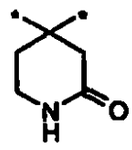


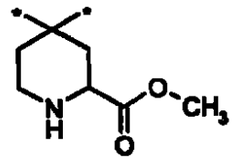
(3.1.26)

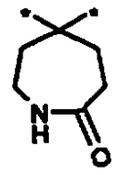


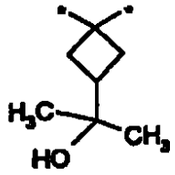
(3.1.27)

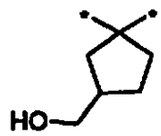

(3.1.28)

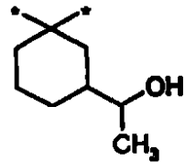

(3.1.29)


(3.1.30)


(3.1.31)


(3.1.32)


(3.1.33)


(3.1.34)

5.4.2 Los sustituyentes R^C y R^D

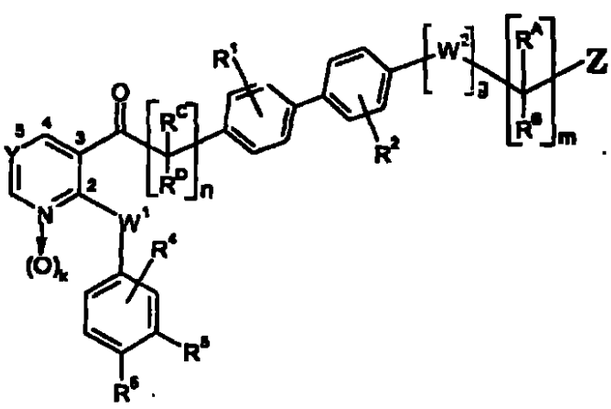
Como ya se ha descrito, R^C y R^D tienen el mismo significado definido anteriormente para R^A y R^B, excepto que uno de ellos debe ser -H, y se seleccionan independientemente el uno del otro y de R^A y R^B. En consecuencia, todas las realizaciones particulares y preferidas de los compuestos de Fórmula (1.0.0) detallados anteriormente con respecto a los sustituyentes R^A y R^B, son en su mayoría también realizaciones particulares y preferidas de los compuestos de Fórmula (1.0.0) con respecto a los sustituyentes R^C y R^D.

5.5 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 de estructura nicotinamídica. El sustituyente R^3 del átomo de nitrógeno se selecciona preferiblemente de -H; -alquilo C_1-C_3; y alcoxi C_1-C_3; y es más preferiblemente -H; $-CH_3$; o $-OCH_3$. En las realizaciones más preferidas de los compuestos de Fórmula (1.0.0), R^3 tiene el significado de -H.

Cuando Q^1 tiene el significado preferido de fenilo; Q^2 tiene el significado

preferido de bifenilo; y j tiene el significado de 0, que es 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 nicotinoílo, es decir, de estructura cetónica. Esta estructura cetónica de los compuestos de Fórmula (1.0.0) se representa mediante la Fórmula (1.0.7):



(1.0.7)

donde todos los sustituyentes y componentes del mismo; es decir, Z; W^1; W^2; Y; g, 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 descritos en detalle en el presente documento, que cuando j es 1 y los compuestos son de estructura nicotinamídica.

5.6.0. Z es un resto de Fórmulas parciales (1.1.1) - (1.1.15)

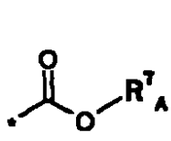
Z es un miembro seleccionado del grupo de restos definidos por las Fórmulas parciales (1.1.1) a (1.1.15) ilustradas adicionalmente más arriba. Los restos de Fórmulas parciales (1.1.1) a (1.1.5) que definen el grupo Z son típicamente pero no necesariamente ácidos, amidas, y grupos heterociclo que actúan como miméticos de

ácido y amida, pero no se limitan a estos tipos de grupos funcionales. Los restos de Fórmulas parciales (1.1.6) a (1.1.9) que definen el grupo Z son típicamente, pero no necesariamente alcoholes terciarios y sus miméticos, especialmente restos análogos de acilo y nitrilo análogos, pero no se limitan a estos tipos de grupos funcionales. Los restos de Fórmulas parciales (1.1.10) a (1.1.15) que definen el grupo Z son típicamente, pero no necesariamente amidas inversas y sus miméticos, pero no se limitan a estos tipos de grupos funcionales. Pueden emplearse otros restos según se describen en el presente documento en el lado derecho de los compuestos de Fórmula (1.0.0). Estos restos son bioisoestéricos en tanto en cuanto permiten que los compuestos de Fórmula (1.0.0) que los contienen logren una inhibición de PDE4 esencialmente equivalente a la lograda por otros restos, especialmente los restos ácido, amida, alcohol, y amida inversa.

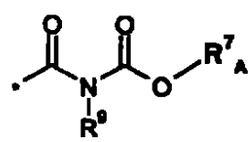
En consecuencia, Z es un miembro seleccionado del grupo de restos definidos por las Fórmulas parciales (1.1.1) a (1.1.15), y dichos restos incluyen los sustituyentes R^7_A, R^7_B y R^7_C, así como R^8, R^9, R^{16}, y R^{17}, y en el caso de la Fórmula parcial (1.1.15) el resto consiste en un sistema de anillos heterociclo que contiene nitrógeno. Todos los restos de Fórmulas parciales (1.1.1) a (1.1.15) están unidos a la porción restante de Fórmula (1.0.0).

<u>5.6.1. Z es un resto de Fórmulas parciales (1.1.1) , (1.1.2), o (1.1.3)</u>

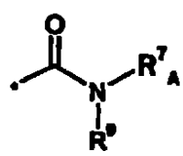
Las realizaciones de la presente invención en las que la definición del grupo Z se ilustra mediante las Fórmulas parciales (1.1.1); (1.1.2); y (1.1.3), son las siguientes:



(1.1.1)



(1.1.2)



(1.1.3)

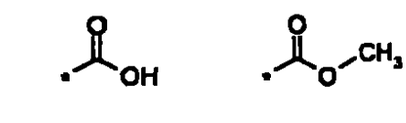
Uno de un número de restos preferidos para definir el grupo Z es el de Fórmula parcial (1.1.1) donde R^7_A tiene el significado de -H, que es un significado preferido de este sustituyente. Cuando R^7 es hidrógeno y m es 1, 2, ó 3 en la Fórmula (1.0.0), da como resultado un ácido carboxílico simple -COOH, y el grupo se vuelve un ácido alcanoico inferior.

R^{10} es un sustituyente opcional de los restos que definen R^7_A y puede haber hasta tres sustituyentes así cuando están presentes. El significado del sustituyente R^{10} incluye fenilo o piridilo en el que dicho fenilo o piridilo está a su vez opcionalmente sustituido con hasta 3 sustituyentes R^{11} donde 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 tal sustitución R^{11}, habrá 1 ó 2 sustituyentes R^{11} que tienen el significado de -F, -Cl, -CH_3, -OH_3 -OH, -CN, o -$N(CH_3)_2$. Preferiblemente, hay 0 ó 1 sustituyente R^{11} y cuando está presente es -F o -Cl. El significado del sustituyente R^{10} incluye adicionalmente -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}, -$NR^{16}S(=O)_2R^{17}$, o -$S(=O)_2NR^{16}R^{17}$.

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; o piridilo. Dichos grupos alquilo, alquenilo, cicloalquilo, fenilo, bencilo, o piridilo están a su vez opcionalmente sustituidos con hasta 3 sustituyentes -F, -Cl, o -CN. Entre los significados adicionales referidos anteriormente de R^{10}, se prefiere que el sustituyente R^{10} cuando esté presente sea piridilo opcionalmente sustituido con -F, -Cl, -OCH_3, -CN, -NO_2, o -$NR^{16}R^{17}$ donde R^{16} y R^{17} son independientemente -H, o -CH_3; o que el sustituyente R^{10} cuando esté presente sea -F, -Cl, -CF_3, -CN, -NO_2, -C(=O)OR^{16}, o -$NR^{16}R^{17}$ donde R^{16} y R^{17} son independientemente -H o -CH_3.

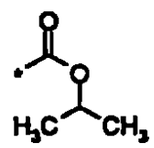
Estas y otras realizaciones preferidas de los compuestos de Fórmula (1.0.0) que

comprenden los restos de la Fórmula parcial (1.1.1) basados en los significados preferidos de R^7_A, como se describe anteriormente incluyen, entre otros, los siguientes grupos ilustrados por las Fórmulas parciales (3.5.1) a (3.5.15):

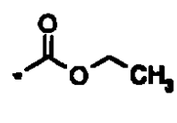


(3.5.1)

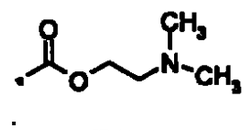
(3.5.2)



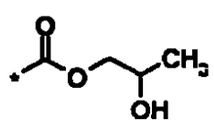
(3.5.3)



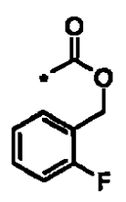
(3.5.4)



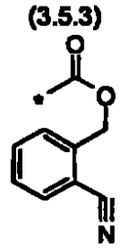
(3.5.5)



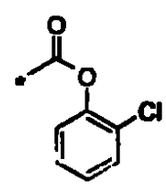
(3.5.6)



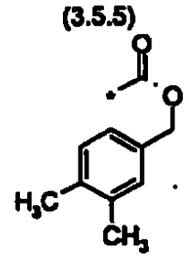
(3.5.7)



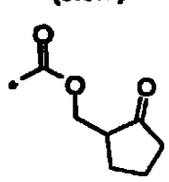
(3.5.8)



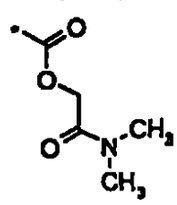
(3.5.9)



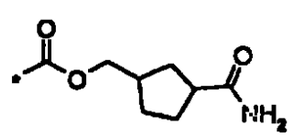
(3.5.10)



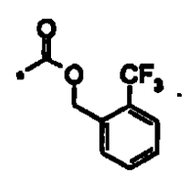
(3.5.11)



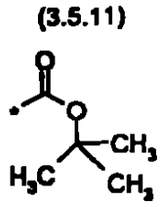
(3.5.12)



(3.5.13)



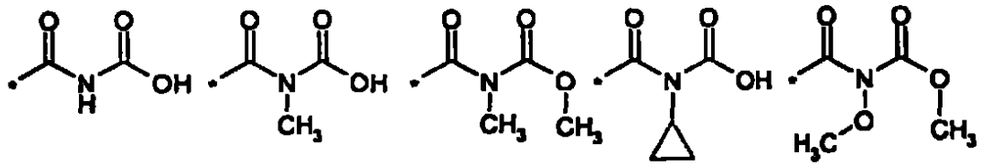
(3.5.14)



(3.5.15)

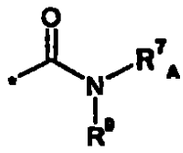
El grupo Z está representado por la Fórmula parcial (1.1.2) en la que el átomo de nitrógeno está sustituido con R^9 donde R^9 tiene el significado de -H; -alquilo C_1-C_4; cicloalquilo C_3-C_7; fenilo; bencilo; -C(=O)OR^{16}; -C(=O)R^{16}; -OR^{16}; -alquil (C_1-C_2)-OR^{16}; o -alquil (C_1-C_2)-C(=O)OR^{16}; donde R^{16} es -H o -alquilo C_1-C_4. R^{16} es preferiblemente -H o CH_3.

En consecuencia, las realizaciones de la presente invención en las que el grupo Z está representado por la Fórmula parcial (1.1.2) puede ilustrarse de la forma siguiente con las Fórmulas parciales (4.1.1) a (4.1.5):



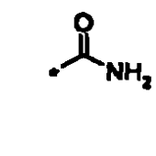
(4.1.1) (4.1.2) (4.1.3) (4.1.4) (4.1.5)

Aquellas realizaciones en las que la definición de Z es la de un grupo amida, se ilustran con la Fórmula parcial (1.1.3):

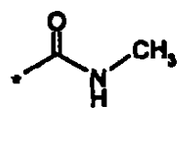


(1.1.3)

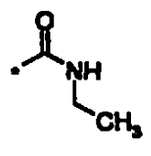
Estas y otras realizaciones de los compuestos de Fórmula (1.0.0) que comprenden los restos de la Fórmula parcial (1.1.3) basados en los significados de R^7_A y R^9 descritos anteriormente incluyen, entre otros, los siguientes grupos ilustrados por las Fórmulas parciales (4.5.1) a (4.5.20):



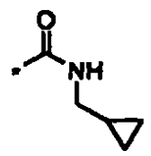
(4.5.1)



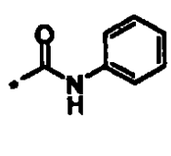
(4.5.2)



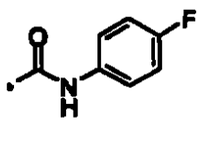
(4.5.3)



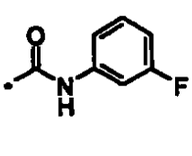
(4.5.4)



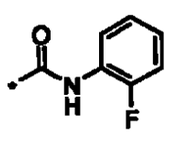
(4.5.5)



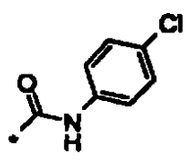
(4.5.6)



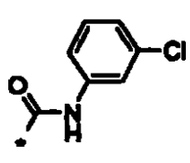
(4.5.7)



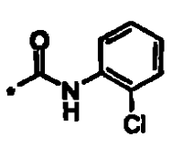
(4.5.8)



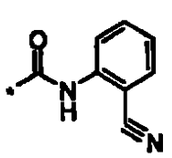
(4.5.9)



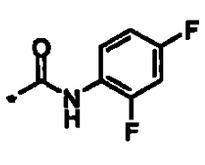
(4.5.10)



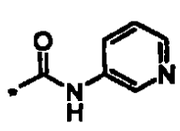
(4.5.11)



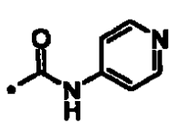
(4.5.12)



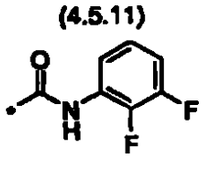
(4.5.13)



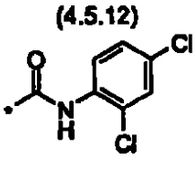
(4.5.14)



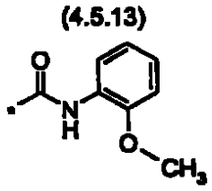
(4.5.15)



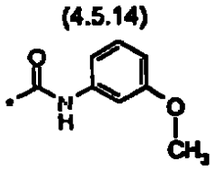
(4.5.16)



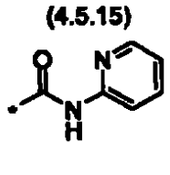
(4.5.17)



(4.5.18)



(4.5.19)

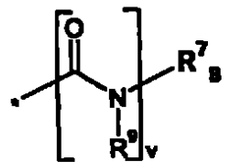


(4.5.20)

5.6.2. Z es un resto de Fórmula parcial (1.1.4)

Las realizaciones preferidas de la presente invención comprenden también aquellos compuestos de Fórmula (1.0.0) en los que el resto terminal **Z** entra dentro del alcance de la Fórmula parcial (1.1.4), es decir, realizaciones de este tipo están comprendidas dentro del alcance del resto **Z** cuando tiene el significado de la Fórmula parcial (1.1.4):

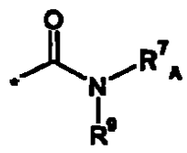
237



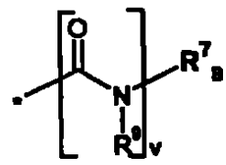
(1.1.4)

donde R^7_B es un heterociclo monociclo o biciclo que es un miembro seleccionado del grupo constituido por 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-5-ilo; 1,3,4-oxadiazol-2-on-5-ilo; tiadiazolilo; morfolinilo; paratiazinilo; oxazolilo; isoxazolilo; tiazolilo; isotiazolilo; pirrolilo; pirazolilo; succinimidilo; glutarimidilo; pirrolidonilo; 2-piperidonilo; 2-piridonilo; 4-piridonilo; piridazin-3-onilo; piridilo; pirimidinilo; pirazinilo; piridazinilo; indolilo; indolinilo; isoindolinilo; benzo[*b*]furanilo; 2,3,-dihidrobenzofuranilo; 1,3-dihidroisobenzofuranilo; 2*H*-1-benzopiranilo; 2*H*-cromenilo; cromanilo; benzotienilo; 1*H*-indazolilo; bencimidazolilo; benzoxazolilo; benzosoxazolilo; 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;

Las Fórmulas parciales (1.1.3) y (1.1.4) son similares y debe advertirse la distinción entre ellas. Las Fórmulas parciales (1.1.3) y (1.1.4) son las siguientes:



(1.1.3)



(1.1.4)

Cuando v es 0, R^7_B está enlazado de forma directa a la porción restante de un compuesto de Fórmula (1.0.0) y es, en consecuencia, fácilmente distinguible de un resto de Fórmula parcial (1.1.3) en el que R^7_A está enlazado a la porción restante de un compuesto de Fórmula (1.0.0) a través del resto de enlace amida -C(=O)NR^9-. Cuando v es 1, por otra parte, tanto los restos R^7_B y R^7_A están ligados a la porción restante de un compuesto de Fórmula (1.0.0) a través del resto de enlace amida -C(=O)NR^9-. 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^7_B y R^7_A. Esta diferencia ha sido ya descrita anteriormente en detalle.

Para facilitar la siguiente descripción, los restos heterociclos monocíclicos y los restos heterociclos bicíclicos se tratan primero conjuntamente y después se analizan como grupos separados.

Uno cualquiera o más átomos de carbono del resto fenilo, bencilo o heterociclilo está sustituido co 0 a 3 sustituyentes R^{14} donde R^{14} tiene los significados y significados preferidos descritos anteriormente con respecto a las Fórmulas parciales (1.1.1), (1.1.2), y (1.1.3). Uno cualquiera o más átomos de nitrógeno, que se apreciará aparecen únicamente en el caso de los restos heterocíclicos, y que no son un punto de unión de dicho resto heterociclo, están opcionalmente sustituidos con hasta 3 sustituyentes R^{15}. Cualquier átomo de azufre que aparezca en un resto heterociclo, que no sea un punto de unión de dicho resto heterociclo, está sustituido con 0, 1, ó 2 átomos de oxígeno.

El sustituyente heterociclo de nitrógeno opcional R^{15} comprende -H; $NR^{16}R^{17}$;-$C(=O)R^{16}$; -OR^{16}; preferiblemente –OCH_3; -alquilo C_1-C_4-OR^{16}; -$C(=O)OR^{16}$; -alquilo 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 donde u es 0, 1, ó 2; preferiblemente ciclopropilo; fenilo; bencilo; piridilo; o quinolinilo. Los grupos alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, bencilo, piridilo y quinolinilo así incluidos están sustituidos opcionalmente con hasta 2 sustituyentes R^{12}.

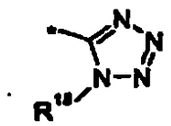
El sub-sustituyente R^{12} comprende -F; -Cl; -CO_2R^{18}; -OR^{16}; -CN; -$C(=O)NR^{18}R^{19}$; -$NR^{18}R^{19}$; -$NR^{18}C(=O)R^{19}$; -$NR^{18}C(=O)OR^{19}$; -$NR^{18}S(=O)_pR^{19}$; -$S(=O)_pNR^{18}R^{19}$, donde p es 1 ó 2, preferiblemente 2; alquilo C_1-C_4, preferiblemente -CH_3; y -alcoxi C_1-C_4, donde R^{12} tiene el significado de -OR^{16} anterior y R^{16} se define como -alquilo C_1-C_4, y preferiblemente R^{12} es -OCH_3; donde dicho alquilo y alcoxi están a su vez independientemente 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 R18 y R19 se seleccionan independientemente de –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 (1.3.1) a (1.3.20) anteriores, ni más adelante, porque el sustituyente R^9 está unido únicamente a un átomo de nitrógeno que no forma parte integral, componente de un resto heterocíclico unido. El sustituyente R^9 es de carácter opcional ya que "-H" está incluido como 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 apunta también la distinción entre los sustituyentes R^9 y R^{15}, ambos de los cuales están unidos únicamente a átomos de nitrógeno en cualquiera de los significados del resto Z. El sustituyente R^{15} está unido únicamente a un átomo de nitrógeno que es

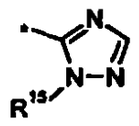
una parte integral componente de cualquier resto heterociclo que pueda definirse mediante el sustituyente R^7_B de Fórmula parcial (1.1.4) y en particular con referencia a los restos heterociclo más específicos de Fórmulas parciales (1.3.1) a (1.3.20), que se muestran anteriormente así como a continuación. El sustituyente R^9, por otra parte, está unido únicamente a un átomo de nitrógeno que a su vez está unido, pero no es parte integral componente de ninguno de los restos heterocíclicos que se define mediante las Fórmulas parciales (1.1.2), (1.1.3), y (1.1.5). El sustituyente R^{15} puede estar unido a uno o más átomos de nitrógeno y dichos átomos de nitrógeno pueden estar presentes en cualquier resto que entre dentro del alcance de la Fórmula parcial (1.1.4) que puede caracterizarse como que contiene o que comprende un resto heterocíclico que contiene nitrógeno.

Como ilustración de realizaciones subgenéricas preferidas de la presente invención en las que el grupo Z tiene el significado de un resto que entra dentro del alcance de la Fórmula parcial (1.1.4), a continuación se muestran los grupos de Fórmulas parciales (1.4.1) a (1.4.28):



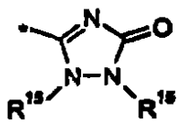
Tetrazol-5-ilo

(1.4.1)



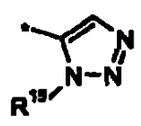
1,2,4-triazol-3-ilo

(1.4.2)



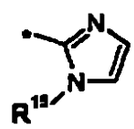
1,2,4-triazol-3-on-5-ilo

(1.4.3)



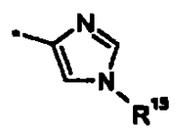
1,2,3-triazol-5-ilo

(1.4.4)



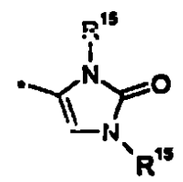
Imidazol-2-ilo

(1.4.5)



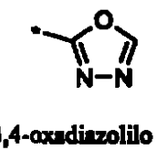
imidazol-4-ilo

(1.4.6)



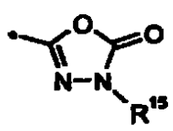
Imidazolidin-2-on-4-ilo

(1.4.7)



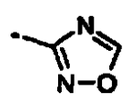
1,3,4-oxadiazolilo

(1.4.8)



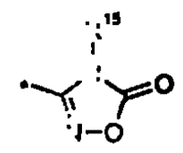
1,3,4-oxadiazol-2-on-5-ilo

(1.4.9)



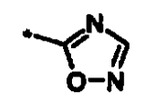
1,2,4-oxadiazol-3-ilo

(1.4.10)



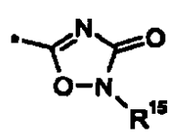
1,2,4-oxadiazol-5-on-3-ilo

(1.4.11)



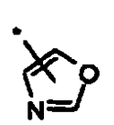
1,2,4-oxadiazol-5-ilo

(1.4.12)



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

(1.4.13)



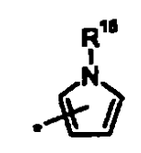
oxazolilo

(1.4.14)



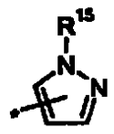
isoxazolilo

(1.4.15)

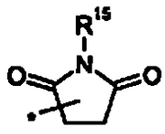


pirrolilo

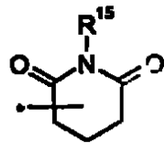
(1.4.16)



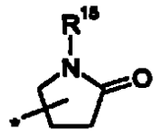
pirazolilo



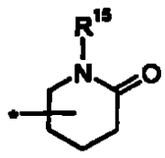
succinimidilo



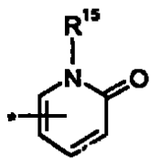
glutarimidilo



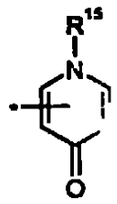
pirrolidinilo



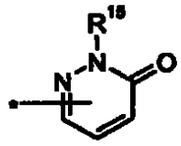
2-piperidonilo
(1.4.21)



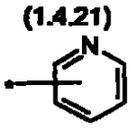
2-piridonilo



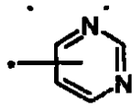
4-piridonilo
(1.4.23)



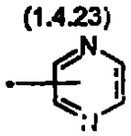
Piridazin-3-onilo
(1.4.24)



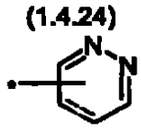
piridilo



pirimidinilo

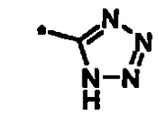


pirazinilo

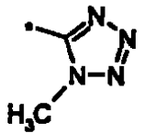


piridazinilo

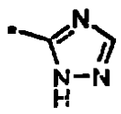
Para proporcionar otra demostración de realizaciones preferidas de los compuestos de Fórmula (1.0.0) con referencia al grupo Z donde es un resto de Fórmula parcial (1.1.4) y v es 0 ó 1, y R^7_n es un grupo heterociclo monocíclico, a continuación se muestran los grupos de Fórmulas parciales (4.8.1) a (4.8.80) a partir de los que se selecciona el resto Z en tales realizaciones preferidas:



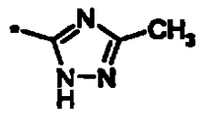
(4.8.1)



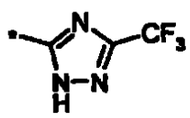
(4.8.2)



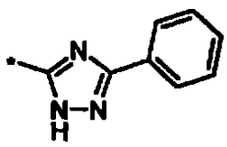
(4.8.3)



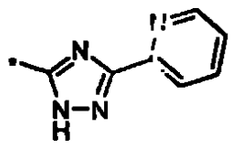
(4.8.4)



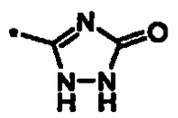
(4.8.5)



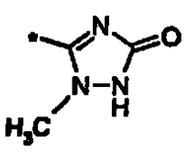
(4.8.6)



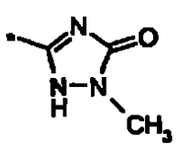
(4.8.7)



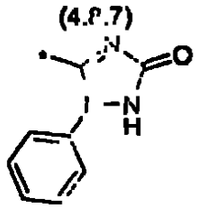
(4.8.8)



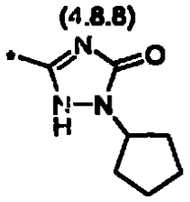
(4.8.9)



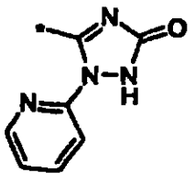
(4.8.10)



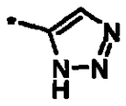
(4.8.11)



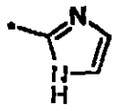
(4.8.12)



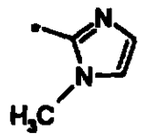
(4.8.13)



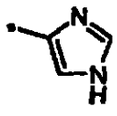
(4.8.14)



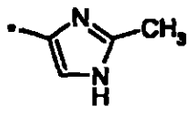
(4.8.15)



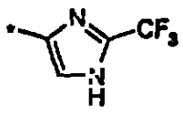
(4.8.16)



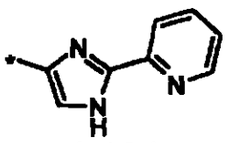
(4.8.17)



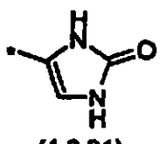
(4.8.18)



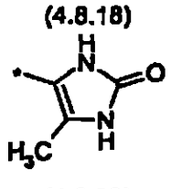
(4.8.19)



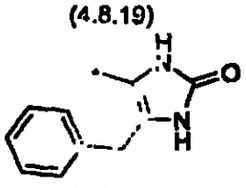
(4.8.20)



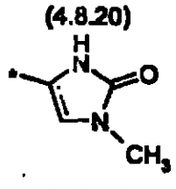
(4.8.21)



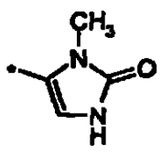
(4.8.22)



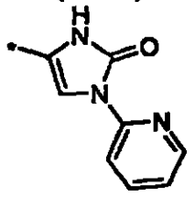
(4.8.23)



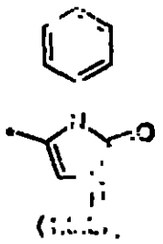
(4.8.24)



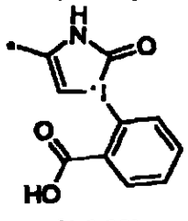
(4.8.25)



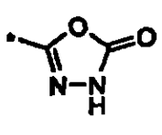
(4.8.26)



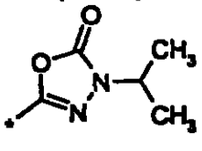
(4.8.27)



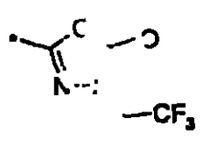
(4.8.28)



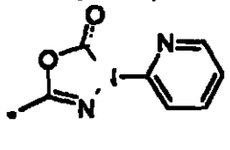
(4.8.29)



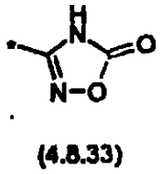
(4.8.30)



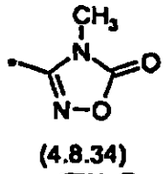
(4.8.31)



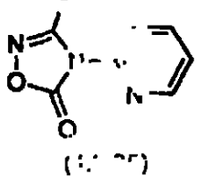
(4.8.32)



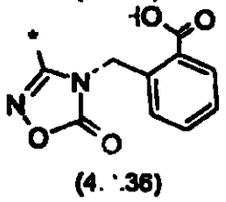
(4.8.33)



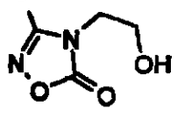
(4.8.34)



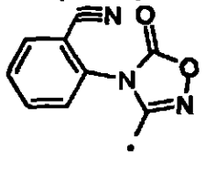
(4.8.35)



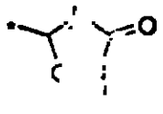
(4.8.36)



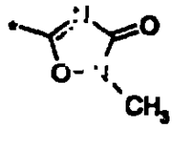
(4.8.37)



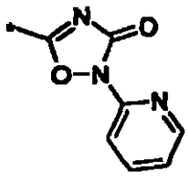
(4.8.38)



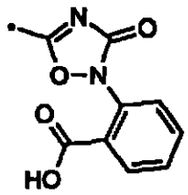
(4.8.39)



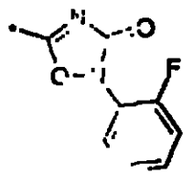
(4.8.40)



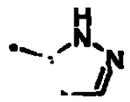
(4.8.41)



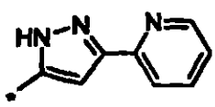
(4.8.42)



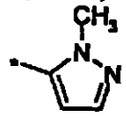
(4.8.43)



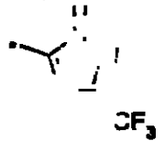
(4.8.44)



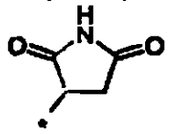
(4.8.45)



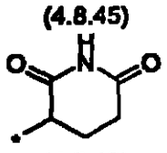
(4.8.46)



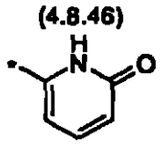
(4.8.47)



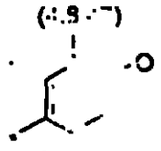
(4.8.48)



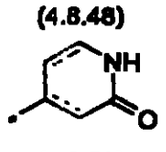
(4.8.49)



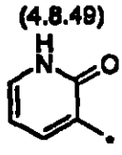
(4.8.50)



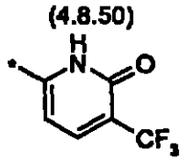
(4.8.51)



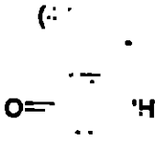
(4.8.52)



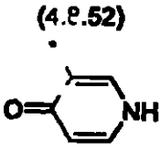
(4.8.53)



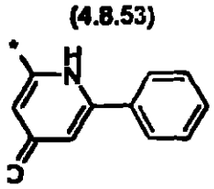
(4.8.54)



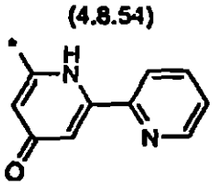
(4.8.55)



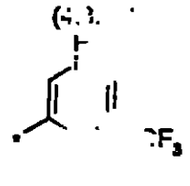
(4.8.56)



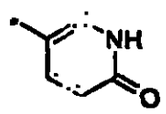
(4.8.57)



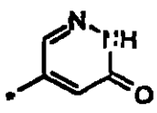
(4.8.58)



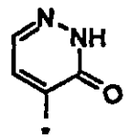
(4.8.59)



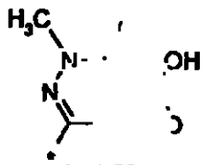
(4.8.60)



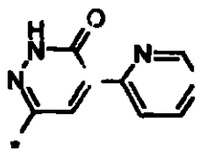
(4.8.61)



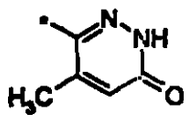
(4.8.62)



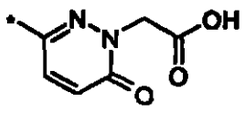
(4.8.63)



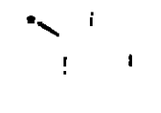
(4.8.64)



(4.8.65)



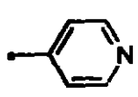
(4.8.66)



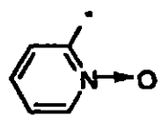
(4.8.67)



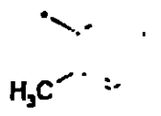
(4.8.68)



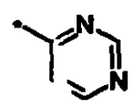
(4.8.69)



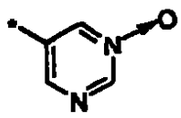
(4.8.70)



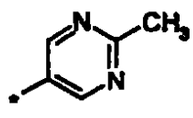
(4.8.71)



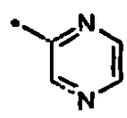
(4.8.72)



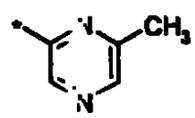
(4.8.73)



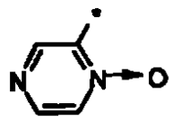
(4.8.74)



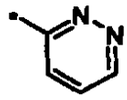
(4.8.75)



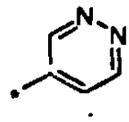
(4.8.76)



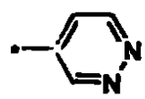
(4.8.77)



(4.8.78)



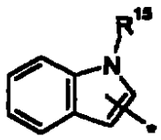
(4.8.79)



(4.8.80)

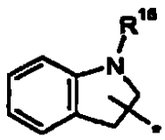
Las realizaciones preferidas de la presente invención en las que el grupo **Z** es un resto de Fórmula parcial (1.1.4) y v es 0 ó 1, incluyen también aquellos en los que el grupo R^7_B es un grupo heterociclo bicíclico seleccionado del grupo constituido por indolilo; indolinilo; isoindolinilo; benzo[*b*]furanilo; 2,3-dihidrobenzofuranilo; 1,3-dihidroisobenzofuranilo; 2*H*-1-benzopiranilo; 2-*H*-cromenilo; cromanilo; benzotienilo; 1*H*-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.

Para proporcionar una demostración adicional de realizaciones preferidas de los compuestos de Fórmula (1.0.0) con referencia al grupo Z cuando es un resto de Fórmula parcial (1.1.4), v es 0 ó 1, y R^7_B es un grupo heterociclo bicíclico, a continuación se muestran los grupos que consisten en las Fórmulas parciales (5.0.1) a (5.0.28) a partir de los que se selecciona el resto Z en tales realizaciones preferidas:



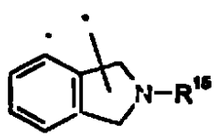
indolilo

(5.0.1)



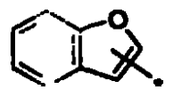
indolinilo

(5.0.2)



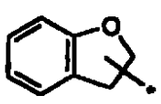
isoindolinilo

(5.0.3)



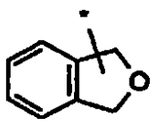
ben *h*]furanilo

(5.0.4)



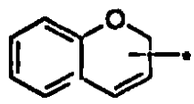
2,3-dihidrobenzo-furanilo

(5.0.5)



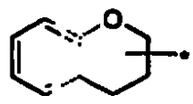
1,3-dihidroisobenzo-furanilo; ftalanilo

(5.0.6)



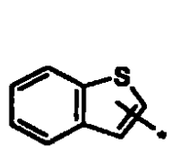
2*H*-1-ben iranilo

(5.0.7)



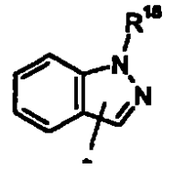
anilo

.0.8)



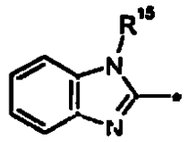
benzotienilo

(5.0.9)



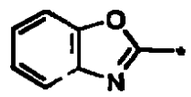
1*H*-indazolilo

(5.0.10)



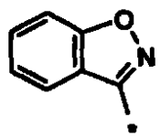
bencimidazolilo

(5.0.11)



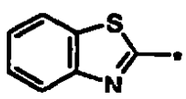
benzoxazolilo

(5.0.12)



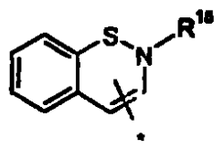
benzoisoxazolil

(5.0.13)



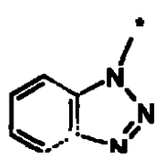
benzotiazolilo

(5.0.14)



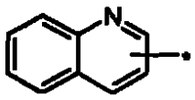
2*H*-1,2-benzotiazinilo

(5.0.15)



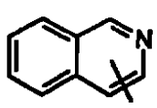
benzotiazolilo

(5.0.16)



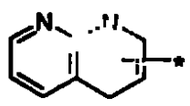
quinolinilo

(5.0.17)



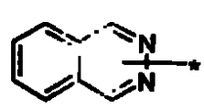
isoquinolinilo

(5.0.18)



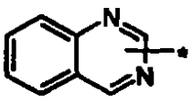
1,8-naftiridinilo

(5.0.19)



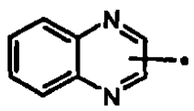
ftalazinilo

(5.0.20)



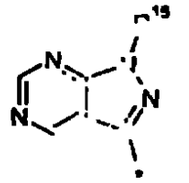
quinazolinilo

(5.0.21)



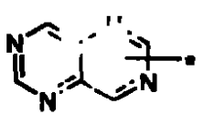
quinoxalinilo

(5.0.22)



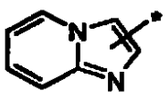
1*H*-pirrolo[3,4-*d*]-piridinilo

(5.0.23)



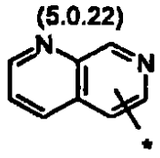
pirimido[5,4-*d*]-pirimidinilo

(5.0.24)



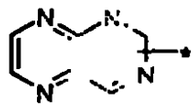
Imidazo-[1,2-*a*]-piridinilo

(5.0.25)



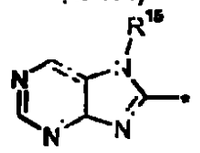
piridopiridinilo

(5.0.26)



pteridinilo

(5.0.27)



1*H*-purinilo

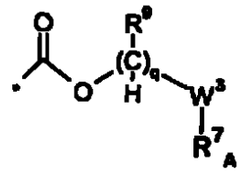
(5.0.28)

donde "*" indica el punto de unión a la posición restante de Fórmula (1.0.0); y donde cada átomo de carbono está sustituido opcionalmente con un sustituyente R^{14}; y donde R^{14} y R^{15} tienen el mismo significado que se define anteriormente; y todas las

formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

5.6.3 Z es un resto de Fórmula parcial (1.1.5)

Hay realizaciones adicionales de los compuestos de Fórmula (1.0.0) en los que el resto **Z** comprende un grupo que entra dentro del alcance de la Fórmula parcial (1.1.5):



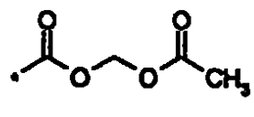
(1.1.5)

donde q es 1, 2, ó 3, siempre que cuando q es 2 ó 3, R^9 tiene el significado de -H en al menos un caso, o dos casos respectivamente; W^3 es -O-; -N(R^9)-; o -OC(=O)- donde R^9 tiene el mismo significado definido anteriormente; y $\mathbf{R^7_A}$ tiene el mismo significado definido anteriormente.

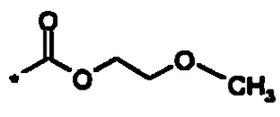
En realizaciones adicionales de los compuestos de Fórmula parcial (1.1.5), q es 1 ó 2, R^9 es -H, o CH_3; W^3 es -O-, -O(C=O)-, o -NH-; y $\mathbf{R^7_A}$ es uno de los restos preferidos ya descritos anteriormente.

Las realizaciones representativas de los compuestos de Fórmula (1.0.0) en los que **Z** entra dentro del alcance de la Fórmula parcial (1.1.5) son aquellos ilustrados por las Fórmulas parciales (6.0.1) a (6.0.6):

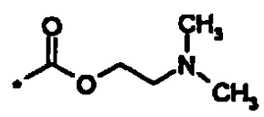
250



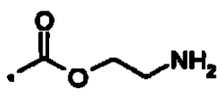
(6.0.1)



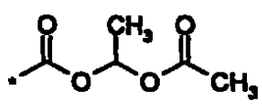
(6.0.2)



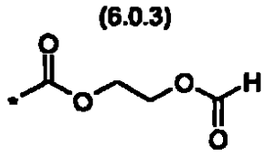
(6.0.3)



(6.0.4)



(6.0.5)



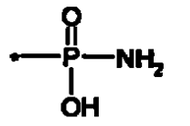
(6.0.6)

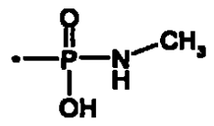
5.6.4 Z es diferente del ácido carboxílico

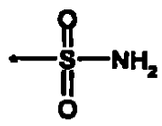
Las realizaciones de los compuestos de Fórmula (1.0.0) incluyen aquellas en las que el resto Z es diferente del ácido carboxílico y es, en su lugar, un ácido de fósforo o de azufre o un derivado de los mismos. Hay un número significativo de tales derivados entre los que puede seleccionarse el resto Z, e incluyen los siguientes: -O-P(=O)$(OH)_2$ (fosfórico); -PH(=O)OH (fosfínico); -P(=O)$(OH)_2$ (fosfónico); -[P(=O)(OH)-O-alquilo C_1-C_4] (alquilfosfono); -P(=O)(OH)-O-alquilo C_1-C_4 (alquilfosfinilo); -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)$_2NHR^{26}$ o -$NHS(=O)_2R^{26}$ (sulfonamido) donde R^{26} es -CH_3, -CF_3, u o-toluilo; y acilsulfonamido seleccionado del grupo constituido por -C(=O)$NHS(=O)_2R^{25}$; -C(=O)$NHS(=O)_2NH_2$; -C(=O)NHS(=O)$_2$[alquilo (C_1-C_4)]$_2$; -C(=O)NHS(=O)$_2$NHalquilo (C_1-C_4); -C(=O)$_2$ 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)$_2R^{25}$, donde R^{25} es -H; -alquilo C_1-C_4; fenilo; o -OR^{16}, donde R^{16} tiene el mismo significado definido anteriormente.

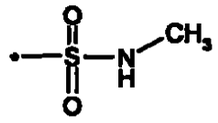
251

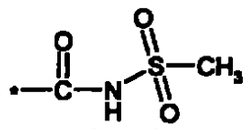
Realizaciones preferidas de los compuestos de Fórmula (1.0.0) en los que Z es un ácido de fósforo o azufre o un derivado de los mismos, y aquellos en los que Z es -$P(=O)(OH)NHR^{25}$ (fosforamido sustituido); -$S(=O)_2NHR^{26}$ o -$NHS(=O)_2R^{26}$ (sulfonamido); o -$C(=O)NHS(=O)_2R^{25}$ (acilsulfonamido); donde R^{26} y R^{25} tienen el mismo significado definido anteriormente. Algunas de estas realizaciones preferidas pueden ilustrarse mediante las Fórmulas parciales (6.5.1) a (6.5.9):

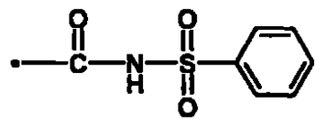

(6.5.1)

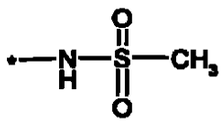

(6.5.2)

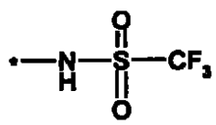

(6.5.3)

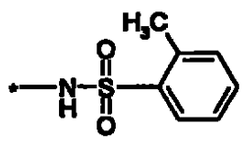

(6.5.4)


(6.5.5)


(6.5.6)


(6.5.7)

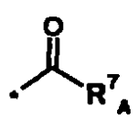

(6.5.8)


(6.5.9)

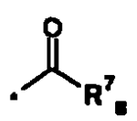
5.6.5 Z es un resto de Fórmulas parciales (1.1.6) a (1.1.9)

En otras realizaciones de los compuestos de Fórmula (1.0.0), el grupo terminal Z es un resto que es un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.1.6), (1.1.7), (1.1.8), y (1.1.9):

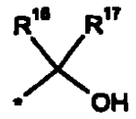
252



(1.1.6)



(1.1.7)



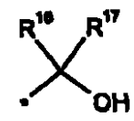
(1.1.8)



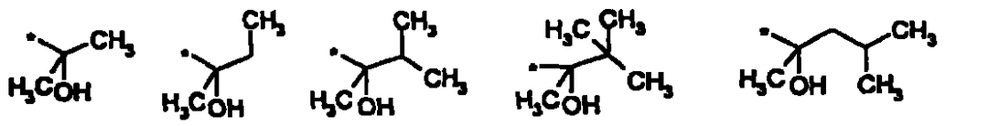
(1.1.9)

donde "*" indica el punto de unión del resto de la Fórmula parcial (1.1.6), (1.1.7), (1.1.8), o (1.1.9) a la porción restante de un compuesto de Fórmula (1.0.0); y R^7_A y R^7_B tienen ambos el mismo significado descrito anteriormente. R^{16} y R^{17} tienen también los mismos significados descritos anteriormente, es decir, cada uno se selecciona independientemente de: -H; -alquilo C_1-C_4; -alquenilo C_2-C_4; cicloalquilo C_3-C_6; fenilo; bencilo; y piridilo; en el que dicho alquilo, alquenilo, cicloalquilo, fenilo, bencilo, o piridilo está sustituido por 0 a 3 sustituyentes seleccionados del grupo constituido por -F, -Cl, -CF_3, -CN, y -alquilo C_1-C_3.

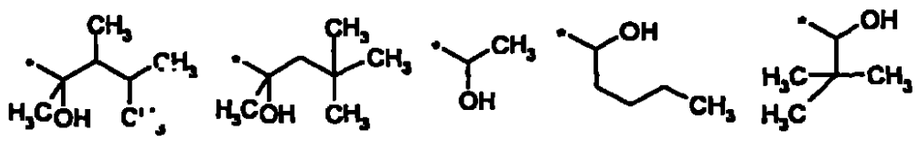
Para ilustrar los significados adicionales de Z que entran dentro del alcance de las Fórmulas parciales (1.1.6), (1.1.7), (1.1.8), y (1.1.9), a continuación se representan los restos de Fórmulas parciales (3.3.1) a (3.3.15) que representan los significados diferentes que entran dentro del alcance de la Fórmula parcial (1.1.8):



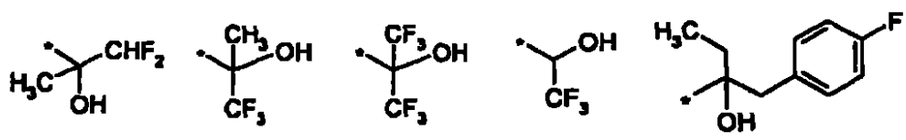
(1.1.8)



(3.3.1) (3.3.2) (3.3.3) (3.3.4) (3.3.5)

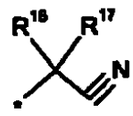


(3.3.6) (3.3.7) (3.3.8) (3.3.9) (3.3.10)

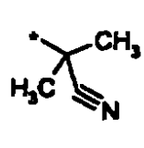


(3.3.11) (3.3.12) (3.3.13) (3.3.14) (3.3.15)

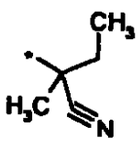
Los significados adicionales de **Z** son aquellos que entran dentro del alcance de la Fórmula parcial (1.1.9), en la que un grupo nitrilo, -C≡N, sustituye el grupo hidroxilo de Fórmula parcial (1.1.8). En consecuencia, a continuación se representan los restos de Fórmulas parciales (3.8.1) a (3.8.10) que representan significados diferentes que entran dentro del alcance de la Fórmula parcial (1.1.9):



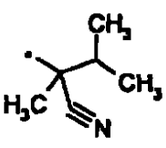
(1.1.9).



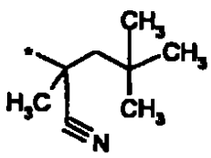
(3.8.1)



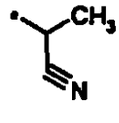
(3.8.2)



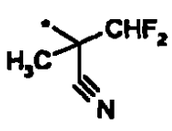
(3.8.3)



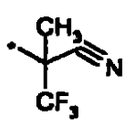
(3.8.4)



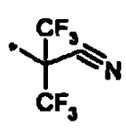
(3.8.5)



(3.8.6)



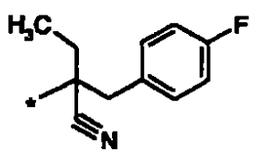
(3.8.7)



(3.8.8)

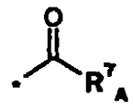


(3.8.9)



(3.8.10)

Para ilustrar los significados adicionales de Z que entran dentro del alcance de las Fórmulas parciales (1.1.6), (1.1.7), (1.1.8), y (1.1.9), a continuación se representan los restos de Fórmulas parciales (3.9.1) a (3.9.9) que representan los significados diferentes que entran dentro del alcance de la Fórmula parcial (1.1.6):

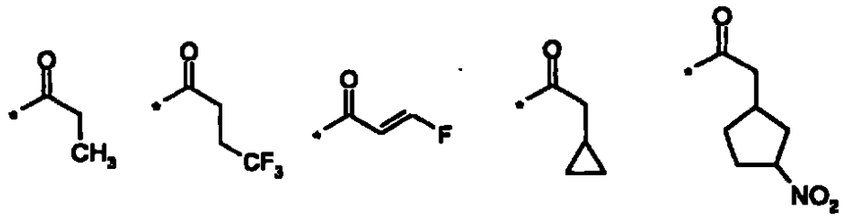


(1.1.6)

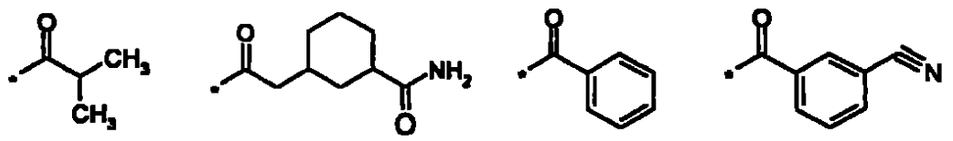
donde R^7_A se selecciona de -H; -alquilo C_1-C_6; -alquenilo C_2-C_6; o -alquinilo C_2-C_6; sustituido por 0 a 3 sustituyentes R^{10}. Preferiblemente, R^7_A es -H. R^7_A puede ser también -alquilo C_1-C_4 que no está sustituido o que está sustituido por 3 -F, o 1 R^{10} que es preferiblemente -F; -Cl; -CF_3; -NO_2; -NC-C(=O)$NR^{16}R^{17}$; o -$NR^{16}R^{17}$. R^7_A se selecciona además de -$(CH_2)_u$-cicloalquilo C_3-C_7 donde u es 0, 1 ó 2 sustituido por 0 a 3

sustituyentes R^{10}, que tiene los mismos significados preferidos definidos anteriormente. R^7_A se selecciona adicionalmente de fenilo o bencilo sustituido por 0 a 3 sustituyentes R^{10} que tienen los mismos significados preferidos definidos anteriormente.

En consecuencia, las realizaciones adicionales de **Z** que entran dentro del alcance de la Fórmula parcial (1.1.6) se ilustran en las Fórmulas parciales 3.9.1) a (3.9.9):



(3.9.1) (3.9.2) (3.9.3) (3.9.4) (3.9.5)



(3.9.6) (3.9.7) (3.9.8) (3.9.9)

<u>5.6.6 Z es un resto de Fórmulas parciales (1.1.10) a (1.1.15)</u>

Z es también un miembro seleccionado del grupo de restos definido por las Fórmulas parciales (1.1.10) a (1.1.15) ilustrado anteriormente. En los restos de Fórmulas parciales (1.1.10) a (1.1.14) el significado de **Z** está constituido por un grupo terminal R^7_C unido a la porción restante de la Fórmula (1.0.0) mediante lo que puede denominarse un grupo de enlace que comprende la porción restante de dichas Fórmulas parciales (1.1.10) a (1.1.14). R^7_C a su vez tiene el significado de un miembro seleccionado independientemente del grupo constituido por los significados de R^7_A y

256

los significados de R^7_B definidos anteriormente.

El grupo de enlace de Fórmula parcial (1.1.10) comprende una estructura de carbamoílo o amida inversa que puede representarse mediante la fórmula: -N(R^9)-C(=O)-, que se lee de izquierda a derecha. El sustituyente R^9 más frecuentemente tiene el significado de -H, de forma que dicho grupo de enlace de amida inversa puede representarse de la forma siguiente, leyendo de izquierda a derecha: -NHC-(=O)-. En consecuencia, cuando Z tiene el significado de la Fórmula parcial (1.1.10), las realizaciones preferidas de los compuestos de Fórmula (1.0.0) tendrán el siguiente extremo a la derecha: -NHC(=O)- R^7_C.

Z puede seleccionarse también como un resto definido por la Fórmula parcial (1.1-10). Cuando ambas apariciones de R^9 tienen el significado de -H como se prefiere, entonces las realizaciones resultantes de los compuestos de Fórmula (1.0.0) tendrán el siguiente extremo a la derecha: -NHC(=O)NH-R^7_C. De forma similar, cuando Z se selecciona como el resto definido por la Fórmula parcial (1.1.12) y el sustituyente R^9 tiene el significado de -H, entonces las realizaciones resultantes de los compuestos de Fórmula (1.0.0) tendrán el siguiente extremo a la derecha: -NHC(=O)O-R^7_C.

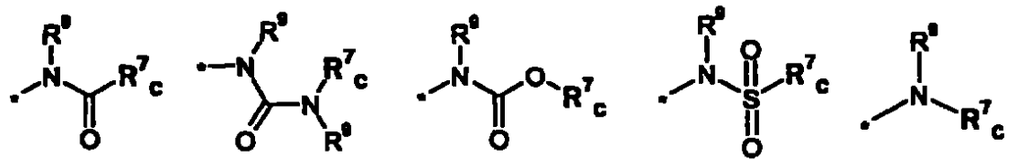
Z puede seleccionarse también como un resto definido por las Fórmulas parciales (1.1.13) o (1.1.14), y en el caso en que el sustituyente R^9 tiene el significado preferido de -H, las realizaciones resultantes de los compuestos de Fórmula (1.0.0) tendrán los siguientes extremos a la derecha: -NHS(=O)$_2$-R^7_C y -NH-R^7_C. Los significados de Z definidos por las Fórmulas parciales (1.1.13) y (1.1.14) no son, sin embargo, igual de preferidos que los significados de Z definidos por las fórmulas parciales (1.1.10) y (1.1.11), y algunas veces (1.1.12).

Finalmente, Z puede seleccionarse como el resto definido por la Fórmula parcial (1.1-6) en la que se une un átomo de nitrógeno mediante un enlace directo a la porción

restante de un compuesto de Fórmula (1.0.0). En algunas realizaciones preferidas, un átomo de carbono en dicho heterociclo que contiene nitrógeno de un heterociclo que está en posición relativa α a dicho nitrógeno puede ser carbonilo, es decir, sustituido con oxo (=O). Los significados preferidos de Z en los compuestos de Fórmula (1.0.0) son los definidos por las Fórmulas parciales (1.1.10) y (1.1.15).

5.6.7 Z es un resto de Fórmulas parciales (1.1.10) a (1.1.14)

Las realizaciones de la presente invención en las que la definición del grupo Z está ilustrada por las Fórmulas parciales (1.1.10); (1.1.11); (1.1.12); (1.1.13); y (1.1.14), son las siguientes:



(1.1.10) (1.1.11) (1.1.12) (1.1.13) (1.1.14)

Uno de un número de restos preferidos para definir el grupo Z es el de Fórmula parcial (1.1.10) donde R^7_C tiene el significado de -alquilo C_1-C_4, preferiblemente metilo, etilo, *n*-propilo, *iso*-propilo, o *terc*-butilo; cicloalquilo C_3-C_6; preferiblemente ciclopropilo, ciclobutilo, ciclopentilo, o ciclohexilo, todos los cuales están unidos directamente o mediante un puente metileno; fenilo; bencilo; o un heterociclo, preferiblemente pirrolilo, pirrolidinilo, imidazolilo, triazolilo; tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, indazolilo, indolilo, isoindolilo, bencimidazolilo, benzoisoxazolilo, benzotriazolilo, quinolinilo, isoquinolinilo, 1,6-naftiridinilo, 1,8-naftiridinilo, o quinazolinilo.

R^9 es un sustituyente que aparece en cada uno de los restos Z representados por las Fórmulas parciales (1.1.10); (1.1.11); (1.1.12); (1.1.13); y (1.1.14). R^9 tiene el significado de -H; -alquil C_1-C_4, preferiblemente metilo; -cicloalquilo C_3-C_7,

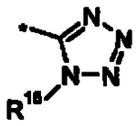
preferiblemente ciclopropilo o ciclopentilo; fenilo; bencilo; piridilo; -OR^{18}; -alquil (C_1-C_2)-OR^{18}; y -alquilo (C_1-C_2)-C(=O)OR^{18}; donde R^{18} es -H o -alquilo C_1-C_4. R^{18} es preferiblemente -H o -CH_3.

R^{10} es un sustituyente opcional de los restos preferidos descritos anteriormente que definen $R^7{}_C$, y puede haber hasta tres sustituyentes así cuando están presentes. El significado del sustituyente R^{10} incluye fenilo o piridilo donde dicho fenilo o piridilo está a su vez sustituido opcionalmente con hasta 3 sustituyentes R^{12} donde R^{12} 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 tal sustitución R^{12}, habrá 1 ó 2 sustituyentes R^{12} que tienen el significado de -F, -Cl, -CH_3, -OCH_3, -OH, -CN, o -$N(CH_3)_2$. El significado del sustituyente R^{10} incluye adicionalmente -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)$_2R^{17}$; o -S(=O)$_2NR^{16}R^{17}$. Preferidos entre los significados referidos anteriormente del sustituyente R^{10} están -F; -Cl; -CF_3; oxo (=O); -OH, -OCH_3, -NO_2, -CN, -C(=O)OH, -C(=O)NH_2, -NH_2, -$N(CH_3)_2$, o -NHS(=O)$_2CH_3$.

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; o piridilo. Dichos grupos alquilo, alquenilo, cicloalquilo, fenilo, bencilo, o piridilo están a su vez opcionalmente sustituidos con hasta 3 sustituyentes -F, -Cl, o -CN.

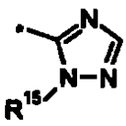
Como ilustración de las realizaciones subgenéricas preferidas de la presente invención en las que el grupo Z tiene el significado de un resto de Fórmulas parciales (1.1.10) a (1.1.14), se exponen a continuación cicloalquilo, fenilo, bencilo, *o*-tolilo, que es un significado preferido de $R^7{}_C$ en los restos sulfonamido de Fórmula parcial (1.1.12)

y los grupos heterociclos monocíclicos que definen R^7_C, de Fórmulas parciales (7.0.1) a (7.0.39):



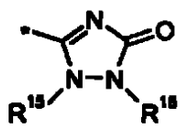
tetrazol-5-ilo

(7.0.1)



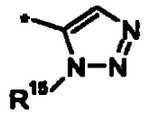
1,2,4-triazol-3-ilo

(7.0.2)



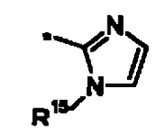
1,2,4-triazol-3-on-5-ilo

(7.0.3)



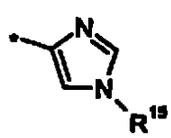
1,2,3-triazol-5-ilo

(7.0.4)



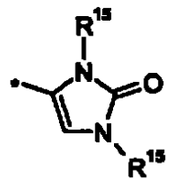
imidazol-2-ilo

(7.0.5)



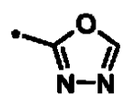
imidazol-4-ilo

(7.0.6)



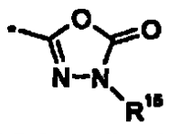
imidazolidin-2-on-4-ilo

(7.0.7)



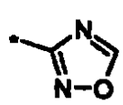
1,3,4-oxadiazolilo

(7.0.8)



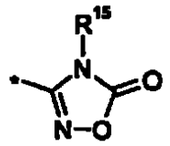
1,3,4-oxadiazol-2-on-5-ilo

(7.0.9)



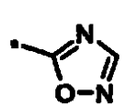
1,2,4-oxadiazol-3-ilo

(7.0.10)



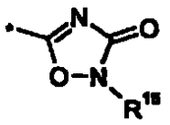
1,2,4-oxadiazol-5-on-3-ilo

(7.0.11)



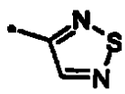
1,2,4-oxadiazol-5-ilo

(7.0.12)



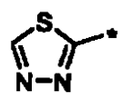
1,2,4-oxadiazol-3-on-5-ilo

(7.0.13)



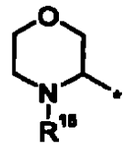
1,2,5-tiadiazol-2-ilo

(7.0.14)



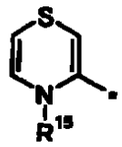
1,3,4-tiadiazolilo

(7.0.15)



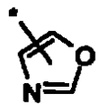
morfolin-3-ilo

(7.0.16)



paratiazin-3-ilo

(7.0.17)



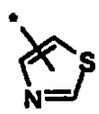
oxazolilo

(7.0.18)



isoxazolilo

(7.0.19)



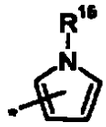
tiazolilo

(7.0.20)



isotiazolilo

(7.0.21)



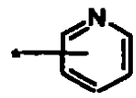
pirrolilo

(7.0.22)



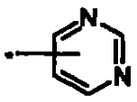
pirazolilo

(7.0.23)



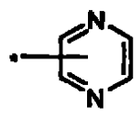
piridilo

(7.0.24)



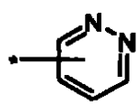
pirimidinilo

(7.0.25)



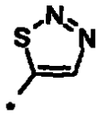
pirazinilo

(7.0.26)



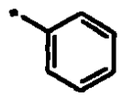
piridazinilo

(7.0.27)

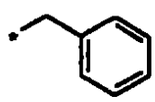


1,2,3-tiadiazol-5-ilo

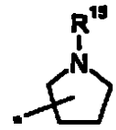
(7.0.28)



fenilo
(7.0.29)



bencilo
(7.0.30)



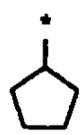
pirrolidinilo
(7.0.31)



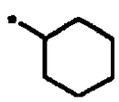
ciclopropilo
(7.0.32)



ciclobutilo
(7.0.33)



ciclopentilo
(7.0.34)



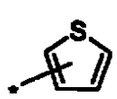
ciclohexilo
(7.0.35)



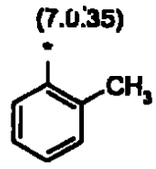
furanilo
(7.0.36)



tetrahidrofuranilo
(7.0.37)



tienilo
(7.0.38)



o-tolilo
(7.0.39)

donde "*" indica el punto de unión de cada Fórmula parcial (7.0.1.) a (7.0.39) a la porción restante de Fórmula (1.0.0); y donde cada átomo de carbono de las Fórmulas parciales (7.0.1.) a (7.0.39) está sustituido opcionalmente con un sustituyente R^{14}; y donde R^{14} y R^{15} tienen el mismo significado que se define anteriormente, y todas las formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

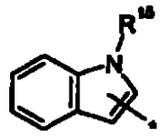
No se muestran sustituyentes R^9 en las Fórmulas parciales (7.0.1.) a (7.0.39) anteriores porque el sustituyente R^9 está unido únicamente a un átomo de nitrógeno que no forma una parte integral componente de un resto heterociclo unido. El sustituyente R^9 es de carácter opcional en tanto en cuanto "-H" está incluido como definición del sustituyente R^9, y en muchas de las realizaciones de los compuestos de Fórmula (1.0.0) este es el significado preferido de R^9. Otro significado preferido de R^9 es $-CH_3$.

Se apunta también la distinción entre los sustituyentes R^9 y R^{15}, los cuales están unidos ambos únicamente a átomos de nitrógeno en cualquiera de los significados del resto Z. El sustituyente R^{15} está unido únicamente a un átomo de nitrógeno que es una parte integral componente de cualquier resto heterociclo que pude definirse mediante el sustituyente R^7_C en las Fórmulas parciales (1.1.10) a (1.1.14) y en particular con referencia a los restos heterociclo más específicos de Fórmulas parciales (7.0.1.) a (7.0.28) y (7.0.31). El sustituyente R^9, por otra parte, se une sólo a un átomo de nitrógeno que a su vez está unido, pero no es una parte integral componente de ninguno de los restos heterociclo que están definidos por las Fórmulas parciales (1.1.10) a (1.1.14). El sustituyente R^{15} puede estar unido a uno o más átomos de nitrógeno y dichos átomos de nitrógeno pueden estar presentes en cualquier resto que entre dentro del alcance de las Fórmulas parciales (1.1.10) a (1.1.14) que pueden caracterizarse como que contienen o comprenden un resto heterociclo que contiene nitrógeno.

Las realizaciones preferidas de la presente invención donde el grupo Z es un resto de Fórmulas parciales (1.1.10) a (1.1.14) incluyen también aquellas en las que el resto R^7_C es un grupo heterociclo bicíclico seleccionado del grupo constituido por indolilo; indolinilo; isoindolinilo; benzo[*b*]furanilo; 2,3-dihidrobenzofuranilo; 1,3-dihidroisobenzofuranilo; 2*H*-1-benzopiranilo; cromanilo; benzotienilo; 1*H*-indazolilo; bencimidazolilo; benzoxazolilo; bencisoxazolilo; benzotiazolilo; benzotriazolilo; ftalazinilo; 1,6-naftiridinilo; 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.

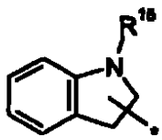
Para proporcionar una demostración adicional más de realizaciones preferidas de los compuestos de Fórmula (1.0.0) con referencia al grupo Z donde es un resto de Fórmulas parciales (1.1.10) a (1.1.14) y R^7_C es un grupo heterociclo bicíclico, a

continuación se muestran los grupos constituidos por las Fórmulas parciales (7.5.1.) a (7.5.29) a partir de la que se selecciona el resto Z en tales realizaciones preferidas:



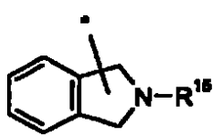
indolilo

(7.5.1)



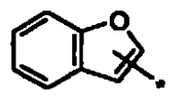
indolinilo

(7.5.2)



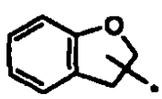
isoindolinilo

(7.5.3)



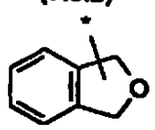
benzo[*b*]furanilo

(7.5.4)



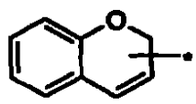
2,3-dihidrobenzo-furanilo

(7.5.5)



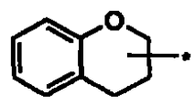
1,3-dihidroisobenzo-furanilo; ftalanilo

(7.5.6)



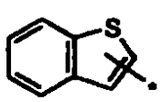
2*H*-1-benzopiranilo

(7.5.7)



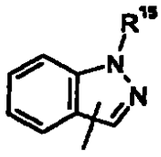
cromanilo

(7.5.8)



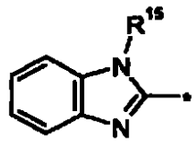
benzotienilo

(7.5.9)



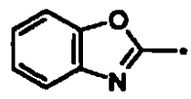
1*H*-indazolilo

(7.5.10)



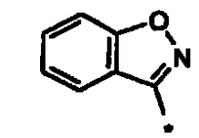
bencimidazolilo

(7.5.11)



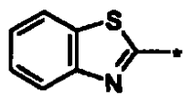
benzoxazolilo

(7.5.12)



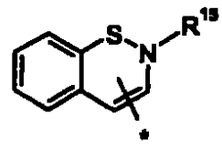
benzoisoxazolil

(7.5.13)



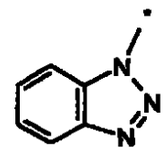
benzotiazolilo

(7.5.14)



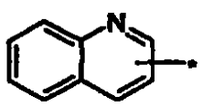
2*H*-1,2-benzotiazinilo

(7.5.15)



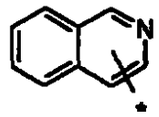
benzotriazolilo

(7.5.16)



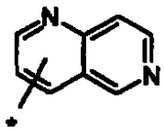
quinolinilo

(7.5.17)



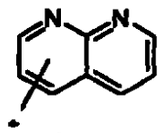
isoquinolinilo

(7.5.18)



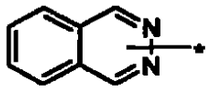
1,6-naftiridinilo

(7.5.19)



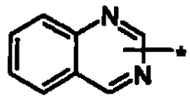
1,8-naftiridinilo

(7.5.20)



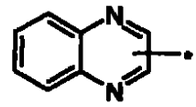
ftalazinilo

(7.5.21)



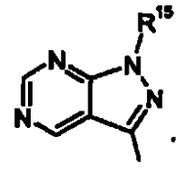
quinazolinilo

(7.5.22)



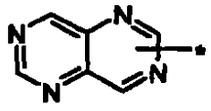
quinoxalinilo

(7.5.23)



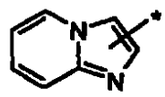
1*H*-pirazolo[3,4-*d*]-pirimidinilo

(7.5.24)



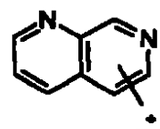
pirimido [5,4-*d*]-pirimidinilo

(7.5.25)



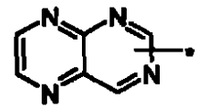
imidazo- [1,2-*a*]-piridinilo

(7.5.26)



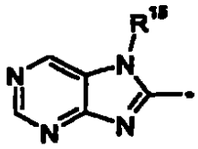
1,7-naftiridinilo

(7.5.27)



pteridilo

(7.5.28)



1*H*-purinilo

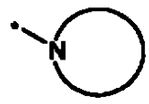
(7.5.29)

donde "*" indica el punto de unión a la porción restante de Fórmula (1.0.0); y donde cada átomo de carbono está sustituido opcionalmente con un sustituyente R^{14}; y donde R^{14} y R^{15} tienen el mismo significado que se define anteriormente, y todas las

formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

5.6.8 Z es un resto de Fórmula parcial (1.1.15)

Las realizaciones preferidas de la presente invención comprenden también aquellos compuestos de Fórmula (1.0.0) en los que el resto terminal Z entra dentro del alcance de la Fórmula parcial (1.1.15), es decir las realizaciones de este tipo están comprendidas en el alcance del resto Z cuando tiene el significado de la Fórmula parcial (1.1.15):



(1.1.15)

Se entenderá que cuando el resto terminal Z está definido por la Fórmula parcial (1.1.15), inherentemente comprende un grupo heterociclo que contiene nitrógeno. Uno cualquiera o más átomos de carbono de dicho grupo heterociclo está sustituido por 0 a 3 sustituyentes R^{14}. En consecuencia, R^{14} es un sustituyente opcional de uno cualquiera o más, hasta un total de tres, de los átomos de carbono de los restos que se incluyen en el alcance de la Fórmula parcial (1.1.6). Dicho sustituyente R^{14} comprende -alquilo C_1-C_4, preferiblemente -CH_3; -cicloalquilo C_3-C_7, preferiblemente ciclopropilo; fenilo; bencilo; piridilo; o quinolinilo; donde dicho resto alquilo, cicloalquilo, fenilo, bencilo, piridilo, o quinolinilo está a su vez opcionalmente sustituido con 1 ó 2 sustituyentes -F, -Cl, -CH_3, -OCH_3, -OR^{16}, -CN, o -$NR^{16}R^{17}$. En las realizaciones preferidas R^{16} y R^{17} son independientemente -H, o -CH_3. Cuando R^{14} está sustituido, se prefiere que el sustituyente sea -F o -Cl. El sustituyente R^{14} comprende 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-

$C(=O)NR^{16}R^{17}$; $-NR^{16}C(=O)R^{17}$ $-NR^{16}R^{17}$; $-NR^{16}C(=O)OR^{17}$; $-NR^{16}S(=O)_2R^{17}$; y $-S(=O)_2NR^{16}R^{17}$. Además de las realizaciones preferidas indicadas anteriormente, cuando R^{14} está presente se prefiere además que tenga el significado de -F, -Cl, $-CF_3$, $-OCH_3$, -CN, o $-NO_2$.

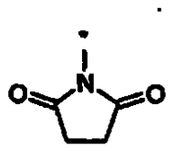
Uno cualquiera o más átomos de nitrógeno incluidos en dichos grupos heterociclos que contienen nitrógeno incluidos en el alcance de la Fórmula parcial (1.1.15), siempre que no sean un punto de unión de dicho grupo heterociclo, están sustituidos opcionalmente con hasta tres sustituyentes R^{15}. Cualquier átomo de azufre presente en dicho grupo heterociclo, siempre que no sea un punto de unión de dicho grupo heterociclo, está sustituido con 0, 1, ó 2 átomos de oxígeno.

El sustituyente heterociclo con nitrógeno opcional R^{15} comprende -H, $-C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$; -alquilo C_1-C_4, preferiblemente $-CH_3$; -alquenilo C_2-C_4; -alcoxi C_2-C_4, preferiblemente $-OCH_3$; -cicloalquilo C_3-C_7, preferiblemente ciclopropilo; fenilo; o bencilo, en el que dicho alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, o bencilo están sustituidos opcionalmente con hasta dos sustituyentes R^{11}.

El sub-sustituyente R^{11} comprende -F; -Cl; $-CO_2R^{18}$; $-OR^{16}$; -CN; $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$; $-NR^{18}C(=O)OR^{19}$; $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, donde p es 1 ó 2, preferiblemente 2; -alquilo C_1-C_4, preferiblemente $-CH_3$; y -alcoxi C_1-C_4, cuando R^{11} tiene el significado de $-OR^{16}$ anterior y R^{16} se define como -alquilo C_1-C_4, preferiblemente $-OCH_3$; cuando dicho alquilo y alcoxi están cada uno a su vez opcionalmente sustituidos con 0 a 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} comprenden -H; o alquilo C_1-C_2, preferiblemente $-CH_3$; opcionalmente sustituido con hasta 3 -F; o -Cl.

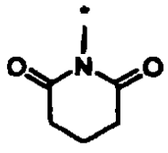
La presente invención concierne además un compuesto de Fórmula (1.0.0) en el

que el grupo terminal Z tiene el significado de un resto de Fórmula parcial (1.1.15) donde el número y posición de los átomos de carbono y el reemplazo de los mismo por uno o más heteroátomos, así como la sustitución de uno o más de dichos átomos de carbono por R^{14} donde R^{14} es oxo (=O), se seleccionan de tal forma que Z comprende un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.7.1) a (1.7.46):



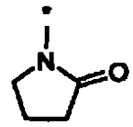
Succinimid-1-ilo

(1.7.1)



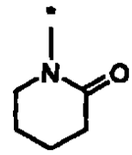
glutarimid-1-ilo

(1.7.2)



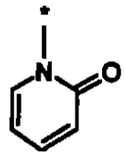
pirrolidin-2-on-1-ilo

(1.7.3)



piperid-2-on-1-ilo

(1.7.4)



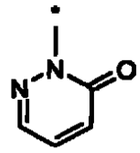
pirid-2-on-1-ilo

(1.7.5)



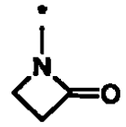
pirid-4-on-1-ilo

(1.7.6)



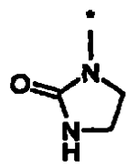
piridazin-3-on-2-ilo

(1.7.7)



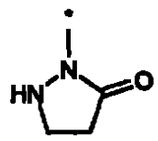
azetidin-2-on-1-ilo

(1.7.8)



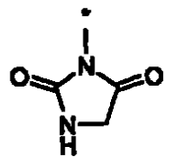
imidazolidin-2-on-1-ilo

(1.7.9)



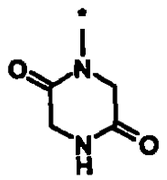
pirazol-5-on-1-ilo

(1.7.10)



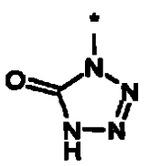
imidazolidin-2,4-dion-1-ilo

(1.7.11)



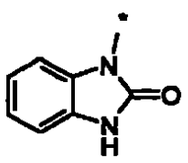
piperazin-2,5-dion-1-ilo

(1.7.12)



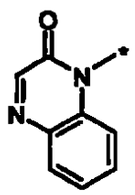
4,5-dihidro-5-oxo 1*H*-tetrazol-1-ilo

(1.7.13)



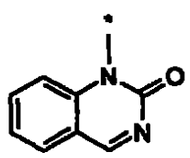
bencimidazolin-2-on-1-ilo

(1.7.14)



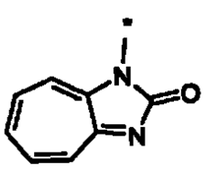
1*H*-quinoxalin-2-on-1-ilo

(1.7.15)



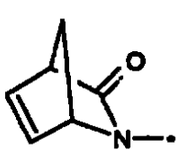
1*H*-quinazolin-2-on-1-ilo

(1.7.16)



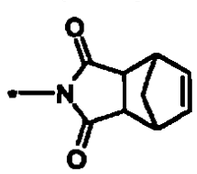
1*H*-cicloheptimidazol-2-on-1-ilo

(1.7.17)



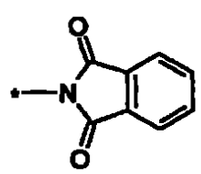
2-azabiciclo[2,2,1]-hept-5-en-3-on-1-ilo 1*H*-tetrazol-1-ilo

(1.7.18)



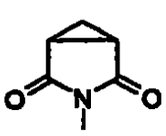
norborn-5-en-2,3-dicarboximid-1-ilo 1*H*-tetrazol-1-ilo

(1.7.19)



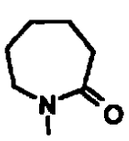
ftalimid-1-ilo; 1*H*-isoindol-1,3(2*H*)-dion-1-ilo

(1.7.20)



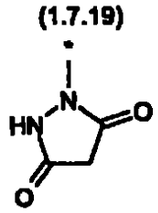
3-azabiciclo[3,1,0]-hexano-2,4-dion-3-ilo

(1.7.21)



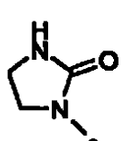
2*H*-azepin- 2-on-1-ilo

(1.7.22)



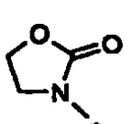
pirazolidin-3,5-dion-1-ilo

(1.7.23)



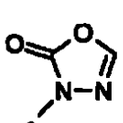
imidazolidin-2-on-1-ilo

(1.7.24)



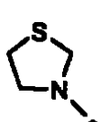
oxazolidin-2-on-1-ilo

(1.7.25)



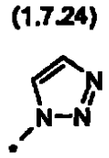
1,3,4-oxadiazol-2(3*H*)-on-3-ilo

(1.7.26)



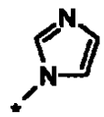
tiazolidin-3-ilo

(1.7.27)



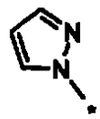
1*H*-1,2,3-triazol-1-ilo

(1.7.28)



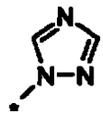
imidazol-1-ilo

(1.7.29)



pirazol-1-ilo

(1.7.30)



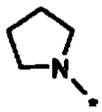
1*H*-1,2,4-triazol-1-ilo

(1.7.31)



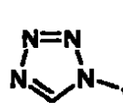
azetidin-1-ilo

(1.7.32)



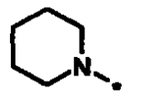
pirrolidin-1-ilo

(1.7.33)



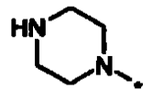
tetrazol -1-ilo

(1.7.34)



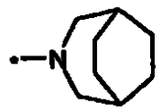
piperidin-1-ilo

(1.7.35)



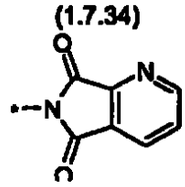
piperazin-1-ilo

(1.7.36)



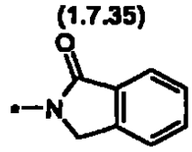
3-azabiciclo[3.2.2]-non-3-ilo

(1.7.37)



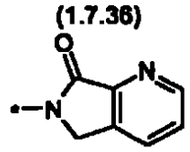
pirrolo[3,4-*b*]piridin-5,7-dion-6-ilo

(1.7.38)



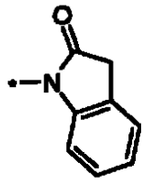
2,3-dihidro-*iso*-indol-1-on-2-ilo

(1.7.39)



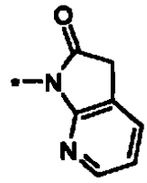
pirrolo[3,4-*b*]piridin-7-on-6-ilo

(1.7.40)



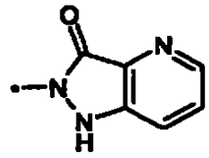
1,3-dihidro-indol-2-on-1-ilo

(1.7.41)



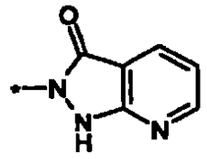
pirrolo[4,5-*b*]piridin-2-on-2-ilo

(1.7.42)



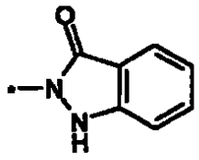
1*H*-pirazolo[4,5-*e*]piridin-7-on-2-ilo

(1.7.43)



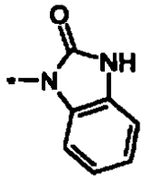
1*H*-pirazolo[4,5-*b*]piridin-4-on-2-ilo

(1.7.44)



1*H*-indazol-3-on-2-ilo

(1.7.45)



1*H*-bencimidazol-2-on-3-ilo

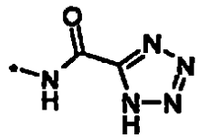
(1.7.46)

Cualquier resto que es un miembro seleccionado del grupo constituido por las

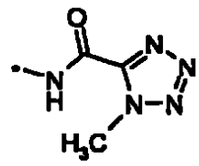
270

Fórmulas parciales (1.7.1) a (1.7.46) representadas anteriormente, incluye la sustitución opcional del mismo con respecto a *(1)* cualesquiera uno o más átomos de carbono del mismo, mediante un sustituyente R^{14} donde R^{14} tiene el mismo significado definido anteriormente; *(2)* cualesquiera uno o más átomos de nitrógeno del mismo, mediante un sustituyente R^{15} donde R^{15} tiene el mismo significado definido anteriormente, y todas las formas tautómeras, y opcionalmente las formas de N-óxido del mismo; o *(3)* un átomo cualquiera de azufre del mismo con 0, 1, ó 2 átomos de oxígeno.

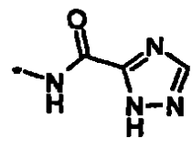
La presente invención se ilustra adicionalmente con respecto a los grupos subgenéricos preferidos que comprenden los compuestos de Fórmula (1.0.0) en los que R^7_C y R^9 de Fórmulas parciales (1.1.10) a (1.1.15) se seleccionan de tal forma que **Z** comprende un miembro seleccionado del grupo constituido por las siguientes Fórmulas parciales (8.0.1) a (8.0.139):



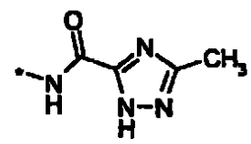
(8.0.1)



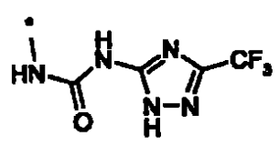
(8.0.2)



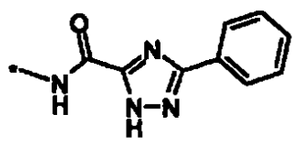
(8.0.3)



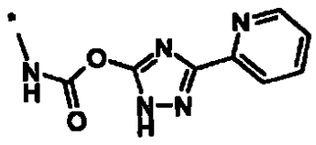
(8.0.4)



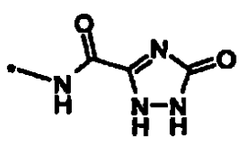
(8.0.5)



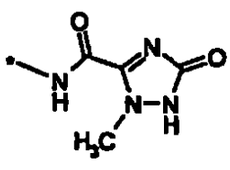
(8.0.6)



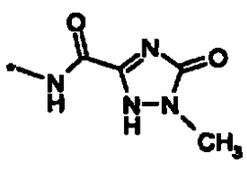
(8.0.7)



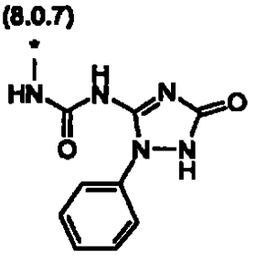
(8.0.8)



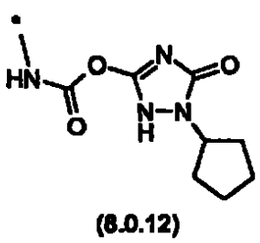
(8.0.9)



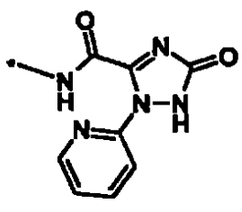
(8.0.10)



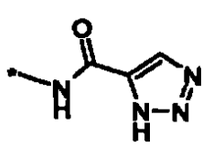
(8.0.11)



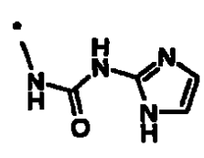
(8.0.12)



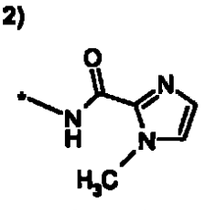
(8.0.13)



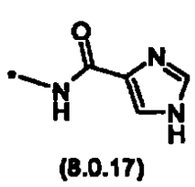
(8.0.14)



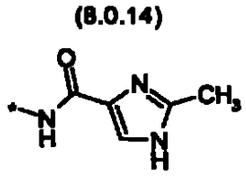
(8.0.15)



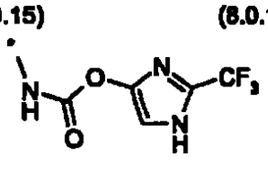
(8.0.16)



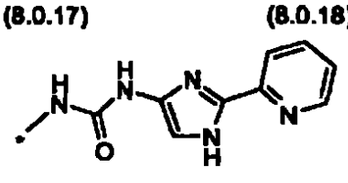
(8.0.17)



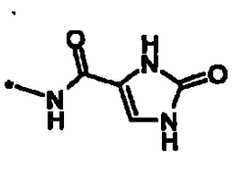
(8.0.18)



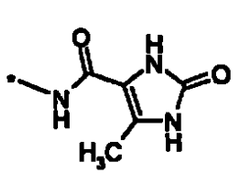
(8.0.19)



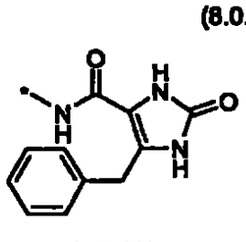
(8.0.20)



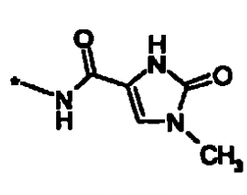
(8.0.21)



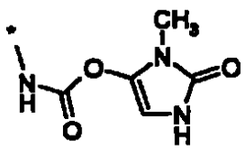
(8.0.22)



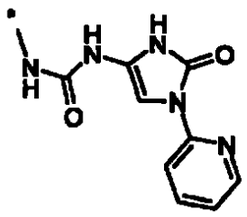
(8.0.23)



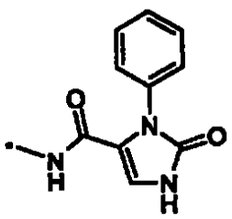
(8.0.24)



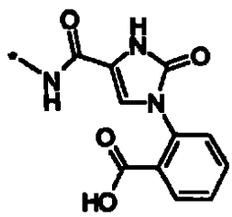
(8.0.25)



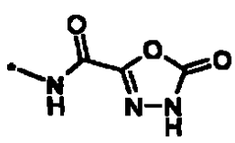
(8.0.26)



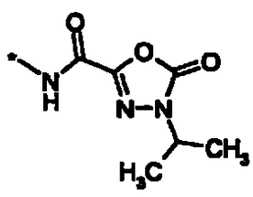
(8.0.27)



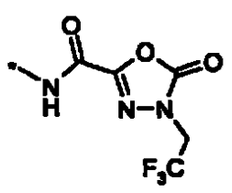
(8.0.28)



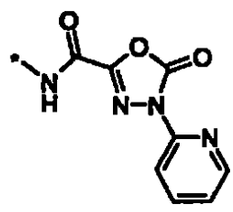
(8.0.29)



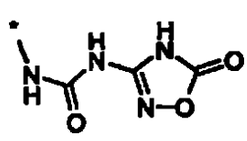
(8.0.30)



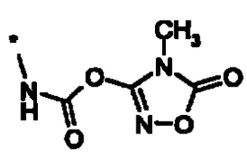
(8.0.31)



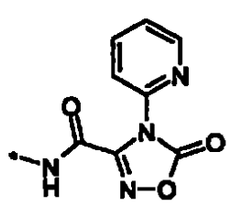
(8.0.32)



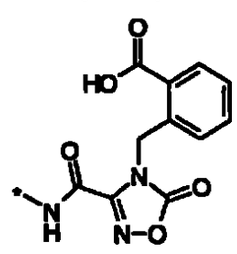
(8.0.33)



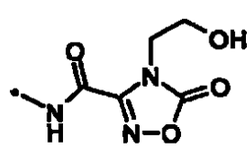
(8.0.34)



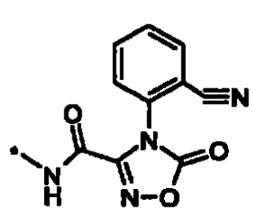
(8.0.35)



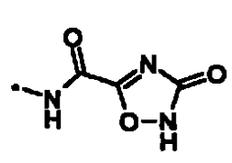
(8.0.36)



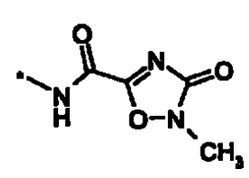
(8.0.37)



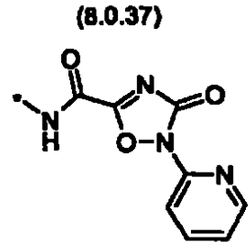
(8.0.38)



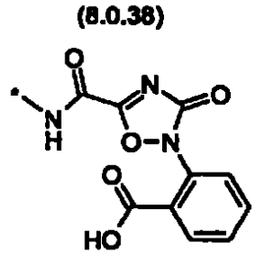
(8.0.39)



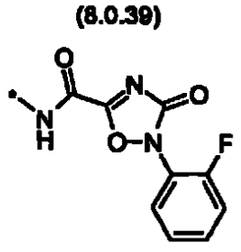
(8.0.40)



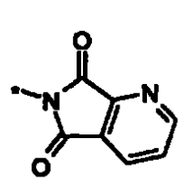
(8.0.41)



(8.0.42)

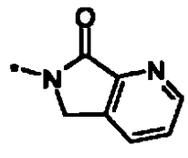


(8.0.43)

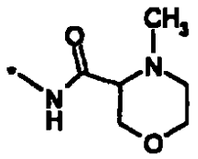


(8.0.44)

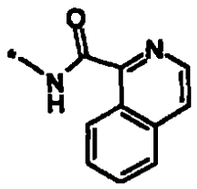
273



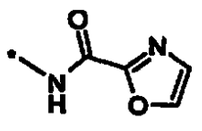
(8.0.45)



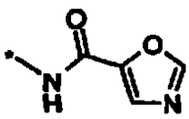
(8.0.46)



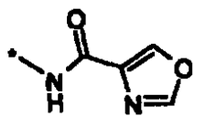
(8.0.47)



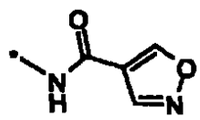
(8.0.48)



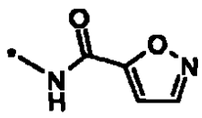
(8.0.49)



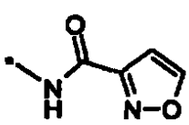
(8.0.50)



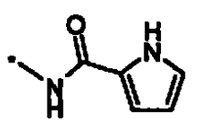
(8.0.51)



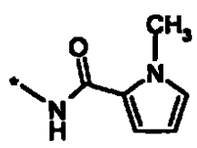
(8.0.52)



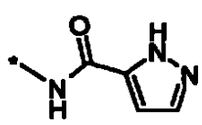
(8.0.53)



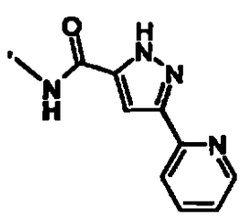
(8.0.54)



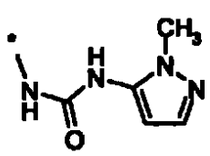
(8.0.55)



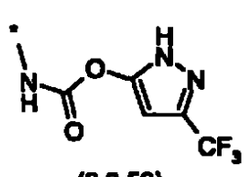
(8.0.56)



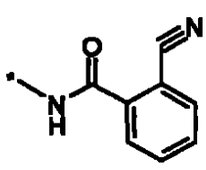
(8.0.57)



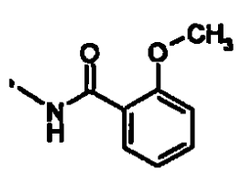
(8.0.58)



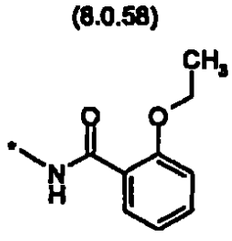
(8.0.59)



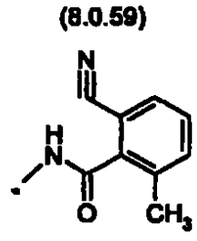
(8.0.60)



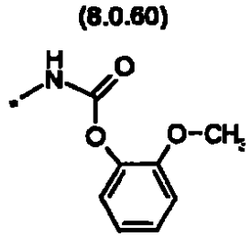
(8.0.61)



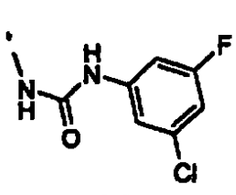
(8.0.62)



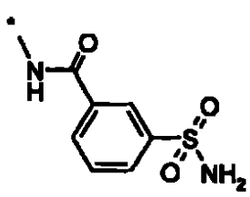
(8.0.63)



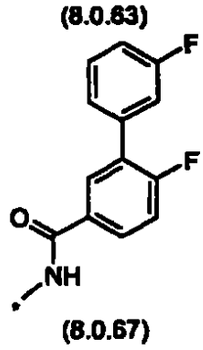
(8.0.64)



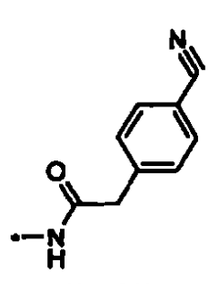
(8.0.65)



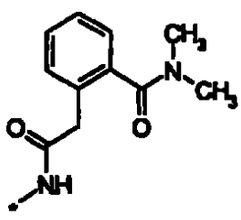
(8.0.66)



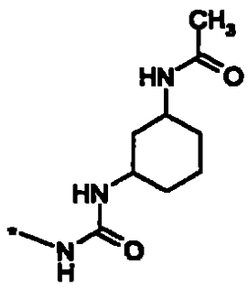
(8.0.67)



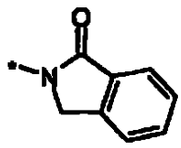
(8.0.68)



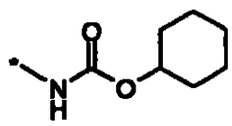
(8.0.69)



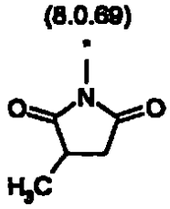
(8.0.70)



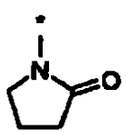
(8.0.71)



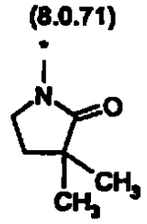
(8.0.72)



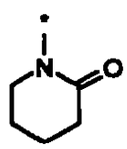
(8.0.73)



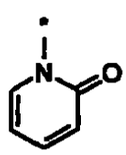
(8.0.74)



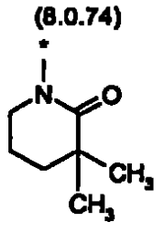
(8.0.75)



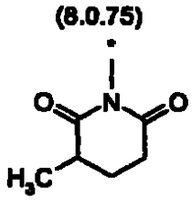
(8.0.76)



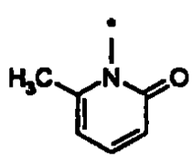
(8.0.77)



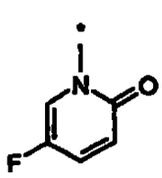
(8.0.78)



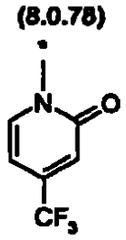
(8.0.79)



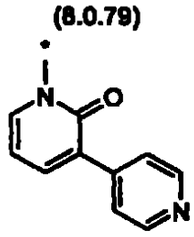
(8.0.80)



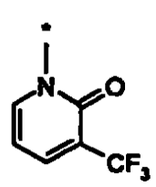
(8.0.81)



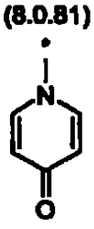
(8.0.82)



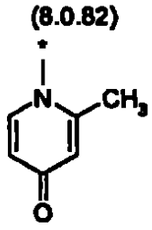
(8.0.83)



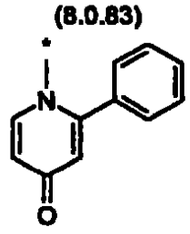
(8.0.84)



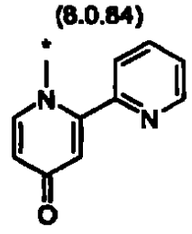
(8.0.85)



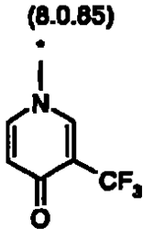
(8.0.86)



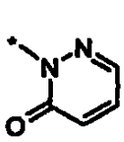
(8.0.87)



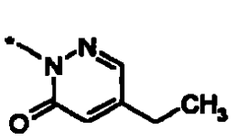
(8.0.88)



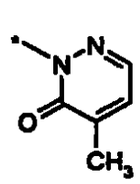
(8.0.89)



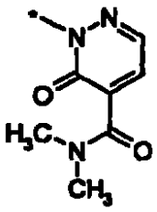
(8.0.90)



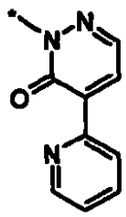
(8.0.91)



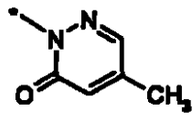
(8.0.92)



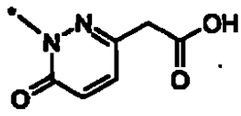
(8.0.93)



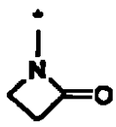
(8.0.94)



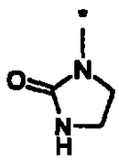
(8.0.95)



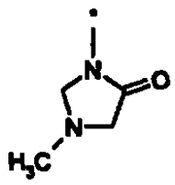
(8.0.96)



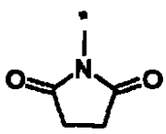
(8.0.97)



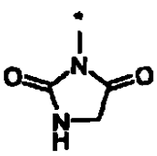
(8.0.98)



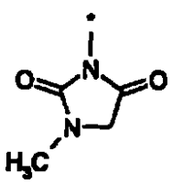
(8.0.99)



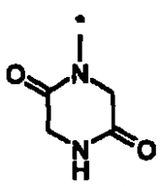
(8.0.100)



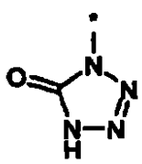
(8.0.101)



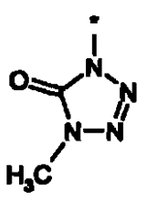
(8.0.102)



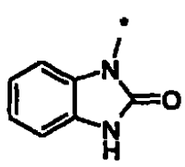
(8.0.103)



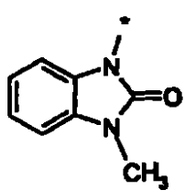
(8.0.104)



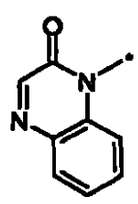
(8.0.105)



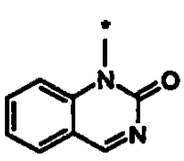
(8.0.106)



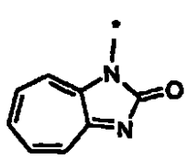
(8.0.107)



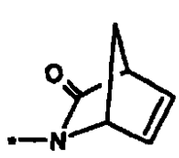
(8.0.108)



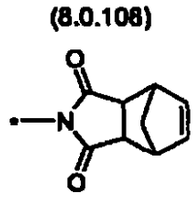
(8.0.109)



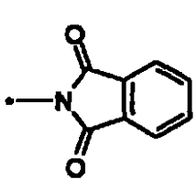
(8.0.110)



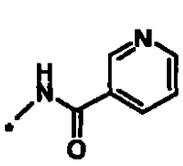
(8.0.111)



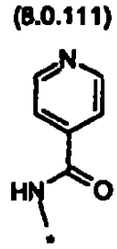
(8.0.112)



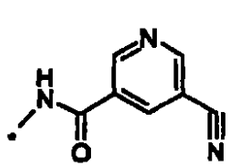
(8.0.113)



(8.0.114)

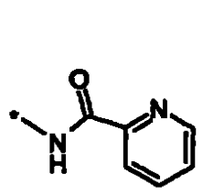


(8.0.115)

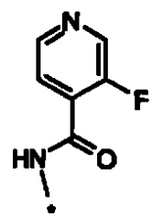


(8.0.116)

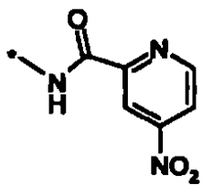
276



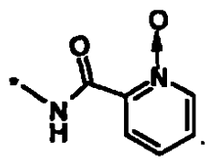
(8.0.117)



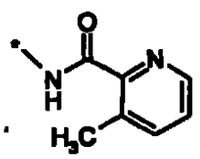
(8.0.118)



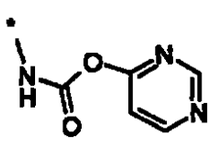
(8.0.119)



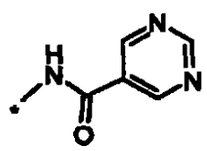
(8.0.120)



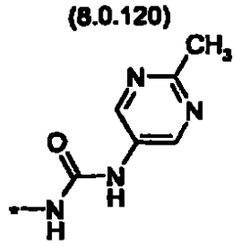
(8.0.121)



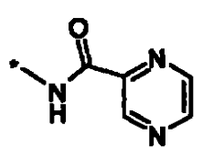
(8.0.122)



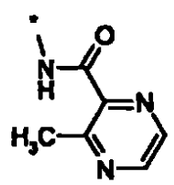
(8.0.123)



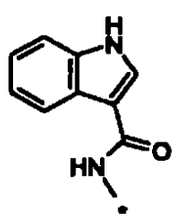
(8.0.124)



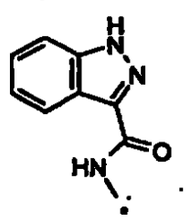
(8.0.125)



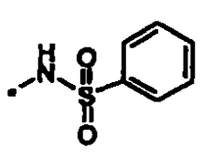
(8.0.126)



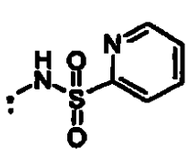
(8.0.127)



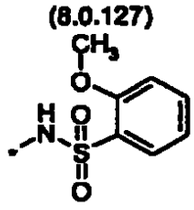
(8.0.128)



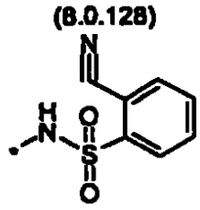
(8.0.129)



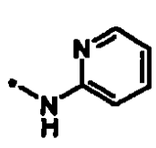
(8.0.130)



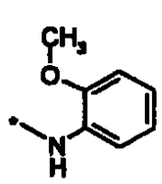
(8.0.131)



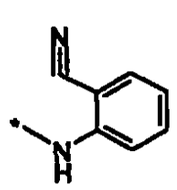
(8.0.132)



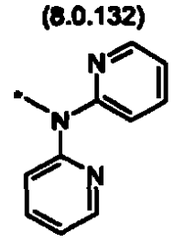
(8.0.133)



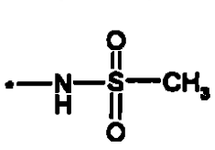
(8.0.134)



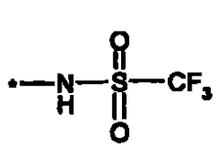
(8.0.135)



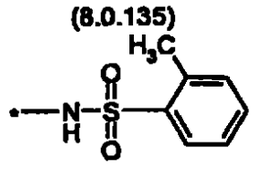
(8.0.136)



(8.0.137)



(8.0.138)



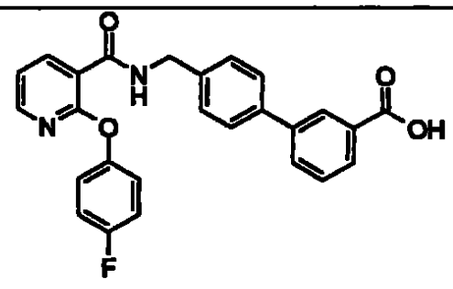
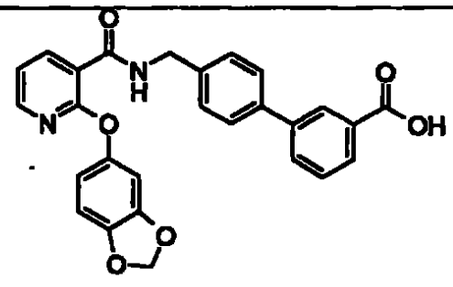
(8.0.139)

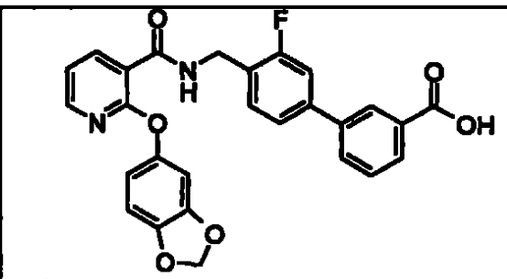
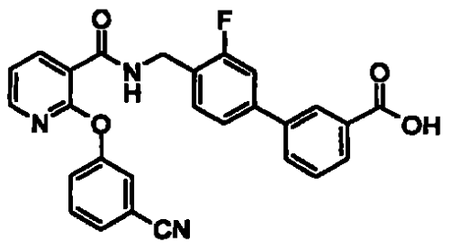
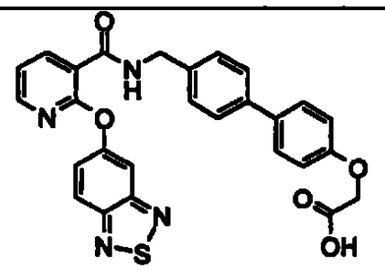
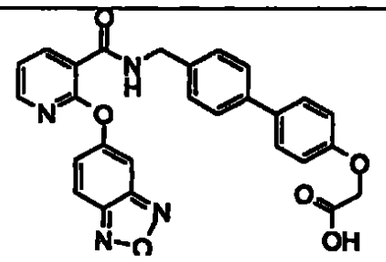
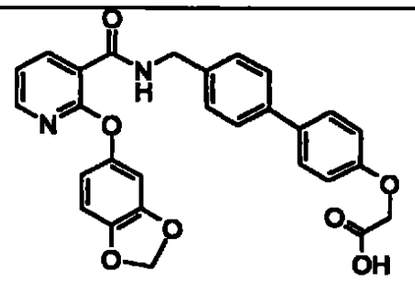
Cualquier resto que es un miembro seleccionado del grupo constituido por las

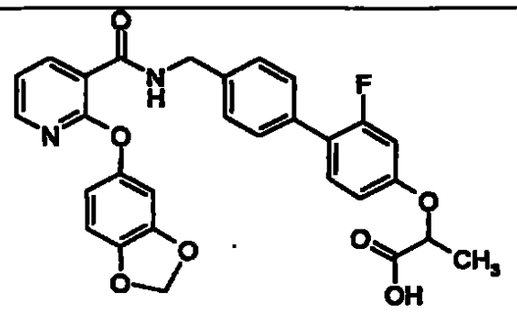
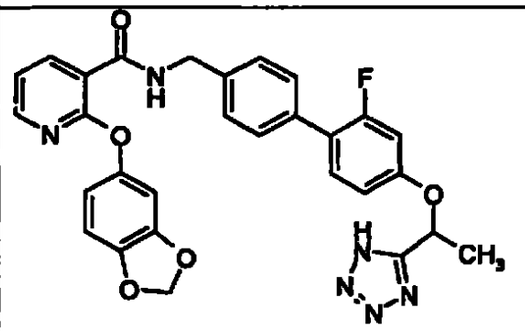
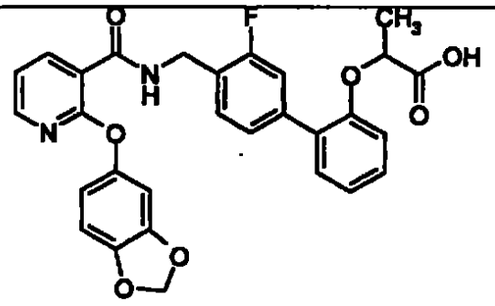
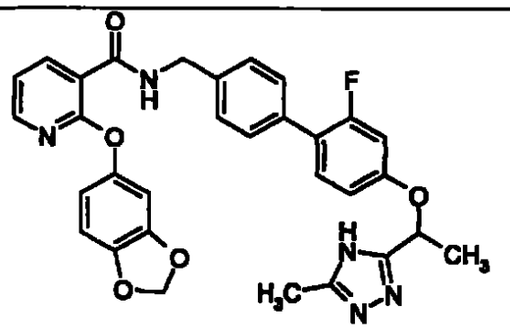
Fórmulas parciales (8.0.1) a (8.0.139) representadas anteriormente, incluye la sustitución opcional del mismo con respecto a *(1)* cualesquiera uno o más átomos de carbono del mismo, con un sustituyente R^{14} donde R^{14} tiene el mismo significado definido anteriormente; *(2)* cualesquiera uno o más átomos de nitrógeno del mismo, con un sustituyente R^{15} donde R^{15} tiene el mismo significado definido anteriormente, y todas las formas tautómeras, y opcionalmente las formas de N-óxido del mismo; o *(3)* un átomo cualquiera de azufre del mismo con 0, 1, ó 2 átomos de oxígeno.

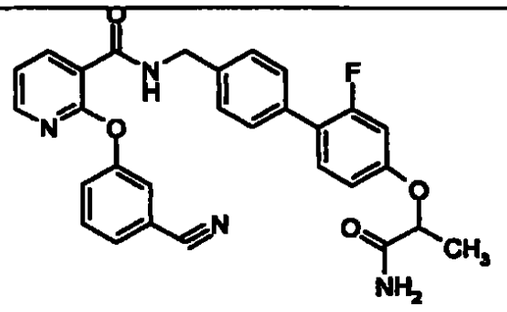
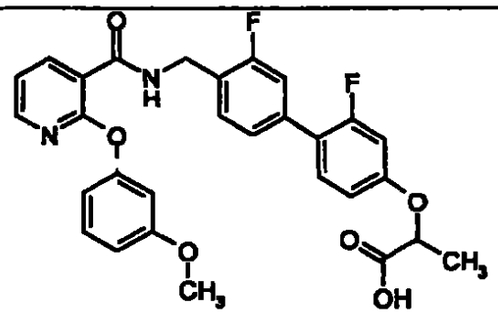
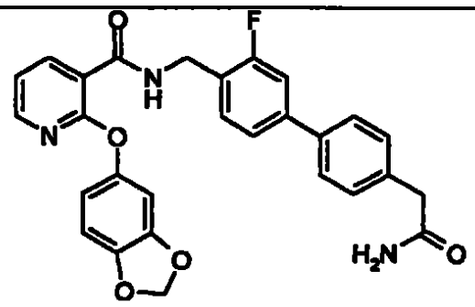
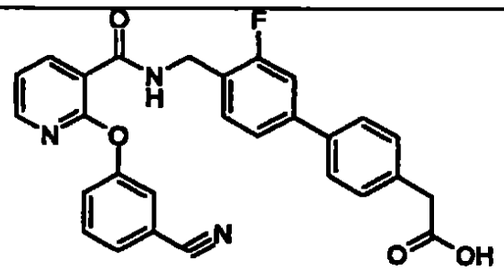
5.7 Especies representativas de Fórmula (1.0.0)

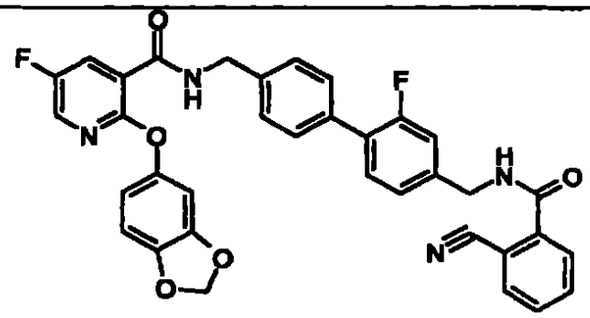
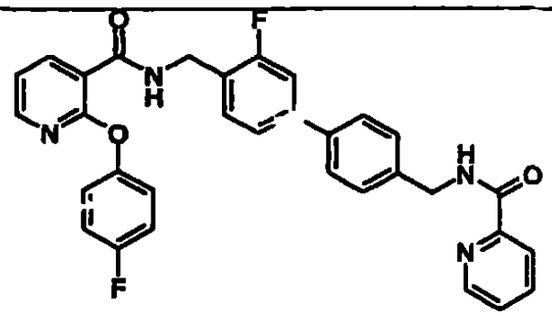
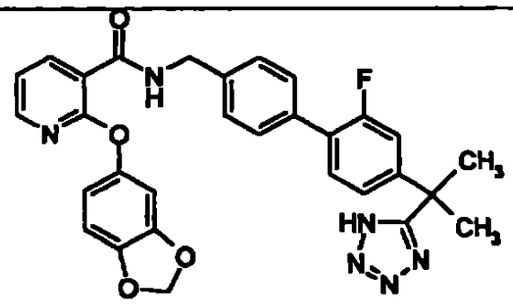
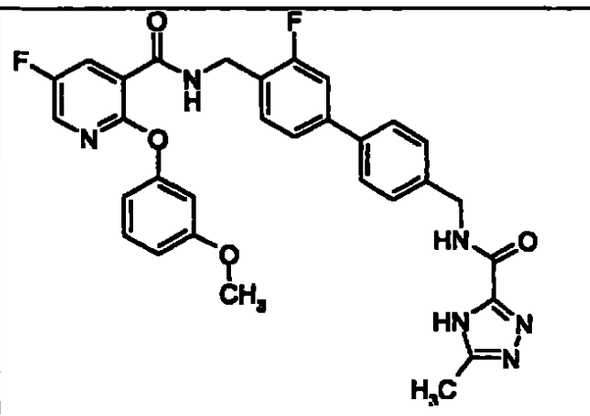
En la descripción anterior se han mostrado diversos aspectos preferidos de los compuestos de Fórmula (1.0.0). Como demostración adicional del alcance y contenido de la presente invención, se presentan los compuestos específicos que comprenden realizaciones de los compuestos de Fórmula (1.0.0). Tales especies de Fórmula (1.0.0) incluyen, pero sin limitación, los siguientes compuestos de Fórmulas (8.5.1) a (8.5.33):

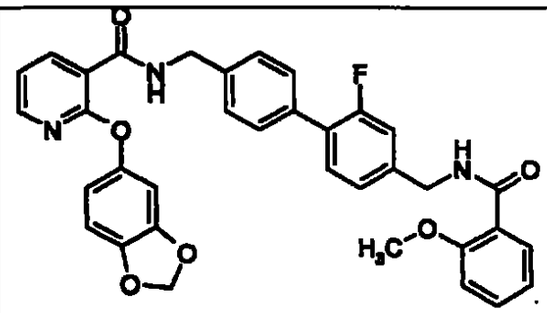
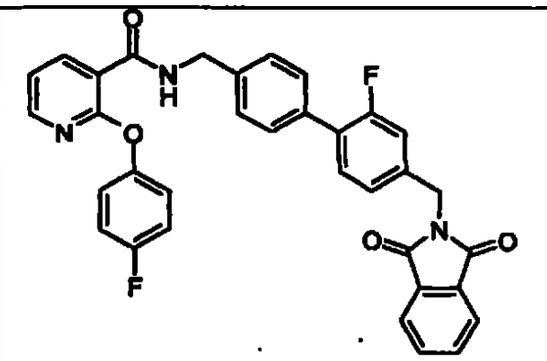
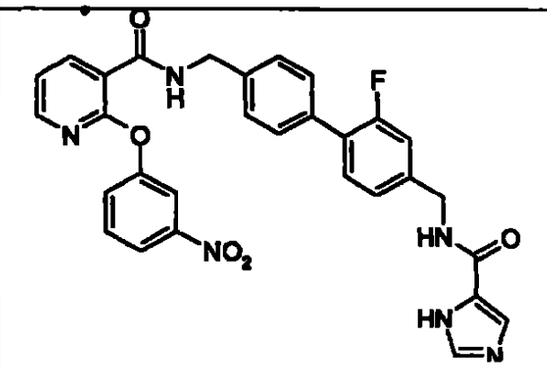
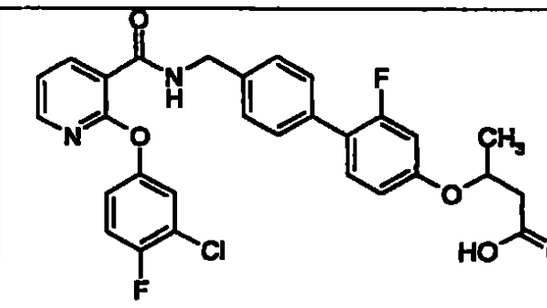
Ácido 4'-[[[2-[4-fluorofenoxil]piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (8.5.1);	
Ácido 4'-[[[[2-benzo[1,3]dioxol-5-iloxi]piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (8.5.2);	

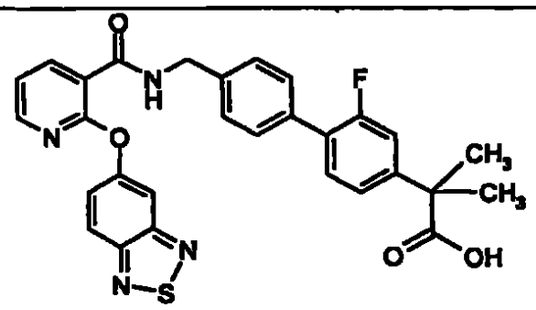
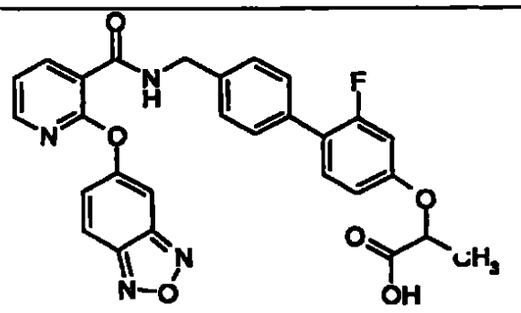
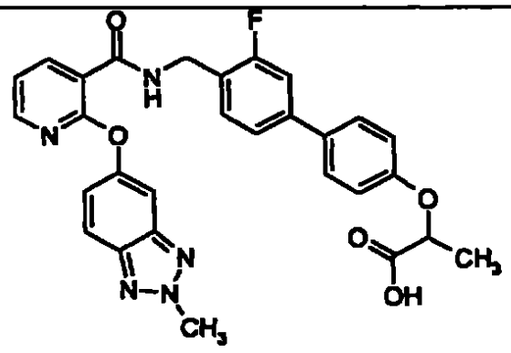
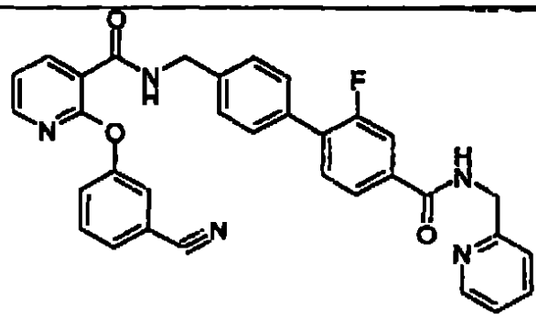
Ácido 4'-[[[[2-benzo[1,3]dioxol-5-iloxi]piridina-3-carbonil]amino]metil]-3'-fluorobifenil-3-carboxílico de Fórmula (8.5.3);	
Ácido 4'-[[[2-[3-cianofenoxi]piridina-3-carbonil]amino]metil]bifenil-3'-fluorobifenil-3-carboxílico de Fórmula (8.5.4);	
Ácido [4'-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]acético de Fórmula (8.5.5);	
Ácido [4'-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]acético de Fórmula (8.5.6);	
Ácido [4'-({[2-(benzo[1,3]dioxol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]acético de Fórmula (8.5.7);	

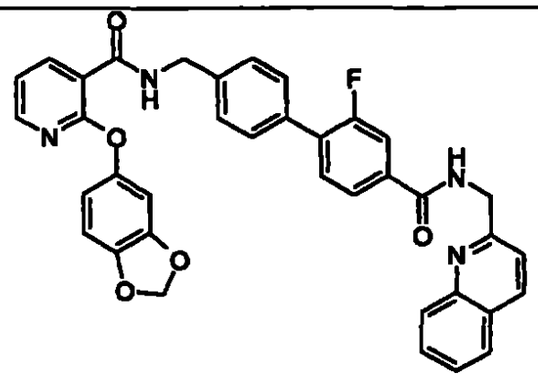
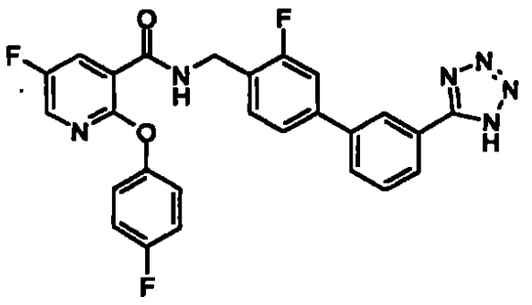
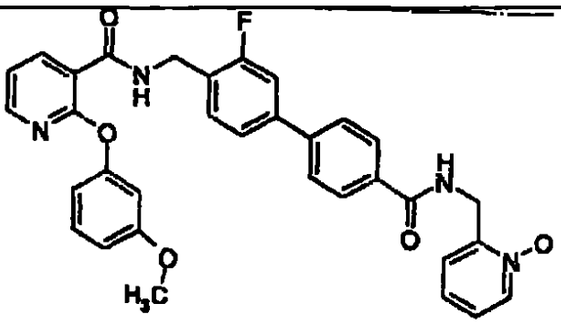
Ácido (±)-2-[4'-({[2-(benzo[1,3]dioxol-5-iloxi)piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-iloxi]propiónico de Fórmula (8.5.8);	
(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-(2'-fluoro-4'-[1-(1H-tetrazol-5-il)etoxi]bifenil-4-ilmetil)nicotinamida de Fórmula (8.5.9);	
Ácido (±)-2-[4'-({[2-(benzo[1,3]dioxol-5-iloxi])iridina-3-carbonil]amino}metil)-3'-fluorobifenil-2-iloxi]propiónico de Fórmula (8.5.10);	
(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-(2'-fluoro-4'-[1-(5-metil-4H-[1,2,4]triazol-3-il)etoxi]bifenil-4-ilmetilnicotinamida de Fórmula (8.5.11);	

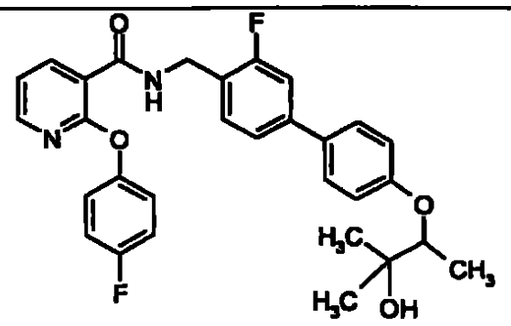
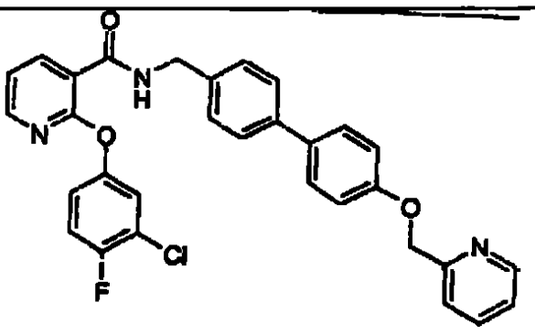
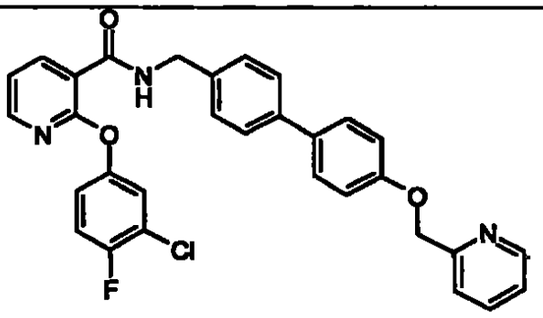
(±)-N-[4'-(1-Carbamoiletoxi)-2'-fluorobifenil-4-ilmetil]-2-(3-cianofenoxi)nicotinamida de Fórmula (8.5.12);	
Ácido (±)-2-[2,3'-difluoro-4'-({[2-(3-metoxifenoxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]propiónico de Fórmula (8.5.13);	
2-(Benzo[1,3]dioxol-5-iloxi)-N-(4'-carbamoilmetil-3-fluorobifenil-4-ilmetil)nicotinamida de Fórmula (8.5.14);	
Ácido [4'-({[2-(3-cianofenoxi)-3-carbonil]amino}metil)-3'-fluorobifenil-4-il]acético de Fórmula (8.5.15);	

2-(Benzo[1,3]dioxol-5-iloxi)-N-(4'-[(2-cianobenzoilamino)metil]-2'-fluorobifenil-4-ilmetil)-5-fluoronicotinamida de Fórmula (8.5.16);	
(3'-fluoro-4'-{[2-(4-fluorofenoxi)nicotinamida]metil}bifenil-4-ilmetil)amida del ácido piridin-2-carboxílico de Fórmula (8.5.17);	
2-(Benzo[1,3]dioxol-5-iloxi)-N-{2'-fluoro-4'-[1-metil-1-(1H-tetrazol-5-il)etil]bifenil-4-ilmetil}nicotinamida de Fórmula (8.5.18);	
5-Fluoro-N-(3-fluoro-4'-{[(5-metil-4H-[1,2,4]triazol-3-carbonil)amino]metil}bifenil-4-ilmetil)-2-(3-metoxifenoxi)nicotinamida de Fórmula (8.5.19);	

2-(Benzo[1,3]dioxol-5-iloxi)-N-{2'-fluoro-4'-[(2-metoxibenzoilamino)metil]bifenil-4-ilmetil}nicotinamida de Fórmula (8.5.20);	
N-[4'-(1,3-Dioxo-1,3-dihidroisoindol-2-ilmetil)-2'-fluorobifenil-4-ilmetil]-2-(4-fluorofenoxi)nicotinamida de Fórmula (8.5.21);	
N-(2'-Fluoro-4'-{[(3H-imidazol-4-carbonil)amino]metil}bifenil-4-ilmetil)-2-(3-nitrofenoxi)nicotinamida de Fórmula (8.5.22);	
Ácido (±)-3-[4'-({[2-(3-cloro-4-fluorofenoxi)piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-iloxi]butírico de Fórmula (8.5.23);	

Ácido 2-[4'-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-il]-2-metilpropiónico de Fórmula (8.5.24);	
Ácido (±)-2-[4'-({[2-(benzo[2,1,3]oxodizol-5-iloxi)piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-iloxi]propiónico de Fórmula (8.5.25);	
Ácido (±)-2-[3'-fluoro-4'-({[2-(2-metil-2H-benzotriazol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]propiónico de Fórmula (8.5.26);	
2-(3-Cianofenoxi)-N-{2'-fluoro-4'[(piridin-2-ilmetil)carbamoil]bifenil-4-ilmetil}nicotinamida de Fórmula (8.5.27);	

2-(Benzo[1,3]dioxol-5-iloxi)-N-(2'-fluoro-4'-[(quinolin-2-ilmetil)carbamoil]bifenil-4-ilmetil)nicotinamida de Fórmula (8.5.28);	
5-Fluoro-2-(4-fluorofenoxi)-N-[3-fluoro-3'-(1H-tetrazol-5-il)bifenil-4-ilmetil]nicotinamida de Fórmula (8.5.29);	
N-{3-Fluoro-4'-[(1-oxipiridin-2-ilmetil)carbamoil]bifenil-4-ilmetil}-2-(3-metoxifenoxi)nicotinamida de Fórmula (8.5.30);	
(+)-N-[3-Fluoro-4'-(2-hidroxi-1,2-dimetilpropoxi)bifenil-4-ilmetil]-2-(4-fluorofenoxi)nicotinamida de Fórmula (8.5.31);	

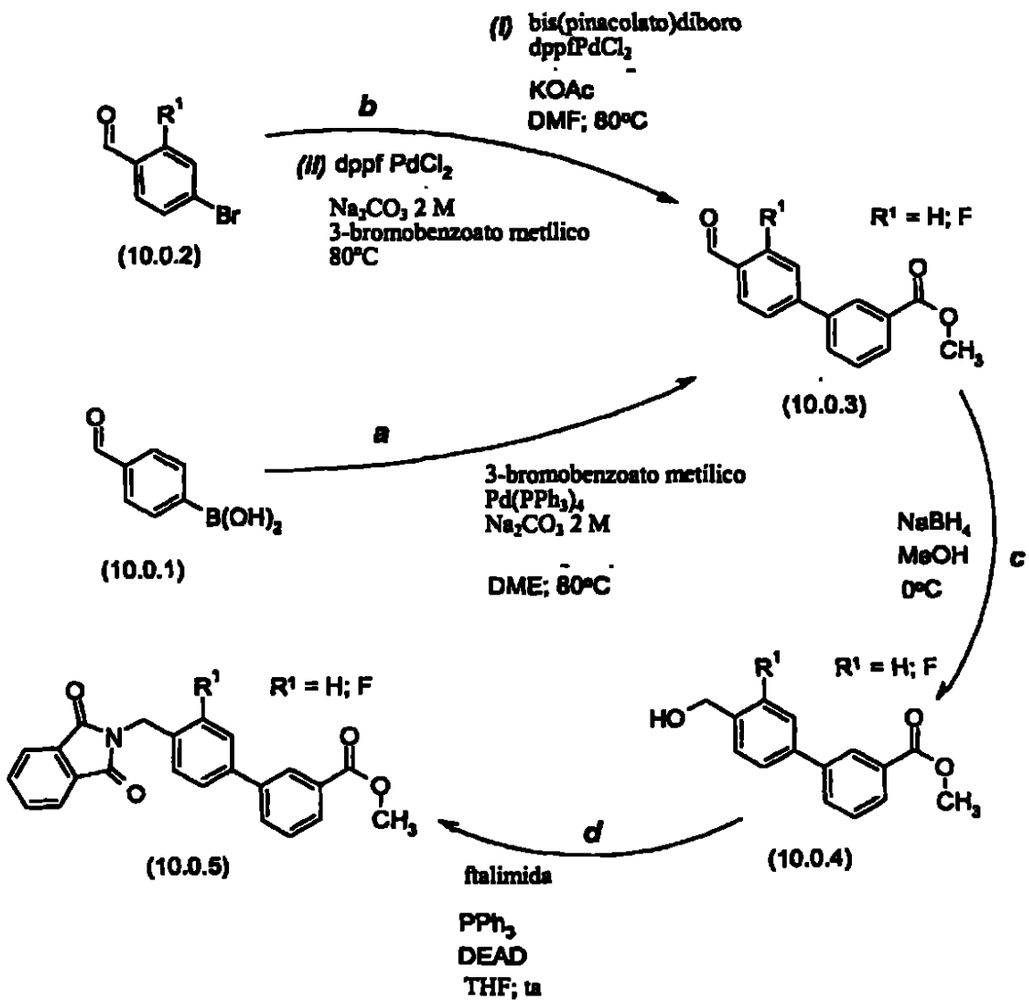
	
N-[2'-Fluoro-4'-(1-hidroxi-1-metiletil)bifenil-4-ilmetil]-2-(4-fluorofenoxi)nicotinamida de Fórmula (8.5.32);	
2-(3-Cloro-4-fluorofenoxi)-N-[4'-(piridin-2-ilmetoxi)bifenil-4-ilmetil]nicotinamida de Fórmula (8.5.33).	

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

6.0 Procesos para preparar los compuestos de Fórmula (1.0.0)

Un procedimiento adecuado para preparar el lado derecho de los compuestos de Fórmula (1.0.0) donde el grupo Q^2 es un resto bifenilo de Fórmula parcial (1.2.1), y el grupo **Z** es un resto carboxilo de Fórmula parcial (1.1.1), se ilustra en el Esquema de Síntesis (10.0.0) a continuación.

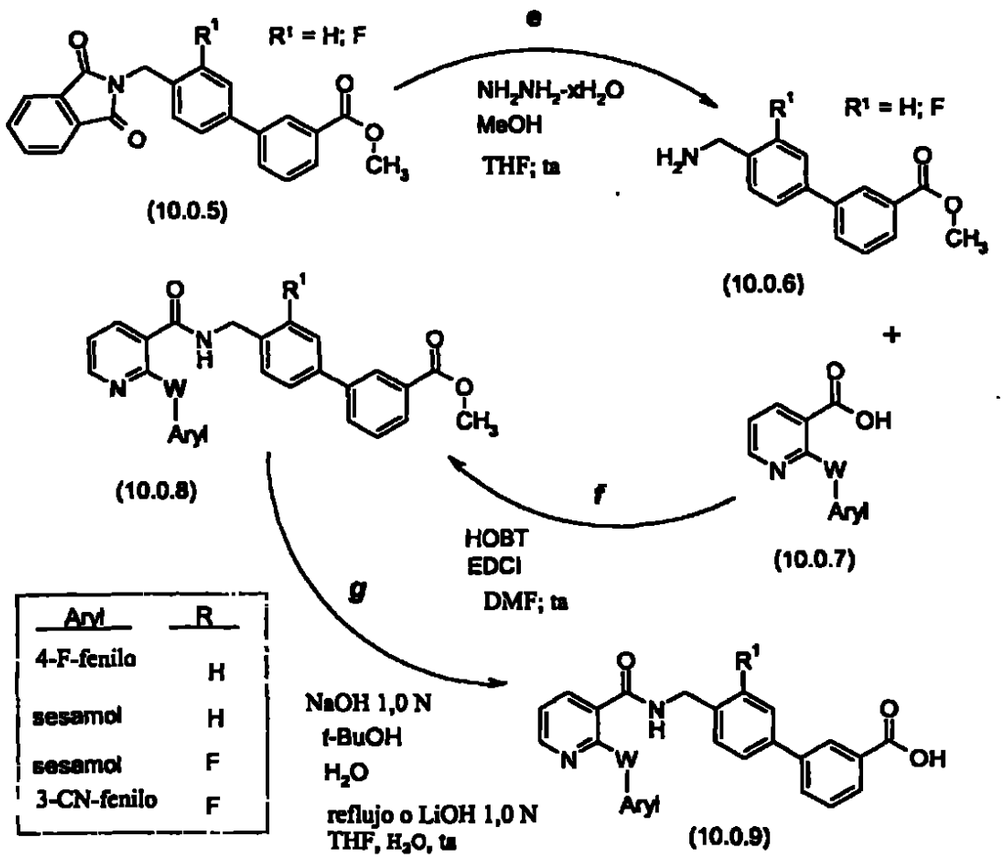
ESQUEMA DE SÍNTESIS (10.0.0)



El lado izquiero de los compuestos de Fórmula (1.0.0) se prepara mediante acoplamiento de amida de un ácido fenoxi-, feniltio-, o fenilsulfonil-nicotínico adecuadamente sustituido al resto de la derecha preparado como se describe anteriormente, después de que el intermedio de la Fórmula intermedia (10.0.5) se convierte a la amina correspondiente. Estas etapas se realizan de acuerdo con el

ESQUEMA DE SÍNTESIS (10.1.0) que se muestra a continuación.

ESQUEMA DE SÍNTESIS (10.1.0)



Una vez que se ha preparado un compuesto de Fórmula (1.0.0) de acuerdo con los ESQUEMAS DE SÍNTESIS (10.0.0) y (10.1.0) descritos anteriormente, pueden prepararse otras realizaciones de los compuestos de Fórmula (1.0.0) mediante reacciones adecuadas con el grupo Z cuando es un grupo carboxilo.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

7.0 Sales farmacéuticas y otras formas

Los compuestos descritos anteriormente de la presente invención pueden utilizarse en forma de ácidos, ésteres, u otras clases químicas de compuestos a los que pertenecen los compuestos descritos. La utilización de esos compuestos en forma de sus sales farmacéuticamente aceptables derivadas de diversos ácidos y bases orgánicos e inorgánicos de acuerdo con métodos notorios en la técnica está también dentro del alcance de la presente invención.

Las formas de sales farmacéuticamente aceptables de los compuestos de Fórmula (1.0.0) se preparan en su mayoría por medios convencionales: Cuando el compuesto de Fórmula (1.0.0) contiene un grupo ácido carboxílico, puede formarse una sal adecuada del mismo haciendo reaccionar el compuesto con una base apropiada para proporcionar la sal de adición de base correspondiente. Los ejemplos de tales bases son hidróxidos de metales alcalinos incluyendo hidróxido potásico, hidróxido sódico, e hidróxido de litio; los hidróxidos de metales alcalino térreos tales como hidróxido de bario e hidróxido cálcico; alcóxidos de metales alcalinos; por ejemplo etanolato potásico y propanolato sódico; y diversas bases orgánicas tales como piperidina, dietanolamina, y *N*-metiglutamina. También se incluyen las sales de aluminio de los compuestos de Fórmula (1.0.0).

Para ciertos compuestos de Fórmula (1.0.0) las sales de adición de ácidos pueden formarse tratando dichos compuestos con ácidos orgánicos e inorgánicos farmacéuticamente aceptables, por ejemplo halohidratos tales como clorhidrato, bromhidrato, yodhidrato; otros ácidos minerales y sus sales correspondientes tales como sulfato, nitrato, fosfato, etc.; y alquil- y monoarilsulfonatos tales como etanosulfonato, toluenosulfonato, y bencenosulfonato; y otros ácidos orgánicos y sus sales correspondientes como acetato, tartrato, maleato, succinato, citrato, benzoato, salicilato, ascorbato, etc.

En consecuencia, las sales de adición de ácidos farmacéuticamente aceptables de los compuestos de Fórmula (1.0.0) incluyen, pero sin limitación: acetato, adipato, alginato, arginato, aspartato, benzoato, bencenosulfonato (besilato), bisulfato, bisulfito, bromuro, butirato, alcanforato, alcanforsulfonato, caprilato, cloruro, clorobenzoato, citrato, ciclopentanopropionato, digluconato, dihidrogenofosfato, dinitrobenzoato, dodecilsulfato, etanosulfonato, fumarato, galacterato (de ácido múcico), galacturonato, glucoheptanoato, gluconato, glutamato, glicerofosfato, hemisuccinato, hemisulfato, heptanoato, hexanoato, hipurato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietanosulfonato, yoduro, isetionato, *iso*-butirato, lactato, lactobionato, malato, maleato, malonato, mandelato, metafosfato, metanosulfonato, metilbenzoato, monohidrogenofosfato, 2-naftalenosulfonato, nicotinato, nitrato, oxalato, oleato, pamoato, pectinato, persulfato, fenilacetato, 3-fenilpropionato, fosfato, fosfonato, ftalato.

Además, las sales básicas de los compuestos de la presente invención incluyen, pero sin limitación sales de aluminio, amonio, calcio, cobre, férricas, ferrosas, de litio, magnesio, mangánicas, manganosas, potásicas, sódicas, y de zinc. Preferidas entre las sales referidas anteriormente están amonio; las sales de metales alcalinos sodio y potasio; y las sales de metales alcalino térreos de calcio y magnesio. Las sales de los compuestos de Fórmula (1.0.0) derivados de bases orgánicas no tóxicas farmacéuticamente aceptables incluyen, pero sin limitación, sales de aminas primarias, secundarias, y terciarias, aminas sustituidas incluyendo las naturales, aminas cíclicas, y resinas de intercambio de iones básicas, por ejemplo, arginina, betaína, cafeína, cloroprocaína, colina, *N,N'*-dibenciletilenodiamina (benzatina), diclohexilamina, dietanolamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilenodiamina, *N*-etilmorfolina, *N*-etilpiperidina, glutamina, glucosalina, histidina,

hidrabamina, *iso*-propilamina, lidocaína, lisina, meglumina, N-metil-D-glucamina, morfolina, piperazina, piperidina, resinas de poliamina, procaína, purinas, teobromina, trietanolamina, trietilamina, trimetilamina, tripropilamina, y tris-(hidroximetil)-metilamina (trometamina).

Los compuestos de la presente invención que comprenden grupos básicos que contienen nitrógeno pueden cuaternizarse con agentes tales como haluros de alquilo C_1-C_4, por ejemplo cloruros, bromuros y yoduros de metilo, etilo, *iso*-propilo y *terc*-butilo; sulfato de dialquilo (C_1-C_3), por ejemplo sulfatos de dimetilo, dietilo, y diamilo; haluros de alquilo C_{10}-C_{18}, por ejemplo cloruros, bromuros y yoduros de decilo, dodecilo, laurilo, miristilo y estearilo; y haluros de arilalquilo C_1-C_4, por ejemplo cloruro de bencilo y bromuro de fenetilo. Tales sales permiten la preparación tanto de compuestos solubles en agua como solubles en aceite de la presente invención.

Entre las sales farmacéuticas referidas anteriormente las preferidas incluyen, pero sin limitación acetato, besilato, citrato, fumarato, gluconato, hemisuccinato, hipurato, clorhidrato, bromhidrato, isotionato, mandelato, meglumina, nitrato, oleato, fosfonato, pivalato, fosfato sódico, estearato, sulfato, sulfosalicilato, tartrato, tiomalato, tosilato, y trometamina.

Las sales de adición de ácidos de compuestos básicos de Fórmula (1.0.0) se preparan poniendo en contacto la forma de base libre con una cantidad suficiente del ácido deseado para producir la sal de forma convencional. La base libre puede generarse poniendo en contacto la forma salina con una base y aislando la base libre de forma convencional. Las formas de base libre difieren algo de sus formas salinas respectivas en ciertas propiedades físicas tales como solubilidad en disolventes polares, pero por lo demás las sales son equivalentes a sus formas de base libre respectivas para los fines de la presente invención.

Como se ha indicado, las sales de 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 alcalinotérreos, o aminas orgánicas. Los metales preferidos son sodio, potasio, magnesio, y calcio. Las aminas orgánicas preferidas son *N,N'*-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilenodiamina, *N*-metil-D-glucamina, y procaína.

Las sales de adición de base de los compuestos ácidos de la presente invención se preparan poniendo en contacto la forma de ácido libre con una cantidad suficiente de la base deseada para producir la sal de forma convencional. El ácido libre puede generarse poniendo en contacto la forma salina con un ácido y aislando el ácido libre de forma convencional. Las formas de ácido libre difieren algo de sus formas salinas respectivas en ciertas propiedades físicas tales como solubilidad en disolventes polares, pero por lo demás las sales son equivalentes a sus formas de ácido libre respectivas para los fines de la presente invención.

Múltiples formas salinas están incluidas en el alcance de la presente invención cuando un compuesto de la presente invención contiene más de un grupo capaz de formar tales sales farmacéuticamente aceptables. Los ejemplos de formas salinas múltiples típicas incluyen, pero sin limitación bitartrato, diacetato, difumarato, dimeglumina, difosfato, disodio, y triclorhidrato.

En vista de lo anterior, puede observarse que la expresión "sal farmacéuticamente aceptable" según se usa en el presente documento se pretende que signifique un ingrediente activo que comprende un compuesto de Fórmula (1.0.0) utilizado en forma de una sal del mismo, especialmente cuando dicha forma salina confiere a dicho ingrediente activo propiedades farmacocinéticas mejoradas en comparación con la forma libre de dicho ingrediente activo o alguna otra forma salina

de dicho ingrediente activo utilizada previamente. La forma salina farmacéuticamente aceptable de dicho ingrediente activo puede también inicialmente conferir una propiedad farmacocinética deseable a dicho ingrediente activo que previamente no poseía, y puede incluso afectar positivamente la farmacodinámica de dicho ingrediente activo con respecto a su actividad terapéutica en el cuerpo.

Las propiedades farmacocinéticas de dicho ingrediente activo que pueden verse afectadas favorablemente incluyen, por ejemplo, la forma en la que dicho ingrediente activo es transportado a través de las membranas celulares, que a su vez puede afectar de forma directa y positiva la absorción, distribución, biotransformación y excreción de dicho ingrediente activo. Aunque la vía de administración de la composición farmacéutica es importante, y diversos factores anatómicos, fisiológicos y patológicos pueden afectar de forma crítica la biodisponibilidad, la solubilidad de dicho ingrediente activo depende habitualmente del carácter de la forma salina en particular del mismo que se utiliza. Además, como apreciarán los expertos en la técnica, una solución acuosa de dicho ingrediente activo proporcionará la absorción más rápida de dicho ingrediente activo en el cuerpo de un paciente en tratamiento, mientras que las soluciones y suspensiones lipídicas, así como las formas farmacéuticas 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 vía de administración más preferida por razones de seguridad, conveniencia, y economía, pero la absorción de tal forma farmacéutica oral puede verse afectada de forma adversa por características físicas tales como la polaridad, emesis provocada por la irritación de la mucosa gastrointestinal, destrucción por enzimas digestivas y pH bajo, absorción o propulsión irregulares en 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 formas salinas farmacéuticamente aceptables puede ser efectiva para superar o aliviar uno o más de los problemas referidos anteriormente que se encuentran en la absorción de formas farmacéuticas orales.

Un compuesto de Fórmula (1.0.0) preparado de acuerdo con los procedimientos descritos en el presente documento puede separarse de la mezcla de reacción en la que finalmente se produce por cualquier medio ordinario conocido por los expertos en la técnica de preparación de compuestos orgánicos. Una vez se ha separado dicho compuesto puede purificarse mediante procedimientos conocidos. Pueden usarse diversos procedimientos y técnicas como medios de separación y purificación, e incluyen, por ejemplo, destilación; recristalización; cromatografía en columna; cromatografía de intercambio de iones; cromatografía en gel; cromatografía por afinidad; cromatografía preparatoria en capa fina; y extracción mediante disolventes.

7.1 Estereoisómeros

Un compuesto en el alcance de la Fórmula (1.0.0) puede ser tal que los átomos que lo constituyen puedan disponerse en el espacio en dos o más formas diferentes, a pesar de tener conectividades idénticas. Como consecuencia, dicho compuesto existe en forma de estereoisómeros. La isomería *cis-trans* es sólo un tipo de estereoisomería. Cuando los estereoisómeros no son imágenes especulares superponibles el uno del otro, son enantiómeros que tiene quiralidad o sentido, debido a la presencia de uno o más átomos de carbono asimétricos en su estructura constituyente. Los enantiómeros son óptimamente activos y por lo tanto pueden distinguirse porque rotan el plano de luz polarizada en cantidades iguales pero en direcciones opuestas.

Cuando hay dos o más átomos de carbono asimétricos en un compuesto de Fórmula (1.0.0), hay dos configuraciones posibles en cada átomo de carbono. Cuando hay presentes dos átomos de carbono asimétricos, por ejemplo, hay cuatro

estereoisómeros posibles. Además, estos cuatro estereoisómeros posibles pueden disponerse en seis posibles pares de estereoisómeros que son diferentes entre sí. Para que un par de moléculas con más de un carbono asimétrico sean enantiómeros, deben tener configuraciones diferentes en cada carbono asimétrico. Esos pares que no están relacionados como enantiómeros tienen una relación estereoquímica diferente denominada relación diastereoisomérica. Los estereoisómeros que no son enantiómeros se denominan diastereoisómeros, o más comúnmente, diastereómeros.

Todos estos aspectos notorios de la estereoquímica de los compuestos de Fórmula (1.0.0) se contemplan como parte de la presente invención. Por lo tanto, dentro del alcance de la presente invención se incluyen los compuestos de Fórmula (1.0.0) que son estereoisómeros, y cuando estos son enantiómeros, los enantiómeros individuales, mezclas racémicas de dichos enantiómeros, y mezclas artificiales, es decir mezclas fabricadas que contienen proporciones de dichos enantiómeros que son diferentes de las proporciones de dichos enantiómeros hallados en una mezcla racémica. Cuando un compuesto de Fórmula (1.0.0) comprende estereoisómeros que son diastereisómeros, se incluyen en el alcance de dicho compuesto los diastereoisómeros individuales así como las mezclas de dos o más cualesquiera de dichos diastereoisómeros en cualquier proporción de los mismos.

A modo de ilustración, en el caso en que hay un único carbono asimétrico en un compuesto de Fórmula (1.0.0), dando como resultado los enantiómeros (-)(*R*) y (+)(*S*) de los mismos; se incluye en el alcance de dicho compuesto todas las formas salinas, profármacos y metabolitos farmacéuticamente aceptables del mismo que son activas terapéuticamente y de utilidad en el tratamiento o prevención de las enfermedades y afecciones descritas adicionalmente en el presente documento. Cuando un compuesto de Fórmula (1.0.0) existe en forma de enantiómeros (-)(*R*) y (+)(*S*), se incluyen también en

el alcance de dicho compuesto el enantiómero (+)(*S*) sólo, o el enantiómero (-)(*R*) sólo, en el caso en que toda, o sustancialmente toda, o una parte predominante de la actividad terapéutica resida únicamente en uno de dichos enantiómeros, y/o residan efectos secundarios no deseados solamente en uno de dichos enantiómeros. En el caso en que no hay sustancialmente diferencia entre las propiedades biológicas de ambos enantiómeros, se incluyen adicionalmente dentro del alcance de dicho compuesto de Fórmula (1.0.0) el enantiómero (+)(*S*) y el enantiómero (-)(*R*) presentes juntos en forma de mezcla racémica o como mezcla no racémica en cualquier relación de cantidades proporcionales de los mismos.

Por ejemplo, las actividades biológicas particulares y/o propiedades físicas y químicas de un par o conjunto de enantiómeros de un compuesto de Fórmula (1.0.0) cuando tales existan, puede sugerir el uso de dichos enantiómeros en ciertas relaciones para constituir un producto terapéutico final. A modo de ilustración, en el caso en que hay un par de enantiómeros, pueden emplearse 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 evaluar las propiedades de los diversos enantiómeros de un compuesto de Fórmula (1.0.0) cuando tales existan, la cantidad proporcional de uno o más de dichos enantiómeros con ciertas propiedades deseadas que constituirán el producto terapéutico final puede determinarse de manera sencilla.

7.2 Isótopos

Se contemplan adicionalmente como incluidos dentro del alcance de un compuesto de Fórmula (1.0.0) las formas marcadas con isótopos de los mismos. Una forma marcada con isótopos de un compuesto de Fórmula (1.0.0) es idéntica a dicho

compuesto excepto por el hecho de que uno o más átomos de dicho compuesto han sido reemplazados por un átomo o átomos que tienen una masa atómica o número másico diferente de la masa atómica o el número másico de dicho átomo que habitualmente se halla en la naturaleza. Los ejemplos de isótopos que están fácilmente disponibles en el mercado y que pueden incorporarse en un compuesto de Fórmula (1.0.0) de acuerdo con métodos bien establecidos, incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, y cloro. Por ejemplo ^{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 del mismo, o una sal farmacéuticamente aceptable de cualquiera de los dos que contiene uno o más de los isótopos mencionados anteriormente y/u otros isótopos de otros átomos se contempla que están dentro del alcance de la presente invención.

Un compuesto de Fórmula (1.0.0) radiomarcado puede usarse de numerosas maneras beneficiosas. Por ejemplo, un compuesto de Fórmula (1.0.0) radiomarcado, por ejemplo uno en el que se ha incorporado un isótopo radioactivo tal como ^{3}H o ^{14}C, será de utilidad en ensayos de distribución tisular del fármaco y/o sustrato. Estos isótopos radiactivos, por ejemplo tritio, ^{3}H, y carbono-14, ^{14}C, son especialmente preferidos por la facilidad de su preparación y detectabilidad eminente. La incorporación de isótopos más pesados, por ejemplo, deuterio, ^{2}H, en un compuesto de Fórmula (1.0.0) proporcionará ventajas terapéuticas basadas en la mayor estabilidad metabólica de dicho compuesto marcado con isótopos. La mayor estabilidad metabólica se traduce directamente en semividas superiores *in vivo* o requisitos de dosificación reducidos, que en la mayor parte de las circunstancias constituirá una realización preferida de la presente invención. Un compuesto de Fórmula (1.0.0) marcado con isótopos puede prepararse usualmente realizando los métodos descritos en los Esquemas de Síntesis y descripción relacionada, los Ejemplos, y Preparaciones del presente documento,

sustituyendo un reactivo fácilmente disponible no marcado con isótopos por su reactivo correspondiente marcado con isótopos.

Puede también incorporarse deuterio ^{2}H a un compuesto de Fórmula (1.0.0) con el fin de manipular el metabolismo oxidativo de dicho compuesto mediante el efecto de isotópico cinético primario. El efecto isotópico cinético primario es un cambio de velocidad de una reacción química que resulta de la sustitución de núcleos isotópicos, que a su vez produce el cambio de los estados de energía fundamentales necesarios para la formación de un enlace covalente subsiguientemente a dicha sustitución isotópica. La sustitución de un isótopo más pesado habitualmente dará como resultado un descenso del estado de la energía energía fundamental para un enlace químico, provocando así una reducción de la velocidad para una etapa de ruptura de enlaces limitantes de la velocidad. Si el evento de ruptura de enlaces sucede en o casi en una zona de tipo silla de montar a lo largo de la coordenada de una reacción con múltiples productos, las relaciones de distribución de productos pueden alterarse de forma sustancial. A modo de ilustración, cuando el deuterio está unido a un átomo de carbono en un sitio no intercambiable, son típicas las diferencias de velocidad de k_M/k_D = 2-7. Esta diferencia de las velocidades, aplicada con éxito a un compuesto de Fórmula (1.0.0) lábil por oxidación, puede afectar dramáticamente el perfil de dicho compuesto *in vivo* y dar como resultado una mejora de las propiedades farmacocinéticas.

Al descubrir y desarrollar los agentes terapéuticos, los expertos en la técnica persiguen optimizar los parámetros farmacocinéticas manteniendo a la vez las propiedades deseables *in vitro*. Es una suposición razonable que muchos compuestos con perfiles farmacocinéticos deficientes padecen la característica de ser lábiles al metabolismo oxidativo. Los ensayos microsómicos hepáticos *in vitro* disponibles hoy en día proporcionan información valiosa sobre el curso de este metabolismo oxidativo, que

a su vez permite el diseño racional de compuestos con deuterio de Fórmula (1.0.0) con estabilidad mejorada a través de la resistencia a tal metabolismo oxidativo. De este modo se obtienen mejoras significativas en los perfiles farmacocinéticos de los compuestos de Fórmula (1.0.0), y pueden expresarse cuantitativamente en términos de aumentos de la *in vivo* (t/2) semivida, concentración para el efecto terapéutico máximo (C_{max}), área bajo la curva de respuesta a la dosis (AUC), y F; y en términos de disminución del aclaración, dosis y coste de los materiales.

A modo de ilustración de lo anterior, se prepara un compuesto de Fórmula (1.0.0) que tiene múltiples sitios potenciales para el metabolismo oxidativo, por ejemplo átomos de hidrógeno bencílicos y átomos de hidrógeno en posición relativa α con respecto a un átomo de nitrógeno, en forma de serie de análogos en los que diversas combinaciones de átomos de hidrógeno son reemplazadas por átomos de deuterio de forma que algunos, la mayoría o todos los átomos de hidrógeno son reemplazados por átomos de deuterio. Las determinaciones de la semivida proporcionan una determinación expeditiva y exacta de la extensión de la mejora de la resistencia al metabolismo oxidativo. De esta forma se determina que puede extenderse la semivida del compuesto progenitor en hasta el 100% como resultado de tal sustitución de hidrógeno por deuterio.

La sustitución de hidrógeno por deuterio en un compuesto de Fórmula (1.0.0) puede usarse también para lograr una alteración favorable del perfil metabólico del compuesto progenitor como modo de disminuir o eliminar metabolitos tóxicos no deseados. Por ejemplo, cuando surge un metabolito tóxico a través de una escisión oxidativa de carbono-hidrógeno, C-H, puede esperarse razonablemente que el análogo deuterado disminuya o elimine en gran medida la producción del metabolito no deseado, incluso en el caso de que la oxidación particular no sea una etapa que

determine la velocidad.

Puede encontrarse información adicional sobre el estado de la técnica en lo que respecta a la sustitución de hidrógeno por deuterio por ejemplo en Hanzlik y cols., *J. Org. Chem.* 55 3992-3997, 1990; Reider y cols., *J. Org. Chem.* 52 3326-3334, 1987; Foster, *Adv. Drug Res.* 14 1-40, 1985; Gillette y cols., *Biochemistry* 33(10) 2927-2937, 1994; y Jarman y cols., *Carcinogenesis* 16(4) 683-688, 1993.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

8.0 Aplicaciones terapéuticas y criterios de valoración clínicos

La descripción a continuación concierne las aplicaciones terapéuticas a las que pueden someterse los compuestos de Fórmula (1.0.0), y donde sea de aplicación una explicación de los criterios de valoración clínicos asociados a tales aplicaciones terapéuticas. También se presenta una descripción de diversos ensayos *in vitro* y experimentos en modelos 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 de Fórmula (1.0.0) es aplicable a un paciente o sujeto que padece una enfermedad o afección como se ha presentado en el presente documento y por lo tanto necesitado de dicho tratamiento. Los resultados beneficiosos son terapéuticos ya sean administrados a animales o humanos. Según se usa en el presente documento los términos "animal" y "animales" se usan meramente con el fin de destacar los humanos por oposición a otros miembros del reino animal. Los compuestos de Fórmula (1.0.0) tienen aplicación terapéutica en el tratamiento de mamíferos, y en particular de humanos. Están incluidas en el alcance de la presente invención todas las subdivisiones principales de la clase de mamíferos (*Mammalia)* con respecto a ser receptores de tratamiento terapéutico como se describe en el presente documento. Los mamíferos pueden ser desde animales domésticos a seres humanos y

por lo tanto son sujetos probables del tratamiento. Esto es de aplicación especialmente a los grupos de animales mamíferos canino y felino. Se estiman otros mamíferos como animales domesticados y es probable su tratamiento de acuerdo con la presente invención a la vista del impacto económico adverso de no tratar las enfermedades y afecciones descritas en el presente documento. Esto es de aplicación especialmente a los grupos de mamíferos equino, bovino, porcino y ovino.

Los compuestos de Fórmula (1.0.0) inhiben la isozima PDE4 y por lo tanto tienen un amplio abanico de aplicaciones terapéuticas, como se describe adicionalmente más adelante, debido al papel esencial que representa la familia PDE4 de isozimas en la fisiología de todos los mamíferos. El papel enzimático realizado por las isozimas PDE4 es la hidrólisis intracelular del adenosin 3',5'-monofosfato (AMPc) en los leucocitos pro inflamatorios. AMPc a su vez, es responsable de mediar los efectos de numerosas hormonas en el cuerpo, y como consecuencia, la inhibición de PDE4 representa un papel significativo en una diversidad de procesos fisiológicos. Hay una extensa bibliografía en la técnica que describe los efectos de los inhibidores de PDE sobre diversas respuestas de inflamación celular, que además de la elevación del AMPc, incluyen la inhibición de la producción de superóxidos, desgranulación, quimiotactismo y liberación del factor necrosante tumoral (RNF) en eosinófilos, neutrófilos y monocitos.

La PDE4 se identificó por vez primera en 1985, Nemoz y cols., *Biochem. Pharmacol.* 34 2997-3000, 1985, y los inhibidores de PDE4 rolipram y denbufilina se estudiaron al principio en ensayos clínicos para indicaciones del SNC tales como la depresión. Subsiguientemente, se estableció que PDE4 es la fosfodiesterasa principal en los leucocitos inflamatorios. Los cuatro subtipos de PDE4, es decir, PDE4A, PDE4B, PDE4C, y PDE4D, se distribuyen ampliamente en los tejidos humanos, según se

determina por la presencia de sus ARNm. PDE4D se expresa en el los tejidos del riñón, timo, intestino delgado, y colon, y se expresa intensamente en los tejidos del cerebro, pulmón, músculo esquelético, próstata, y leucocitos de sangre periférica (PBL). Se expresa sólo débilmente en los tejidos del corazón, placenta, hígado, páncreas, bazo, testículo, y ovario. PDE4A y PDE4B se expresan también intensamente en los tejidos del cerebro y músculo esquelético, y sólo de forma débil en tejidos de la placenta, hígado y ovario. PDE4C se expresa intensamente en el tejido de músculo esquelético también, y se expresa también débilmente en tejido de ovario. PDE4C no es detectable habitualmente en la mayoría de los tejidos mencionados anteriormente.

La familia PDE4 de isozimas es la forma predominante de fosfodiesterasas halladas en los tipos celulares implicados en enfermedades inflamatorias crónicas, y entre los tipos celulares derivados de la médula ósea, únicamente las plaquetas no expresan PDE. PDE4 es la principal enzima que metaboliza AMPc en células inmunitarias e inflamatorias, y es una de las dos enzimas principales que metabolizan AMPc en el músculo liso de las vías respiratorias. PDE4 está presente exclusivamente en neutrófilos, eosinófilos, basófilos, y monocitos, mientras que se ha demostrado también actividad de PDE3 y PDE1 en los macrófagos, y actividad de PDE7 en los linfocitos T. Los efectos antiinflamatorios beneficiosos de los inhibidores de PDE han sido demostrados hasta la fecha usando experimentos *in vitro*, que han establecido que tales compuestos inhiben la generación de superóxidos en monocitos, eosinófilos, y neutrófilos humanos; la liberación de mediadores en basófilos, macrófagos, y neutrófilos; y la liberación del TNFα en monocitos y macrófagos. Los inhibidores de PDE inhiben también la liberación de mediadores de las células inflamatorias como los monocitos y macrófagos derivados de monocitos, mastocitos pulmonares, linfocitos T, linfocitos B, macrófagos alveolares, y eosinófilos.

Se han observado también efectos antiinflamatorios beneficiosos *in vivo* hasta ahora, incluyendo la inhibición de filtraciones microvasculares a los pulmones de cobayas sensibilizadas, y la reducción de la hiperreactividad bronquial y eosinofilia en monos cynomolgus tras provocación repetida con antígenos. Se ha demostrado también hasta ahora que los inhibidores de PDE4 suprimen potentemente la liberación de TNF α desde fagocitos mononucleares.

8.1 Asma

Una de las enfermedades respiratorias más importante que puede tratarse con inhibidores de PDE4, especialmente con inhibidores de PDE4D del tipo dentro del alcance de los compuestos de Fórmula (1.0.0) es el asma, un trastorno crónico, cada vez más común que se encuentra en todo el mundo y caracterizado por la obstrucción de las vías respiratorias intermitente reversible, hiperreactividad e inflamación. La causa del asma no ha sido determinada todavía, pero la expresión patológica más común del asma es la inflamación de las vías respiratorias, que puede ser significativa incluso en las vías respiratorias de pacientes con asma leve. Basándose en la biopsia bronquial y estudios de lavado se ha demostrado claramente que el asma implica la infiltración de mastocitos, eosinófilos, y linfocitos T en las vías respiratorias del paciente. El lavado broncoalveolar (BAL) en asmáticos atópicos demuestra la activación de interleucina (IL)-3, IL-4, IL-5 y factor estimulante de colonias de granulocitos/macrófagos (GM-CSF) que sugiere la presencia de una población de linfocitos T tipo T-cooperador 2 (Th2).

Los compuestos de Fórmula (1.0.0) inhiben PDE4 en los eosinófilos humanos y son por lo tanto de utilidad en el tratamiento de asma atópica y no atópica. El término "atópico" se refiere a una predisposición genética al desarrollo de reacciones de hipersensibilidad (inmediata) tipo I contra antígenos medioambientales comunes. La

manifestación clínica más común es la rinitis alérgica mientras que el asma bronquial, la dermatitis atópica, y la alergia a alimentos se da menos frecuentemente. En consecuencia, la expresión "asma atópica" según se usa en el presente documento es sinónimo de "asma alérgica", es decir, asma bronquial que es una manifestación alérgica en una persona sensibilizada. El término "asma no atópica" según se usa en el presente documento se pretende que se refiera a otro tipo de asmas, especialmente asma idiopática o asma "verdadera" que está provocada por una variedad de factores incluyendo el ejercicio vigoroso, partículas irritantes, estreses psicológicos, etc.

El uso de compuestos de Fórmula (I.0.0) para tratar asma atópica o asma no atópica está establecido y se demuestra mediante los modelos de inhibición de PDE, inhibición de la activación de eosinófilos, y los modelos de infiltración celular descritos a continuación.

Inflamación pulmonar en monos cynomolgus alérgicos

En este procedimiento se evalúa la capacidad de las combinaciones de los agentes terapéuticos de la presente invención de inhibir los incrementos en el contenido celular inflamatorio del fluido del lavado bronquioalveolar inducido por el antígeno *Ascaris* en sujetos monos cynomolgus. Usando un diseño de entrecruzamiento, se tratan 8-10 monos cynomolgus sensibles a *Ascaris* con vehículo o fármaco. En un momento apropiado previo al tratamiento, se anestesia cada mono (quetamina 10 mg/kg + xilazina 1 mg/kg, i.m.) y se intuba con un tubo endotraqueal con manguito. Se realiza un lavado broncoalveolar (BAL) usando un lavado de 15 ml de solución salina tamponada con fosfato (PBS) administrada a través de un broncoscopio de fibra óptica pediátrico insertado a través del tubo endotraqueal y acuñado en un bronquio de tercera a quinta generación. Se aspira suavemente el fluido de lavado y se recoge en una jeringuilla. Después de completar el BAL, cada animal se expone durante 2 minutos a una

concentración de aerosol de *Ascaris suum* que dobla la resistencia del sistema respiratorio determinada en experimentos previos. Se devuelve a cada mono a su jaula y 24 horas después se realiza un segundo lavado, usando 15 ml de PBS, en el lado opuesto del pulmón. Una semana después del ensayo inicial, se inviertén los monos control y tratados y se repite el experimento. Para determinar la composición porcentual de cada tipo de leucocito, se obtienen dos portas con las muestras de BAL de cada mono centrifugando 2 x 150 µl de fluido de lavado durante 2 minutos a 500 rpm en una centrifugadora Cytospin. Se tiñen los portas con Diff-Quick para el recuento diferencial de células y se identifican las células mediante criterios morfológicos estándar. Se determinan los números de leucocitos totales por militro de fluido BAL diluyendo 20 µl de muestra en 20 ml de Isoton, añadiendo 3 gotas de Zapoglobin para lisar los eritrocitos y leer la muestra usando un contador Coulter. Se hacen comparaciones entre la relación de aumento de eosinófilos de lavado alveolar bronquial, niveles de citoquina o mediador, antes de la provocación con antígeno comparado con 24 horas después de la provocación con antígeno, con y sin tratamiento con fármacos.

En el modelo de ensayo anterior, las combinaciones de agentes terapéuticos de la presente invención exhiben actividad antiinflamatoria en dosificaciones en el intervalo de 0,001 a 0,1 mg/kg *i.v.* o 0,01 a 10,0 mg/kg *p.o.* o 0,001 a 0,1 mg/kg *i.t.*

Otro ensayo de utilidad, basado en el uso de primates es el descrito en Turner y cols., "Characterization of a primate model of asthma using anti-allergy/anti-asthma agents," *Inflammation Research* 45 239-245, 1996.

Actividad antiinflamatoria - La actividad antiinflamatoria de las combinaciones de agentes terapéuticos de la presente invención se demuestra por la inhibición de la activación de eosinófilos medida mediante la producción de LTE4 estimulada mediante perlas de sephadex en sangre humana completa.

Ensayo de sangre entera para determinar LTE4 usando perlas de sephadex como estimulante. Un día antes del ensayo, cubrir tubos de vidrio con silicona con Sigmacote (Sigma, nº de cat SL-2). Antes de extraer la sangre, diluir los compuestos en DMSO 1000X, añadir 1 µl de DMSO o compuesto a cada tubo respectivo, y colocar la gradilla de tubos en un baño de agua a 37ºC. Se extrae la sangre en tubo Vacutainer nº 6480 heparinizado (143 USP unidades de heparina sódica, 10 ml), 10 tubos = 100 ml de sangre. Juntar los tubos de sangre en dos tubos cónicos de 50 ml. Añadir 1 ml de sangre entera a cada tubo con silicona que contiene DMSO o compuesto, agitar con un VORTEX y después incubar a 37ºC durante 15 minutos. Para preparar la suspensión de perlas de Sephadex G-15 (Pharmacia, nº de cat 17-0020-01), añadir 3,3 g de Sephadex G-15, mezclar con 20 ml de PBS en un vaso de precipitados de 100 ml después mezclar con una barra de agitación magnética. Después de 15 minutos, añadir 100 µl de perlas de Sephadex G-15 a cada tubo excepto los tubos de Sephadex que darán el valor de la línea base de la liberación de LTE4. Agitar en un vórtice e incubar durante 90 minutos a 37ºC. Después de 90 minutos de incubación, añadir 20 µl de EDTA al 15%, agitar en una VORTEX y centrifugar durante 5 minutos a 1000 rpm. Después eliminar y reservar la muestra de plasma para analizar. Los niveles de LTE4 se determinan con el kit Cysteinyl-LT ELISA de Cayman (nº de cat. 520501). El porcentaje de inhibición se calcula como 100 X 1 - (concentración de LTE4 en la muestra tratada con fármaco dividido entre la concentración de LTE4 en las muestras control no tratadas con fármaco).

Los compuestos de Fórmula (1.0.0) son activos en el procedimiento de ensayo anterior en concentraciones en el intervalo de 0,0001 µM a 20,0 µM, siendo las realizaciones preferidas activas en concentraciones en el intervalo de 0,5 nM a 1000 nM.

A partir de lo anterior puede observarse que los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento de enfermedades inflamatorias u obstructivas de las vías respiratorias u otras afecciones que implican la obstrucción de las vías aéreas. En particular son de utilidad para el tratamiento del asma bronquial.

En vista de su actividad antiinflamatoria, su influencia sobre la hiperreactividad de las vías respiratorias y su perfil en relación a la inhibición de la isoenzima PDE, en particular como inhibidores selectivos de PDE4, los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento, en particular el tratamiento profiláctico, de enfermedades obstructivas o inflamatorias de las vías respiratorias. Así, mediante la administración continuada y regular durante periodos de tiempo prolongados, los compuestos de Fórmula (1.0.0) son de utilidad para proporcionar protección avanzada contra la recurrencia de broncoconstricción u otro ataque sintomático como consecuencia de enfermedades obstructivas o inflamatorias de las vías respiratorias. Los compuestos de Fórmula (1.0.0) son también de utilidad para el control, mejora o inversión del estado basal de tales enfermedades.

Con respecto a su actividad broncodilatadora los compuestos de Fórmula (1.0.0) son de utilidad como broncodilatadores, por ejemplo en el tratamiento de la broncoconstricción crónica o aguda, y para el tratamiento sintomático de enfermedades obstructivas o inflamatorias de las vías respiratorias.

Las palabras "tratamiento" y "tratando" según se usan en la presente memoria descriptiva y las reivindicaciones en relación a las enfermedades obstructivas o inflamatorias de las vías respiratorias debe entenderse, en consecuencia, como que engloban tanto los modos profiláctico como sintomático de terapia.

En vista de la descripción anterior, puede observarse que la presente invención se refiere también a un procedimiento para el tratamiento de la hiperreactividad de las

vías respiratorias en los mamíferos; a un procedimiento para efectuar la broncodilatación en los mamíferos; y en particular, a un procedimiento para tratar enfermedades obstructivas o inflamatorias de las vías respiratorias, especialmente el asma, en un sujeto mamífero que lo necesite, comprendiendo dicho método la administración a dicho sujeto mamífero de una cantidad efectiva de un compuesto de Fórmula (1.0.0).

Las enfermedades obstructivas o inflamatorias de las vías respiratorias a las que es de aplicación la presente invención incluyen asma; neumoconiosis; neumonía eosinófila crónica; enfermedad obstructiva crónica pulmonar ode la vías respiratorias crónica (COAP o COPD); y síndrome disneico agudo del adulto (ARDS), así como la exacerbación de la hiperreactividad de las vías respiratorias consecuente con otras terapias con fármacos, por ejemplo, aspirina o terapia con β-agonistas.

Los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento del asma de cualquier tipo, etiología, o patogénesis; incluyendo asma intrínseca atribuida a alteraciones patofisiológicas, asma extrínseca provocada por algún factor medioambiental, y asma idiopática por causas desconocidas o no aparentes. Los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento de asma alérgica (atópica/bronquial/mediada por Ig-E); y son de utilidad también en el tratamiento de asma no atópica, incluyendo por ejemplo asma bronquítica, asma enfisematosa, inducida por el ejercicio, y ocupacional; asma infecciosa como secuela de infecciones microbiales, especialmente bacterianas, fúngicas, protozóicas, o virales; y otras asmas no alérgicas, por ejemplo asma incipiente (síndrome de sibilancias en el niño).

Los compuestos de Fórmula (1.0.0) son adicionalmente de utilidad en el tratamiento de neumoconiosis de cualquier tipo, etiología, o patogénesis; incluyendo por ejemplo aluminosis (enfermedad de los trabajadores de la bauxita); antracosis (asma

de los mineros); asbestosis (asma de los montadores de calderas); calicosis (enfermedad del sílex); ptilosis provocada por la inhalación del polvo de las plumas de avestruz; siderosis provocada por la inhalación de partículas de hierro; silicosis (enfermedad de los amoladores); bisinosis (asma del polvo del algodón); y neumoconiosis del talco.

8.2 Enfermedad pulmonar obstructiva crónica (COPD)

Los compuestos de Fórmula (1.0.0) son de utilidad adicionalmente para el tratamiento de COPD o COAD incluyendo bronquitis crónica, enfisema pulmonar o disnea asociada a ellas. La COPD se caracteriza por la obstrucción irreversible progresiva de las vías respiratorias. La bronquitis crónica está asociada a la hiperplasia e hipertrofia de las glándulas que segregan moco de la submucosa en las vías respiratorias cartilaginosas mayores. La hiperplasia de las células caliciformes, la infiltración de células inflamatorias a la mucosa y submucosa, edema, fibrosis, tapones de moco y músculo liso aumentado se encuentran todos en los bronquiolos terminales y respiratorios. Se sabe que las vías respiratorias menores son el sitio principal de obstrucción de las vías respiratorias. El enfisema se caracteriza por la destrucción de la pared alveolar y pérdida de la elasticidad pulmonar. También se han identificado numerosos factores de riesgo como relacionados a la incidencia de COPD. Está bien establecida la relación entre fumar tabaco y COPD. Otros factores de riesgo incluyen la exposición al polvo del carbón y diversos factores genéticos. Véase Sandford y cols., "Genetic risk factors for chronic obstructive pulmonary disease", *Eur. Respir. J.* 10 1380-1391, 1997. La incidencia de COPD está aumentando y representa una carga económica pesada para las poblaciones de naciones industrializadas. La COPD en sí misma se presenta clínicamente con un amplio abanico de variación desde la bronquitis crónica simple sin incapacitación hasta pacientes con un estado gravemente incapacitado con fallo respiratorio crónico.

La COPD se caracteriza por la inflamación de las vías respiratorias, como es el caso del asma, pero las células inflamatorias que se han encontrado en el fluido de lavado broncoalveolar y el esputo de los pacientes son neutrófilos en lugar de eosinófilos. También se encuentran niveles elevados de mediadores de la inflamación en los pacientes con COPD, incluyendo IL-8, LTB_4, y TNF-α, y el epitelio superficial y subepitelio de los bronquios de tales pacientes se ha visto que están infiltrados con linfocitos T y macrófagos. El alivio sintomático de los pacientes con COPD puede proporcionarse mediante el uso de broncodilatadores β-agonistas y anticolinérgicos, pero no se altera el progreso de la enfermedad. La COPD se ha tratado usando teofilina, pero sin mucho éxito, aunque reduce el recuento de neutrófilos en el esputo de pacientes con COPD. También han fracasado los esteroides como esperanza de agentes de tratamiento de la COPD satisfactorios.

En consecuencia, el uso de los compuestos de Fórmula (1.0.0) para tratar COPD y sus enfermedades de obstrucción de las vías respiratorias relacionadas e incluidas, representan un avance significativo en la técnica. La presente invención no se limita a ningún modo de acción particular o ninguna hipótesis en lo que se refiere a la forma en la que se han conseguido los objetivos terapéuticos deseados mediante el uso de los compuestos de Fórmula (1.0.0). Sin embargo, se reconoce en la técnica que PDE4 es la PDE predominante en los neutrófilos y macrófagos; Cheng y cols., "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 y cols., "Differential inhibition of human neutrophil functions: role of cyclic AMP-specific, cyclic GMP-insensitive phosphodiesterase," *Biochem. Pharmacol.* 40 699-707, 1990; Schudt y cols., "Influence of selective phosphodiesterase inhibitors of human

neutrophil functions and levels of cAMP and Cai," *Naunyn Schmiedebergs Arch. Pharmacol.* 344 682-690, 1991; y Tenor y cols., "Cyclic nucleotide phosphodiesterase isoenzyme activities in human alveolar macrophages," *Clin. Exp. Allergy* 25 625-633, 1995.

Para proporcionar un mejor entendimiento de la presente invención, se infiere aquí que los compuestos de Fórmula (1.0.0) inhiben las PDE4 en los neutrófilos, dando como resultado un quimiotactismo, activación, adherencia, y desgranulación reducidos; Schudt y cols., referencia anterior; Nelson y cols., "Effect of selective phosphodiesterase inhibitors on the polymorphonuclear leukocyte respiratory Burst," *J. Allergy Clin. Immunol.* 86 801-808, 1990; y Bloeman y cols., "Increased cAMP levels in stimulated neutrophils inhibit their adhesion to human bronchial epithelial cells," *Am. J. Physiol.* 272 L580-587, 1997.

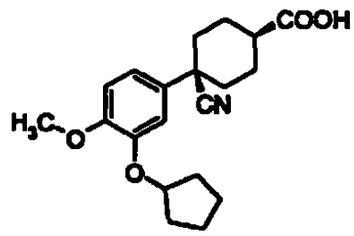
Se infiere también que los compuestos de Fórmula (1.0.0) reducen la producción de aniones de superóxido mediadas por las PDE4 en los neutrófilos de la sangre periférica, y que regulan la síntesis de leucotrienos mediada por las PDE4, Wright y cols., referencia anterior; Schudt y cols., referencia anterior; Bloeman y cols., referencia anterior; Al Essa, y cols., "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 y cols., "Cyclic AMP-elevating agents down regulate the oxidative burst induced by granulocyte-macrophage colony stimulating factor (GM-CSF) in adherent neutrophils," *Clin. Exp. Immunol.* 101 502-506, 1995; y Ottonello y cols., "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.

Se infiere además que los compuestos de Fórmula (1.0.0) inhiben la expresión de CD11b/CD18; Berends y cols., "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; y Derian y cols., "Inhibition of chemotactic peptide-induced neutrophil adhesion to vascular endothelium by cAMP modulators," *J. Immunol.* 154 308-317, 1995.

Se infiere además que los compuestos de Fórmula (1.0.0) inhiben las PDE de los macrófagos alveolares, reduciendo así la liberación de factores quimiotácticos y TNF-α; y que los compuestos de Fórmula (1.0.0) aumentan la síntesis y facilitan la liberación de los monocitos de la citoquina antiinflamatoria IL-10, que a su vez es capaz de disminuir la generación de TNF-α, IL-1β, y GM-CSF mediante células mononucleares del fluido sinovial, aumentando así el perfil antiinflamatorio global de los inhibidores de PDE4 de Fórmula (1.0.0); Schudt y cols., "PDE isoenzymes as targets for anti-asthma drugs," *Eur. Respir. J.* 8 1179-1183, 1995; y Kambayashi y cols., "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.

La aplicación de inhibidores de PDE4 al tratamiento de COPD en pacientes humanos ha sido demostrada en ensayos clínicos. Se ha demostrado que el tratamiento con SB-207.499, representado por la Fórmula (0.1.9) anterior, con una dosis de 15 mg dos veces al día durante seis semanas da como resultado aumentos de FEV_1 y capacidad vital máxima (FVC); Brown, M.W. "SB-207499", *Anti-inflamm. Immunomodulatory Invest. Drugs* 1 39-47, 1999. La eficacia clínica de SB-207.499 se ha demostrado también en un ensayo de cuatro semanas que ha proporcionado evidencia de FEV_1 mejorado; y en un estudio de seis semanas en pacientes con COPD que recibían 15 mg

dos veces al día que ha proporcionado también pruebas de FEV_1 mejorado; Brown, referencia anterior. El SB-207.499 ha sido descrito adicionalmente anteriormente y se representa mediante la Fórmula (0.1.9):



SB-207,499 (0.1.9)

8.3 Bronquitis y bronquiectasia

De acuerdo con las diversas y particulares actividades de inhibición descritas anteriormente poseídas por los compuestos de Fórmula (1.0.0), son de utilidad en el tratamiento de bronquitis de cualquier tipo, etiología o patogénesis, incluyendo, por ejemplo, bronquitis aguda que tiene un curso corto pero intenso y que es provocada por la exposición al frío, inhalación de sustancias irritantes, una infección aguda; bronquitis laringotraqueal aguda que es una forma de obstrucción laríngea no diftérica; bronquitis araquidónica que está provocada por la presencia de un cacahuete en un bronquio; bronquitis catarral que es una forma de bronquitis aguda con una secreción mucopurulenta profusa; bronquitis crónica que es una forma de bronquitis de larga continuidad con una tendencia más o menos marcada a la recurrencia tras etapas de quiescencia, debido a ataques repetidos de bronquitis aguda o enfermedades crónicas generales, caracterizadas por ataques de tos, expectoración escasa o profusa, y por cambios secundarios del tejido pulmonar; bronquitis diftérica caracterizada por toses violentas y paroxismos de disnea; bronquitis seca caracterizada por una escasa secreción

de esputo al toser; bronquitis asmática infecciosa que es un síndrome marcado por el desarrollo de síntomas de broncoespamo después de infecciones del tubo respiratorio en personas con asma; bronquitis productiva que es bronquitis asociada a una tos productiva; bronquitis por estafilococos o estreptococos que están provocadas por estafilococos o estreptococos; y bronquitis vestibular en la que la inflamación se extiende a los alvéolos, que son a veces visibles bajo la pleura como granulaciones amarillo-blanquecinas como semillas de mijo.

La bronquiectasia es una dilatación crónica de los bronquios marcada por una aliento fétido y tos paroxística con la expectoración de materia mucopurulenta. Puede afectar al tubo de modo uniforme, en cuyo caso se denomina bronquiectasia cilíndrica, o puede tener lugar en cavidades irregulares, en cuyo caso se denomina bronquiectasia saculada. Cuando los tubos bronquiales dilatados tienen engrosamientos bulbosos terminales, se usa el término bronquiectasia fusiforme. En aquellos casos en los que el estado de dilatación se extiende a los bronquiolos, se denomina bronquiectasia capilar. Si la dilatación de los bronquios es de forma esférica, la afección se denomina bronquiectasia quística. La bronquiectasia seca se da cuando la infección implicada es episódica y puede acompañarse de hemoptisis, expectoración de sangre o esputo manchado de sangre. Durante los periodos quiescentes de bronquiectasia seca, la tos que tiene lugar no es productiva. La bronquiectasia folicular es un tipo de bronquiectasia en la que el tejido linfoide de las regiones afectadas crece mucho, y mediante la proyección al lumen bronquial puede distorsionar gravemente y obstruir parcialmente el bronquio. En consecuencia, los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento beneficioso de los diversos tipos descritos anteriormente de bronquiectasia como resultado directo de su inhibición de las isozimas PDE4.

La utilidad de los compuestos de Fórmula (1.0.0) como agentes

broncodilatadores o broncoespasmolíticos para tratar el asma bronquial, la bronquitis crónica y enfermedades y trastornos relacionados descritos en el presente documento, puede demostrarse a través del uso de numerosos modelos animales *in vivo* diferentes conocidos en la técnica, incluyendo los descritos en los párrafos siguientes.

Actividad broncoespasmolítica *in vitro* - En el siguiente método de ensayo se demuestra la capacidad de los compuestos de Fórmula (1.0.0) de provocar la relajación del músculo liso traqueal en cobayas. Se sacrifican las cobayas (350-500 g) con pentotal sódico (100 mg/kg i.p.). Se diseccciona la tráquea y se corta una sección de 2-3 cm de longitud. Se secciona transversalmente la tráquea en las placas de cartílago alternas para dar anillos de tejido de 3-5 mm de grosor. Se eliminan los discos proximal y distal. Se montan los anillos individuales verticalmente sobre soportes de acero inoxidable, uno de los cuales se fija en la base de un baño de órganos, mientras que el otro se conecta a un transductor isométrico. Los anillos se bañan en solución de Krebs (composición μM: $NaHCO_3$ 25; NaCl 113; KCl 4,7; $MgSO_4 \cdot 7\ H_2O$ 1,2; KH_2PO_4 1,2; $CaCl_2$ 2,5; glucosa 11,7) a 37°C y se gasifica con O_2/CO_2 (95:5; v/v). Se preparan los anillos de esta forma, se cargan previamente con 1 g, se genera tono espontáneo y, después de un periodo de equilibrado (45-60 m), se relajan de forma consistente al añadir fármacos espasmolíticos. Para verificar la actividad espasmolítica, se disuelven los compuestos de Fórmula (1.0.0) en solución salina fisiológica y se añaden en cantidades crecientes al baño de órganos en intervalos de 5 m para dar una curva de efecto en función de la concentración acumulada.

En el modelo de ensayo anterior, los compuestos de Fórmula (1.0.0) producen una relajación relacionada con la concentración de las preparaciones de anillos traqueales de cobaya en concentraciones en el intervalo de 0,001 a 1,0 μM.

La actividad antiinflamatoria de las combinaciones de agentes terapéuticos de la

presente invención se demuestra por la inhibición de la producción de TNF α en sangre humana completa estimulada con lipopolisacárido (LPS). Se analizan los compuestos en presencia de agonistas beta (10 ng/ml) e Indometacina (1 μM). Se preparan 250 ml de tampón de ensayo HEPES 200 mM en RPMI 1640 filtrado. Lo siguiente se realiza a temperatura ambiente en el banco. Se prepara un cóctel de "IP" en un tubo de polipropileno de 50 ml añadiendo 0,4 ml de Indometacina (solución madre 4 mM) y 0,4 ml de agonista beta (solución madre 0,04 mg/ml) para un volumen final de 40 ml con tampón de ensayo. Se preparan los compuestos a partir de patrones en polvo madre en DMSO para dar soluciones a 200 ó 60 mM. Se hacen diluciones en serie semilogarítmicas de ocho puntos en viales de cristal o microtubos. Se añade 0,01 ml de cada dilución de compuesto a los tubos de polipropileno de 5 ml donde se añade 0,490 ml de tampón de ensayo y 0,50 ml de cóctel de "IP" para un v.f. de 1,0 ml. (Concentración final (C.f.) de compuesto de ensayo 100-0,1 μM). Se prepara la solución de LPS de tal forma que se añade 0,08 ml de LPS (solución madre de 1 mg/ml) a 40 ml de tampón de ensayo para una c.f. de 2 μg/ml. 6. Se prepara una solución de DMSO al 2% añadiendo 200 μl de DMSO a 9,8 ml de tampón de ensayo. Se añaden 10 ml de cóctel IP a la solución de DMSO al 2%. Este cóctel se usa para los pocillos de control de tal forma que la c.f. de ensayo de Indometacina es 1 μM y la c.f. de agonista beta es de 10 ng/ml. Lo siguiente se realizan bajo la campana de cultivo tisular. Se añade 0,0125 ml de compuesto diluido al pocillo apropiado en placas Costar de 96 pocillos estériles de fondo en U nº 3790. Se añade 0,0125 ml de LPS a todos los pocillos (c.f. 0,1 μg/ml) excepto a los pocillos de control negativo. Se introduce sangre completa humana extraída recientemente (~22 ml por placa de 96 pocillos) habitualmente cuatro recipientes de tapa verde por donante en tubos de heparina estériles mantenidos a 37ºC. Se añaden 0,225 ml de sangre entera a las placas. Se cubre, se incuba a 37ºC, y se

mueve suavemente durante cuatro horas. Se centrifugan las placas a 2000 rpm durante 10 minutos. Se preparan los patrones de ELISA. Se retiran 100 μl de suero en una placa de fondo plano. Se diluye hasta una relación 1:20 eliminando 15 μl y añadiendo 285 μl de diluyente RD6. Se congela a -20°C. Para analizar se descongela y se añaden 200 μl a un R & D Systems TNFα ELISA. Se procesan las placas de acuerdo con el protocolo de R & D Systems. Se lee la placa a 450 nm usando SoftMax Pro. Se analizan e interpretan con el programa Java Fitter para determinar los valores de CI_{50}. Se representa una curva de respuesta en función de la dosis de los datos expresados como porcentaje del control. Se generan un mínimo de seis puntos triplicados para cada compuesto. Se calculan los valores de CI_{50} usando el programa de ajuste de curvas Java Fitter bajo el parámetro de "IC50 fix both".

En el modelo de ensayo anterior, las combinaciones de agentes terapéuticos de la presente invención producen una inhibición relacionada con la concentración de la producción de TNFα en concentraciones en el intervalo de 0,001 a 1,0 μM.

8.4 Rinitis alérgica y de otros tipos; Sinusitis

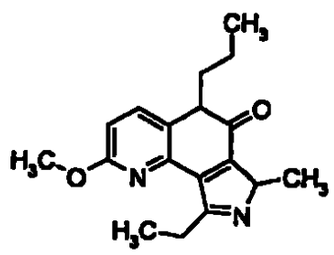
La rinitis alérgica se caracteriza por obstrucción nasal, picor, rinorrea acuosa, estornudos y anosmia ocasional. La rinitis alérgica se divide en dos categorías de enfermedad, estacional y perenne, en la que la primera se atribuye al polen o esporas de moho exterior, mientras que la última se atribuye a los alérgenos comunes tales como los ácaros del polvo de casa, caspa animal, y esporas de los mohos. La rinitis alérgica generalmente muestra una respuesta temprana y una respuesta tardía. La respuesta temprana se asocia a la desgranulación de los mastocitos, mientras que la respuesta tardía se caracteriza por la infiltración de eosinófilos, basófilos, monocitos, y linfocitos T. Estas células liberan también una variedad de mediadores de la inflamación, todos los cuales pueden contribuir a la inflamación que se exhibe en la respuesta tardía.

Una forma particularmente prevalente de rinitis alérgica estacional es la fiebre del heno, que viene marcada por conjuntivitis aguda con lagrimeo y picor, hinchazón de la mucosa nasal, mucosidad nasal, ataques repentinos de estornudos, y a menudo 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 en los que pueden usarse los compuestos de Fórmula (1.0.0) como agentes terapéuticos incluyen rinitis catarral aguda que es un resfriado de cabeza que incluye congestión aguda de la membrana mucosa de la nariz, marcada por sequedad y seguida de secreción de mucosa aumentada de la membrana, respiración impedida a través de la nariz, y algo de dolor; rinitis atrófica que es una forma crónica marcada por la destrucción de la membrana mucosa y las glándulas; rinitis purulenta que es rinitis crónica con la formación de pus; y rinitis vasomotora que es una rinitis no alérgica en la que los cambios transitorios del tono vascular y permeabilidad con los mismos síntomas de la rinitis alérgica son provocados por estímulos tales como enfriamiento leve, fatiga, ira, y ansiedad.

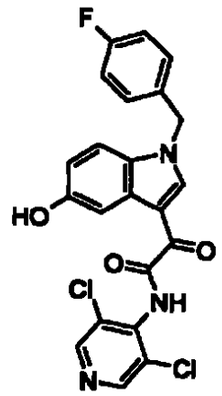
Existe una conexión reconocida entre la rinitis alérgica y el asma. La rinitis alérgica es un acompañamiento frecuente del asma, y se ha demostrado que el tratamiento de la rinitis alérgica mejora el asma. Se han usado también datos epidemiológicos para demostrar una relación entre la rinitis grave y el asma más grave. Por ejemplo, se ha demostrado que el compuesto D-22888, en desarrollo preclínico para el tratamiento de la rinitis alérgica, exhibe un fuerte efecto antialérgico e inhibe la rinorrea en el cerdo expuesto a antígenos. Véase, Marx y 30 cols. "D-22888 - a new PDE4 inhibitor for the treatment of allergic rhinitis and other allergic disorders," *J. Allergy Clin. Immunol.* 99 S444, 1997. Se ha demostrado que otro compuesto experimental, AWD-12.281, es activo en un modelo en rata de rinitis alérgica. Véase

Poppe y cols. "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. Los compuestos D-22888 y AWD-12.281 ya han sido descritos antes y se representan con la 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 a la rinitis en términos de proximidad anatómica así como por una etiología y patogénesis compartida en algunos casos. La sinusitis es la inflamación de un seno nasal y esta afección puede ser purulenta o no purulenta, así como aguda o crónica. Dependiendo del seno nasal donde se localiza la inflamación, la afección se conoce como sinusitis etmoidal, frontal, maxilar, o esfenoidal. El seno etmoidal es un tipo de seno paranasal, localizado en el hueso etmoides. El seno frontal es uno de los senos pareados paranasales, localizados en el hueso frontal. El seno maxilar es uno de los senos pareados paranasales localizados en el cuerpo del maxilar. En consecuencia, los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento beneficioso de la sinusitis aguda o crónica, pero especialmente de la sinusitis crónica.

8.5 Artritis reumatoide, osteoartritis, dolor, fiebre, y gota

La artritis se define como inflamación de las articulaciones, y la artritis reumatoide es una enfermedad sistémica crónica primordialmente de las articulaciones, habitualmente 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 anquilosis y deformidad. La artritis reumatoide es una enfermedad autoinmunitaria que provoca parálisis de etiología desconocida que afecta a más del 1% de la población.

Según se usa en el presente documento, el término "artritis reumatoide" se pretende que incluya dentro de su alcance cuando sea aplicable formas relacionadas y asociadas de artritis notorias en la técnica, ya que éstas pueden tratarse también con los compuestos de Fórmula (1.0.0). En consecuencia, el término "artritis reumatoide" incluye artritis aguda, que es artritis marcada por dolor, calor, enrojecimiento, e hinchazón debidos a la inflamación, infección o traumatismo; artritis gotosa aguda, que es artritis aguda asociada a la gota; artritis inflamatoria crónica, que es la inflamación de las articulaciones en trastornos crónicos tales como artritis reumatoide; artritis degenerativa, que es osteoartritis; artritis infecciosa, que es artritis provocada por bacterias, rickettsia, micoplasmas, virus, hongos, o parásitos; artritis de Lyme, que es artritis de las articulaciones largas asociada a la enfermedad de Lyme 20; artritis proliferativa, que es inflamación de las articulaciones con proliferación del sinovio, observada en la artritis reumatoide; artritis soriásica, que es un síndrome en el que la soriasis aparece asociada a artritis inflamatoria; y 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 destrucción progresiva de la articulación son la inflamación, las

respuestas celulares y humorales anormales, y la hiperplasia sinovial. La patología celular particular de la artritis reumatoide incluye la presencia de linfocitos T y monocitos. Los linfocitos T, que son predominantemente linfocitos T con memoria, constituyen hasta el 50% de las células recuperadas del tejido sinovial de los pacientes con artritis reumatoide; y de los monocitos encontrados en el mismo tejido, del 30-50% son células presentadoras de antígeno, lo que es indicativo del carácter autoinmunitario de la enfermedad. Las citoquinas proinflamatorias, por ejemplo IL-1, IL-4, IL-5, IL-6, IL-9, IL-13, y TNF- α, son los contribuyentes principales a las lesiones, inflamación, hiperplasia, del tejido articular, formación de cataratas y resorción ósea. Véase Firestein, G.S. y Zvaifier, W.J., "How important are T-cells in chronic rheumatoid synovitis?" *Arth. Rheum.* 33 768-773, 1990. Esto ha sido demostrado, por ejemplo, por el hecho de que los anticuerpos monoclonales (mab) contra TNF-α han demostrado ser una esperanza en los ensayos clínicos de artritis reumatoide (AR); Maini y cols. "Beneficial effects of tumor necrosis factor-alpha (TNF- α blockade in rheumatoid arthritis (RA)," *Clin. Exp. Immunol.* 101 207-212, 1995.

Los inhibidores de PDE4 de Fórmula (1.0.0) son de utilidad en el tratamiento de artritis reumatoide como resultado de su capacidad de suprimir la actividad de una diversidad de células inflamatorias, incluyendo basófilos, eosinófilos, y mastocitos. Estas actividades inhibidoras de los compuestos de fórmula (1.0.0) han sido ya descritas anteriormente, al igual que su amplio espectro de acción antiinflamatoria *in vitro* mediante la liberación de especies reactivas de oxígeno, prostaglandinas, y citoquinas inflamatorias, por ejemplo IL-5, IFN-γ, y TNF-α. Véase adicionalmente Cohan y cols., "*In vitro* pharmacology of the novel phosphodiesterase Type IV inhibitor, CP-80.633", *J. Pharm. Exp. Ther.* 278, 1356-1361, 1996; y Barnette y cols., "SB207499 (Ariflo), a potent and selective second generation phosphodiesterase 4 inhibitor: *in vitro* anti-

inflammatory actions," *J. Pharm. Exp. Ther.* 284, 420-426, 1998. Los inhibidores de PDE4 de Fórmula (1.0.0) son también de utilidad en el tratamiento de artritis reumatoide como resultando de su efectividad en la inhibición de la proliferación de linfocitos T mediada por numerosos agentes diferentes, incluyendo antígenos tales como los ácaros del polvo de casa, que ha sido demostrada en la técnica; Barnette y cols., referencia anterior. La capacidad de los compuestos de fórmula (1.0.0) de facilitar la liberación de citoquina IL-10 a partir de los monocitos, que es a su vez capaz de disminuir la generación de TNF-α, IL-1, IL-4, IL-5, IL-6, IL-9, IL-13, y GM-CSF por los mononucleocitos del fluido sinovial, aumenta adicionalmente el perfil antiinflamatorio global de los inhibidores de PDE4 de Fórmula (1.0.0); Kambayashi y cols, referencia anterior. Adicionalmente, la capacidad de los compuestos de fórmula (1.0.0) de inhibir la liberación de TNF-α por los monocitos estimulados puede correlacionarse con modelos animales de inflamación en los que puede demostrarse que los efectos antiinflamatorios corresponden a la supresión de la acumulación de TNF-α. Un modelo animal así implica la inhibición de la liberación de TNF-α inducida por LPS en ratones mediante la administración oral de un inhibidor de PDE4; Cheng y cols., "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. Otro modelo animal así implica la inhibición de edema en la pata de rata, inducida por carragenina, mediante la administración oral de rolipram; Singh y cols, "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 (Supl. 2) S153-S154, 1997.

La gota se refiere a un grupo de trastornos del metabolismo de la purina, y la gota completamente desarrollada se manifiesta mediante diversas combinaciones de

hiperuricemia, artritis inflamatoria aguda recurrente característica inducida por los cristales de monohidrato de urato monosódico, depósitos tofáceos de dichos cristales en y alrededor de las articulaciones de las extremidades, que pueden llevar a la destrucción de las articulaciones e incapacitación grave, y urolitiasis de ácido úrico. La gota reumática es otro nombre de la artritis reumatoide. La gota tofácea es gota en la que hay depósitos de tofo o calcáreos de urato sódico. Algunos agentes terapéuticos son de utilidad en el tratamiento tanto de gota como la inflamación que la acompaña, por ejemplo, fenilbutazona y colchicina; mientras que otros agentes terapéuticos poseen únicamente propiedades uricosúricas, por ejemplo sulfinpirazona y benzbromarona.

La fiebre o pirexia, pueden ser resultado de una cualquiera de un gran número de factores diferentes, pero con respecto a la presente invención tal fiebre es la manifestada en la fiebre faringoconjuntival o la fiebre reumática, o la que se manifiesta durante la inflamación. Concomitante a la inflamación es el dolor, especialmente el experimentado en las articulaciones y tejido conectivo de aquellos que sufren la artritis reumatoide y gota.

En consecuencia, los compuestos inhibidores de PDE4 de Fórmula (1.0.0) proporcionan resultados beneficiosos en el tratamiento de la gota, y fiebre y dolor asociados a la inflamación.

Se han usado también modelos animales de la artritis reumatoide en la técnica con el fin de demostrar la correlación entre la modulación *in vivo* de TNF-α mediante inhibidores de PDE4 y su utilidad en el tratamiento de la artritis reumatoide. Se ha demostrado en la técnica la actividad de rolipram en modelos animales de inflamación aguda tales como el modelo de artritis adyuvante en el ratón; Sekut y cols., "anti-inflammatory activity of phosphodiesterase (PDE) IV inhibitors in acute and chronic models of inflammation," *Olin Exp. Inmunol.* 100(1) 126-132, 1995. La capacidad del

rolipram de reducir la gravedad de la enfermedad en el modelo de artritis inducida por colágeno II (CIA) después de la inyección sc. o ip. ha sido demostrada en la técnica; Nyman y cols., "Amelioration of collagen II induced artritis in rats by Type IV phosphodiesterase inhibitor rolipram," *Olin. Exp. Immunol.* 108 415-419, 1997. En este estudio el régimen de dosificación de rolipram era de 2 mg/kg dos veces al día durante cinco días antes del inicio de la artritis, y retrasó significativamente la aparición de síntomas artríticos. Después del cese del tratamiento los animales de ensayo desarrollaron artritis y alcanzaron la misma puntuación máxima de artritis que el grupo control. En el mismo estudio rolipram se administró también 3 mg/kg dos veces al día en el momento en el que aparecía la artritis. Este tratamiento cambió drásticamente el desarrollo de la enfermedad por el que el progreso de la gravedad se paró e incluso después del cese del tratamiento, la puntuación de artritis no alcanzó los niveles observados en los animales sin tratamiento. Los investigadores fueron también capaces de demostrar una regulación por disminución potente de la expresión del ARNm de TNF-α e IFN-γ en los nódulos linfáticos regionales, lo que sugiere que el efecto principal de rolipram se ejerce en la fase efectora del proceso de inflamación. Nyman y cols, referencia anterior.

Inhibición de la Producción de TNF-α por los 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 puede determinarse de acuerdo con el protocolo descrito en EP 411 754 (Badger y cols.) y WO 90/15534 (Hanna). Las publicaciones referenciadas describen también dos modelos de choque endotóxico que pueden usarse para determinar la actividad inhibidora *in vivo* de los compuesto de fórmula (1.0.0). Se detallan los protocolos usados en estos modelos y los compuestos de ensayo demuestran un resultado positivo al reducir los niveles en suero de TNF-α inducidos por la

inyección de endotoxina.

Los inhibidores de PDE4 selectivos tales como RP73401 han demostrado que exhiben una mejora significativa de la enfermedad, especialmente mejoras en la destrucción articular, sinovitis, y fibrosis, en modelos animales tales como los que implican la artritis inducida por pared celular estreptocócica (SCW); Souness y cols., "Potencial of phosphodiesterase Type IV inhibitors in the treatment of rheumatoid arthritis," *Drugs* 1 541-553, 1998.

De interés particular para el tratamiento de la artritis reumatoide es la observación de que los inhibidores de PDE4 tienen efectos positivos en el lugar de acción de la enfermedad. Por ejemplo se ha demostrado que RP73401 disminuye la expresión del ARNm de TNF-α en la interfase del paño sinovial/cartílago de las articulaciones de la patas de los ratones tratados con colágeno II. Souness y cols., referencia anterior. También se ha estudiado RP73401 clínicamente en los pacientes con artritis reumatoide en un estudio controlado por placebo, de doble ciego de Phase II de 35 pacientes con artritis reumatoide a los que se administra 400 pg del compuesto t.i.d. El compuesto fue capaz de inducir una tendencia positiva hacia la mejora clínica asociada a una reducción en la proteína reactiva C y en los niveles de IL-6 en suero. Chikanza y cols., "The clinical effects of RP73401 phosphodiesterase Type 4 inhibitor in patients with rheumatoid arthritis", *Br. J. Rheumatol.* 36: Abstr. Suppl. I, 186, 1997.

Ensayos sobre la acumulación aumentada de AMPc en tejidos intactos usando células U-937 -

Otro ensayo adecuado para demostrar la actividad inhibidora de PDE4 de los compuestos de fórmula (1.0.0) es uno que utiliza las células U-937 a partir de una línea celular de monocitos humanos que se ha demostrado que contiene una gran cantidad de PDE4. Para evaluar la inhibición de la actividad de PDE4 en células intactas, se incuban

células U-937 no diferenciadas con una densidad de aproximadamente 10^5 células por tubo de reacción con concentraciones en el intervalo de 0,01 a 1000 pM de compuesto de ensayo durante un minuto, y con 1 μM de prostaglandina E2 durante cuatro minutos más. Cinco minutos después de iniciar la reacción, se lisan las células mediante la adición de ácido perclórico al 17,5%, después de lo cual el pH se lleva a neutro añadiendo carbonato potásico 1M. El contenido en AMPc del tubo de reacción se mide usando técnicas de radioinmunoensayo (RIA). Se describe un protocolo detallado para realizar este ensayo en Brooker y cols., "Radioimmunoassay of cyclic AMP and cyclic GMP," *Adv. Cyclic Nucleotide Res.*10 1-33, 1979.

8.6 Trastornos relacionados con la eosinofilia

La capacidad de los compuestos inhibidores de PDE4 de Fórmula (1.0.0) de inhibir la activación de eosinófilos como parte de su actividad antiinflamatoria global ha sido descrita anteriormente. En consecuencia, los compuestos de fórmula (1.0.0) son de utilidad en el tratamiento terapéutico de trastornos relacionados con los eosinófilos. Tales trastornos incluyen eosinofilia, que es la formación y acumulación de un número anormalmente grande de eosinófilos en la sangre. El nombre del trastorno se deriva de "eosin", una tinción o tinte de color rosado que comprende un bromoderivado de fluoresceína que tiñe fácilmente los "leucocitos eosinófilos" en la sangre de los pacientes que son así fácilmente identificados. Un trastorno eosinófilo particular que puede tratarse de acuerdo con la presente invención es la eosinofilia de infiltración pulmonar que se caracteriza por la infiltración del parénquima pulmonar por los eosinófilos. Este trastorno induce especialmente el síndrome de Loffler, que es una afección caracterizada por las infiltraciones transitorias de los pulmones, acompañadas de tos, fiebre, disnea, y eosinofilia.

Otros trastornos eosinófilos incluyen la neumonía eosinófila crónica, que es una

enfermedad pulmonar intersticial crónica caracterizada por tos, disnea, malestar, fiebre, sudores nocturnos, pérdida de peso, eosinofilia, y una radiografía de tórax que revela infiltraciones no segmentadas, no migratorias en la periferia pulmonar; eosinofilia pulmonar tropical, que es una forma subaguda o crónica de filariasis oculta, que habitualmente implica *Brugia Malayi, Wuchereria bancrofti,* o *filariae* que infecta animales, se da en el trópico, y se caracteriza por silbidos y toses nocturnos episódicos, eosinofila sorprendentemente elevada, e infiltraciones reticulonodulares difusas de los pulmones; aspergilosis bronconeumónica, que es una infección de los bronquios y pulmones por hongos *Aspergillus* que da como resultado un estado de enfermedad marcado por lesiones granulomatosas inflamatorias en los senos nasales y pulmones, pero también en la piel, oído, órbita, y algunas veces en los huesos y meninges, y que conlleva aspergiloma, el tipo más común de aspergiloma formado por la colonización de *Aspergillus* en un bronquio o cavidad pulmonar.

El término "granulomatoso" quiere decir que contiene granulomas, y el término "granuloma" se refiere a cualquier pequeña agregación delimitada nodular de células inflamatorias mononucleares o una colección tal de macrófagos modificados que se parecen a las células epiteliales, habitualmente rodeada por un aro de linfocitos, observándose comúnmente fibrosis alrededor de la lesión. Algunos granulomas contienen eosinófilos. La formación de granulomas representa una respuesta de inflamación crónica iniciada por diversos agentes infecciosos y no infecciosos. Un número de tales afecciones granulomatosas son tratables usando un compuesto de fórmula (1.0.0), por ejemplo, angitis granulomatosa alérgica, también denominada síndrome de Churg-Strauss, que es una forma de vasculitis necrosante sistémica en la que hay una implicación pulmonar prominente, generalmente manifestada por eosinofilia, reacciones granulomatosas, y habitualmente asma grave. Un trastorno

relacionado es la poliarteritis nodosa (PAN), que está marcada por múltiples lesiones arteriales inflamatorias y destructivas y es una forma de vasculitis necrosante sistémica que implica las arterias de tamaño pequeño y medio con signos y síntomas como resultado del infarto y cicatrización del sistema de órganos afectado, en particular los pulmones. Otros trastornos relacionados con los eosinófilos que pueden tratarse de acuerdo con la presente invención son aquellos que afectan las vías respiratorias que son inducidos u ocasionados por una reacción a un agente terapéutico no relacionado con ningún compuesto de Fórmula (1.0.0).

8.7 Dermatitis atópica, urtic.. .a, conjuntivitis, y uveítis

La dermatitis atópica es un trastorno cutáneo inflamatorio y crónico observado en individuos con una predisposición hereditaria a un umbral cutáneo disminuido a pruritos, que a menudo viene acompañado de rinitis alérgica, fiebre del heno, y asma y que está caracterizada principalmente por un picor extremo. La dermatitis atópica se denomina también dermatitis alérgica, y eczema alérgico o atópico.

La dermatitis atópica (AD) es la enfermedad inflamatoria crónica cutánea más común en los niños pequeños, y afecta del 10% al 15% de la población durante la niñez. La dermatitis atópica se asocia frecuentemente al asma y alergias y se ha venido conociendo hasta ahora como un componente de la denominada "triada atópica", dado que ocurre frecuentemente en individuos con asma y/o rinitis alérgica. Véase Leung Dym, *Atopic Dermatitis*: *from Pathogénesis to treatment*, R.G. Landes Co., Austin, Texas, 1-226, 1996. En consecuencia, la disfunción inmunitaria asociada a la dermatitis atópica puede tratarse con agentes terapéuticos que son inhibidores de PDE4. Por ejemplo, se ha informado de que rolipram, Ro-201724, y denbufilina producen una inhibición relacionada con la concentración de la proliferación de mononucleocitos de la sangre periférica humana (HPBM) en pacientes normales así como en sujetos con

dermatitis atópica. Véase, respectivamente, Torphy y cols., *Drugs and the Lung*, Editores Page y Metzger, Raven Press, New York, 1994; y O'Brien, *Mol. Medicine Today*, 369, 1997. Estos estudios determinaron también que la respuesta proliferativa de HPBM en los pacientes con dermatitis atópica era más sensible a la inhibición de PDE4 que la proliferación observada en HPBM de sujetos normales.

Los linfocitos T tipo Th2 que segregan citocinas que expresan el antígeno asociado a linfocitos cutáneos representan un papel central en la inducción de respuestas de IgE locales y el reclutamiento de eosinófilos en esta enfermedad. La inflamación crónica observada en la dermatitis atópica se considera que es un resultado de diversos factores interdependientes, tales como la exposición a alérgenos repetida o persistente, que puede conllevar la expansión de linfocitos Th2. Se ha demostrado que existe una frecuencia aumentada de linfocitos T específicos de alérgenos que producen niveles aumentados de IL-4, IL-5, e IL-3 en la sangre de pacientes con dermatitis atópica. Véase Leung Dym y cols., "Allergic and immunological skin disorders," *JAMA* 278(22) 1914-1923, 1997. Esto es significativo porque IL-4 e IL-3 inducen la expresión de la molécula de adhesión vascular 1 (VCAM-1), una molécula de adhesión implicada en la migración de mononucleocitos y eosinófilos a los sitios de inflamación tisular. Adicionalmente, IL-5 es un mediador clave de la activación de eosinófilos, que es una característica común de enfermedad atópica.

Se ha sabido desde hace tiempo que la concentración aumentada de AMPc en los linfocitos y basófilos está asociada a una liberación de mediador disminuida de esas células, y más recientemente se ha comunicado que la histamina que actúa sobre los receptores H2 aumenta los niveles de AMPc e inhibe la producción de IL-4 en las células Th2 murinas. Se presupone, en consecuencia, que se presentan respuestas β-adrenérgicas alteradas o actividad de PDE4 potenciada de las respuestas inflamatorias

de los leucocitos en enfermedades atópicas tales como dermatitis atópica. Una respuesta de AMPc disminuida puede ser el resultado de una actividad potenciada de PDE4 que tiene una base genética o que es una afección adquirida.

Se han realizado estudios que comparan los distintos tipos celulares de pacientes atópicos con los de voluntarios sanos, y los resultados han demostrado que la actividad aumentada de AMPc-PDE en células atópicas se correlaciona con una función celular inflamatoria e inmunitaria anormal en la dermatitis atópica. Además, la enzima PDE4 de los leucocitos atópicos es más sensible a los inhibidores de PDE4 que la enzima PDE4 de los leucocitos normales, y se ha demostrado una diferencia de hasta 14 veces superior. Véase Chan y Hanifin, "Differential inhibitory effects of cAMP phosphodiesterase isoforms in atopic and normal leukocytes," *J. Lab. Clin. Med.*, 121 (1) 44-51, 1993. Puede observarse también una sensibilidad aumentada en la inhibición de la proliferación de mononucleocitos de la sangre periférica de donantes atópicos al ser tratados con inhibidores de PDE4. Por ejemplo se ha observado que rolipram es más efectivo en la inhibición de la proliferación de PBMC estimulada por PHA en dermatitis atópica que en la inhibición de la proliferación de PBMC estimulada por PHA normal, con una CI_{50} = 280 nM comparada con un CI_{50} = 2600 nM, respectivamente.

Adicionalmente, se ha demostrado que una variedad estructuralmente diversa de inhibidores de selectivos PDE4 son efectivos en la reducción de la eosinofilia cutánea en las cobayas que ha sido mediada por una variedad de agentes tales como PAF, ácido araquidónico, plasma activado por zimosan, y proteína de anafilaxis cutánea. Véase Beasley y cols., "Synthesis and evaluation of a novel series of phosphodiesterase 4 inhibitors. A potential treatment for asthma," *Bioorg. Med. Chem. Letts.* 8 2629-2634, 1998. Tales datos muestran la utilidad de los inhibidores de PDE4 en el tratamiento de las enfermedades cutáneas dirigidas por eosinófilos. Tal tratamiento es mediante la

administración tópica, por ejemplo, atirozam tópico aplicado bilateralmente durante ocho días a veinte pacientes en un ensayo clínico se ha demostrado que inhibe de forma efectiva todos los parámetros inflamatorios ensayados, demostrando tanto mejoras cualitativas como cuantitativas sin efectos adversos. Véase Hanifin y cols., "Type 4 phosphodiesterase inhibitors have clinical and *in vitro* anti-inflammatory effects in atopic dermatitis," *J. Invest. Dermatol.* 107 51-56, 1996.

En consecuencia, los inhibidores de PDE4 de Fórmula (1.0.0) son de utilidad para el tratamiento beneficioso de la dermatitis atópica como se describe anteriormente. Un área relacionada de aplicación terapéutica por la que los compuestos de Formula (1.0.0) producen también resultados beneficiosos es en el tratamiento de urticaria. La urticaria es una reacción vascular, habitualmente transitoria, que implica la dermis superior, representando un edema localizado provocado por la dilatación y permeabilidad aumentada de los capilares, y marcada por el desarrollo de ronchas o habones. Muchos estímulos diferentes son capaces de inducir una reacción de urticaria, y puede clasificarse de acuerdo con las causas que la precipitan como: inmunomediada, mediada por complemento que pueden implicar mecanismos inmunológicos o no inmunológicos, inducida por material urticante, inducida por agentes físicos, inducida por estrés, o idiopática. La afección puede designarse también como aguda o crónica dependiendo de la duración del ataque. El angioedema es la misma respuesta en la dermis profunda o en los tejidos subcutáneos o submucosos.

Los tipos más comunes de urticaria que son tratables con los compuestos de Fórmula (1.0.0) son la urticaria colinérgica que se caracteriza por la presencia de ronchas con puntos distintivas rodeadas de zonas de eritema, que se cree que son una reacción de hipersensibilidad no inmunológica en la que la acetilcolina liberada de los terminales nerviosos parasimpáticos o motores induce la liberación de mediadores de

los mastocitos, y evocados por estados de esfuerzo, estrés, o calor ambiental aumentado; urticaria fría que es la urticaria precipitada por el aire, agua u objetos fríos, que se da en dos formas: en la forma de autosoma dominante que se asocia a fiebres, artralgias, y leucocitosis, las lesiones presentes son pápulas y máculas eritematosas, que escuecen, y en la forma adquirida más común que es habitualmente idiopática y autolimitada; la urticaria de contacto que es una respuesta localizada o generalizada transitoria de ronchas y explosión provocada por la exposición a agentes urticantes que se absorben rápidamente; urticaria gigante que es angioedema; y urticaria papular que es una erupción cutánea persistente que representa una reacción de hipersensibilidad a las picaduras de insectos.

En consecuencia, los inhibidores de PDE4 de Fórmula (1.0.0) son de utilidad para el tratamiento beneficioso de diversos tipos de urticaria como se describe anteriormente. Un área de aplicación terapéutica relacionada para la que los compuestos de Fórmula (1.0.0) producen también efectos beneficiosos es en diversos usos oftálmicos, en particular en el tratamiento de conjuntivitis y uveítis.

La conjuntiva es una membrana delicada que delimita el párpado y cubre el área expuesta de la membrana esclerótica. La conjuntivitis es una inflamación de la conjuntiva que generalmente consiste en hiperemia conjuntival asociada a una secreción. Los tipos más comunes de conjuntivitis, que pueden tratarse con los compuestos de Fórmula (1.0.0), son la conjuntivitis actínica producida por la luz ultravioleta; conjuntivitis catarral aguda que es una conjuntivitis infecciosa aguda asocicada al resfriado o catarro y caracterizada por hiperemia vívida, edema, pérdida de traslucidez, y secreciones mucosas o mucopurulentas; conjuntivitis aguda contagiosa que es una conjuntivitis mucopurulenta, epidémica provocada por *Haemophilus aegyptius* que se tiene los mismos síntomas que la conjuntivitis catarral aguda y se

llama también de "ojo rosa"; la conjuntivitis alérgica que es un componente de la fiebre del heno; la conjuntivitis atópica que es conjuntivitis alérgica del tipo inmediato provocada por alérgenos que se extienden por el aire, por ejemplo, pólenes, polvos, esporas, y caspa animal; conjuntivitis catarral crónica que es una conjuntivitis leve, crónica únicamente con una leve hiperemia y secreciones mucosas; conjuntivitis purulenta que es una conjuntivitis aguda provocada por bacterias o virus, en particular gonococos, meningococos, neumococos, y estreptococos, y caracterizada por una inflamación grave de la membrana conjuntiva y una secreción copiosa de pus; y conjuntivitis primaveral que es una conjuntivitis bilateral que se da estacionalmente, de causas desconocidas, que afecta a los niños, especialmente a los niños y caracterizada por pápulas planas y un exudado grueso, gelatinoso. En consecuencia, los inhibidores de PDE4 de Fórmula (1.0.0) son de utilidad para el tratamiento beneficioso de los diversos tipos de conjuntivitis descritas anteriormente. Un área relacionada de aplicación terapéutica para la que los compuestos de Fórmula (1.0.0) producen también resultados beneficiosos es el tratamiento de uveítis.

La úvea es la capa media vascular o túnica del ojo, que comprende el iris, cuerpo ciliado, y coroides. La uveítis es una inflamación de toda o parte de la úvea y comúnmente implica las otras túnicas del ojo, es decir, la esclerótica y la córnea, así como la retina. Los tipos más comunes de uveítis, que pueden tratarse con los compuestos de Fórmula (1.0.0), son la uveítis anterior que es la uveítis que implica las estructuras del iris y/o cuerpo ciliar, incluyendo iritis, ciclitis, e iridociclitis; uveítis granulomatosa que es uveítis de cualquier parte del tracto uveal pero particularmente la porción posterior, caracterizada por las recolecciones nodulares de células epiteloides y células gigantes rodeadas de linfocitos; uveítis no granulomatosa que es una inflamación de la porción anterior del tracto uveal, es decir el iris y el cuerpo ciliar;

uveítis facoantígena que es un tipo de uveítis inducida por lentes, es una uveítis anterior grave similar a la oftalmia simpática observada semanas o incluso meses después de la cirugía de lentes extracapsulares u otro traumatismo de la cápsula; y uveítis posterior que es la uveítis que implica el segmento posterior del ojo, incluyendo coroiditis y coriorretinitis. En consecuencia, los inhibidores de PDE4 de Fórmula (1.0.0) son de utilidad para el tratamiento beneficioso de los diversos tipos de uveítis como se describen anteriormente.

8.8 Soriasis

La soriasis es una dermatosis escamosa común, crónica, con herencia poligénica y un curso fluctuante caracterizado por microabcesos y pústulas espongiformes, así como parches eritematosos, secos, que se descaman de varios tamaños. La soriasis es una enfermedad cutánea común que afecta aproximadamente al 2% de la población, y más de 1 ½ millones de pacientes en los Estados Unidos consultan anualmente a los médicos para obtener un tratamiento. La soriasis es habitualmente recurrente y en algunos casos puede ser muy debilitante. La etiología de la psoriasis es desconocida, pero parece ser una enfermedad autoimunitaria con predisposición genética.

La soriasis implica una gran infiltración de linfocitos 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 la proliferación y diferenciación de queratinocitos. Además, del 5% al 10% de los pacientes con soriasis desarrollan artritis soriásica, cuyos síntomas son muy similares a los de la artritis reumatoide. El amplio espectro de actividades antiinflamatorias que presentan los inhibidores de PDE4, ya analizadas anteriormente, permite que tales inhibidores se usen beneficiosamente en el tratamiento de la soriasis.

Se ha demostrado que el tratamiento de las células basales epidérmicas, en

cultivo primario, con el inhibidor de PDE Ro 20-1724 conlleva un aumento de tres veces la concentración de AMPc. Se ha demostrado también que el tratamiento de cortes epidérmicos soriasicos y cortes epidérmicos con soriasis queratomizada con Ro 20-1724 da como resultado una elevación muy marcada de concentraciones de AMPc en relación a los controles. Específicamente, se ha observado un aumento del 1395% de la concentración de AMPc en epidermis con soriasis queratomizada. Los inhibidores de PDE4 han demostrado también que inhiben la respuesta inflamatoria de numerosos mediadores mediante la administración tópica o sistémica. Por ejemplo, se ha demostrado que rolipram inhibe la inflamación de oídos inducida por aceite de crotón en el ratón en dosis tópicas desde 0,03 mg por oído. El inhibidor selectivo de PDE4 Ro 20-1724 se ha investigado también en dos estudios de doble ciego comparando su efectividad con el vehículo, donde se ha demostrado que mejora las lesiones soriásicas sin efectos sistémicos o cutáneos adversos.

8.9 Esclerosis múltiple y otras enfermedades inflamatorias autoinmunitarias

Una esclerosis es una induración, o endurecimiento, y se refiere especialmente al endurecimiento por una parte por inflamación, y por la formación aumentada de tejido conjuntivo y en enfermedades de la sustancia intersticial. El término "esclerosis" se usa principalmente para tales endurecimientos del sistema nervioso debidos a la deposición de tejido conjuntivo, o para designar el endurecimiento de los vasos sanguíneos. La esclerosis múltiple (MS) es una enfermedad en la que hay focos de desmielinación de diversos tamaños por toda la sustancia blanca del sistema nervioso central, que algunas veces se extiende a la sustancia gris, dando como resultado debilidad, falta de coordinación, parestesias, alteraciones del habla, y enfermedades visuales. La esclerosis múltiple es una enfermedad de etiología desconocida con un curso prolongado que

implica muchas remisiones y recaídas.

La esclerosis múltiple es una enfermedad autoinmunitaria que además de la inflamación crónica y desmielinación, da como resultado también la gliosis en el sistema nervioso central. Hay diversos subtipos de la enfermedad, incluyendo la esclerosis múltiple primaria progresiva, y la esclerosis múltiple remitente recidivante. Estos subtipos de enfermedad pueden distinguirse entre sí basándose en el curso de la enfermedad, en el tipo de inflamación implicada, y a través del uso de obtención de imágenes por resonancia magnética (MRI). Es también posible que el mecanismo básico de la enfermedad cambie durante el curso de la esclerosis múltiple, siendo sustituido un proceso basado en la inflamación más tardepor uno que implica la desmielinación y el daño neuronal. Véase Weilbach y Gold, "Disease modifying treatments for multiple esclerosis. What is on the horizon?" *CNS Drugs* 11 133-157, 1999.

Las lesiones inflamatorias de esclerosis multiple están localizadas, pero son predominantes en la materia blanca del sistema nervioso central, aunque las placas escleróticas caracterizadas por la desmielinación son el sello de la enfermedad. El desarrollo de la desmielinación, a su vez, está provocado por la necrosis de los oligodendrocitos, y la desmielinación está asociada a un infiltrado compuesto principalmente de linfocitos T y macrófagos, que junto a las células locales tales como los astrocitos, microglia y células endoteliales cerebrales microvasculares, expresan el complejo mayor de histocompatibilidad (MHC) clase II. Estas células están así implicadas en la presentación de antígeno y se han identificado una respuesta inflamatoria, y numerosas citoquinas proinflamatorias, incluyendo TNF-α, TNF-β, IL-1, IL-6 e IFN-γ en el tejido cerebral de los pacientes con esclerosis múltiple y su presencia se asocia generalmente a lesiones activas. En particular el TNF-α ha sido el foco de

atención debido a que media en las lesiones de la mielina y oligodendrocitos *in vitro*, induce la expresión de astrocitos para que expresen las moléculas de adhesión de superficie, y está asociado a la alteración de la barrera sanguínea cerebral.

Se han usado modelos animales para demostrar el papel de TNF-α en la esclerosis múltiple, por ejemplo en la administración experimental en encefalomielitis alérgica (EAE) de anticuerpos contra TNF o los receptores de TNF solubles se ha demostrado que proporciona un efecto protector. Véase Selmaj y cols, "Prevention of chronic relapsing experimental autoimmune encephalomyelitis by soluble tumor necrosis factor," *J. Neuroimmunol.* 56 135-141, 1995. Se ha comunicado también una correlación directa entre el nivel de ARNm de TNF-α y el progreso de la EAE. Véase Reeno y cols., "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. Otras pruebas que demuestran que TNF-α es un mediador en la esclerosis múltiple es la concentración aumentada de TNF-α en el fluido cerebroespinal de los pacientes con esclerosis múltiple durante el curso de la enfermedad. Además, un ratón transgénico que sobre expresa el TNF-α en el sistema nervioso central ha demostrado signos de la desmielinación espontánea, mientras que los ratones transgénicos inactivado con TNF-α han demostrado un efecto protector. Véase Probert y cols., "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; y Liu y cols., "TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination," *Nature Med.* 4 78-83, 1998.

Dado que los inhibidores de PDE4 también reducen el TNF-α, son beneficiosos en el tratamiento de la esclerosis múltiple por que el TNF-α representa un papel

fundamental en la mediación de la esclerosis múltiple, como se analiza anteriormente. Por ejemplo, en un modelo de monos titi de encefalomielitis alérgica experimental, se ha observado que rolipram suprime la aparición de signos clínicos y evita las anormalidades en las imágenes obtenidas por MRI. En otro estudio de los efectos de rolipram sobre la encefalomielitis alérgica experimental recidivante crónica, en ratones SJL, se ha demostrado que rolipram mejora los síntomas clínicos y los cambios patológicos en este modelo. Véase Genain y cols., "Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phosphodiesterase," *Proc. Natl. Acad. Sci. USA* 92 3601-3605, 1995; y Sommer y cols., "Therapeutic potential of phosphodiesterase Type 4 inhibition in chronic autoimmune demyelinating disease," *J. Neuroimmunol.* 79 54-61, 1997.

Además de inhibir la actividad de PDE4 y la producción de TFN-α, los compuestos de Fórmula (1.0.0) poseen también actividad como agentes inmunosupresores y son especialmente de utilidad en el tratamiento de enfermedades autoimunitarias en las que la inflamación es una parte constitutiva de la enfermedad autoinmunitaria, o en las que la inflamación es parte de la etiología de la enfermedad autoinmunitaria o en las que la inflamación está implicada de otro modo en la enfermedad autoinmunitaria. De forma alternativa, los compuestos de Fórmula (1.0.0) son agentes antiinflamatorios de utilidad en el tratamiento de enfermedades inflamatorias en las que las reacciones autoinmunitarias son una parte constitutiva de la enfermedad o en las que las reacciones autoinmunitarias son una parte de la etiología de la enfermedad inflamatoria, o en las que las reacciones autoinmunitarias están implicadas de otro modo en la enfermedad inflamatoria. En consecuencia, los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento de la esclerosis múltiple, como se analizó en detalle anteriormente.

Otras enfermedades autoimnunitarias/inflamatorias que pueden tratarse mediante agentes terapéuticos que comprenden los compuestos de Fórmula (1.0.0) incluyen, pero sin limitación, trastornos hematológicos autoimnunitarios tales como la anemia hemolítica, anemia aplásica, anemia eritrocitopénica pura, púrpura trombocitopénica idiopática; lupus eritematoso sistémico; policondritis; esclerodermа; granulomatosis de Wegner; dermatomiositis; hepatitis activa crónica; miastenia grave; síndrome de Stevens-Johnson; esprue idiopática; enfermedades autoinmunitarias inflamatorias del intestino tales como colitis ulcerosa y enfermedad de Crohn; oftalmopatía endocrina; enfermedad de Grave; sarcoidosis; alveolitis; neumonitis por hipersensibilidad crónica; cirrosis biliar primaria; diabetes juvenil (diabetes melitus tipo I); uveítis anterior; uveítis granulomatosa (posterior); queratoconjuntivitis seca; queratoconjuntivitis epidémica; fibrosis pulmonar intersticial difusa (fibrosis pulmonar intersticial); fibrosis pulmonar idiopática; fibrosis quística; artritis soriásica; glomerulonefritis con y sin síndrome nefrótico incluyendo glomerulonefritis aguada, síndrome nefrótico idiopático y nefropatía de cambios mínimos; enfermedades de la piel inflamatorias/hiperproliferativas incluyendo soriasis, y dermatitis atópica analizadas en detalle anteriormente, dermatitis de contacto, dermatitis de contacto alérgica, pénfigo familiar benigno, pénfigo eritematoso, pénfigo foliáceo, y pénfigo vulgar.

Además, los compuestos de Fórmula (1.0.0) pueden usarse como agentes inmunosupresores para prevenir el rechazo de aloinjertos tras el trasplante de órganos, cuando tales órganos típicamente incluyen tejido de médula ósea, intestino, corazón, riñón, hígado, pulmón, páncreas, piel y cornea.

8.10 Enfermedad inflamatoria del intestino

La colitis ulcerosa (UC) es una ulceración crónica, recurrente del colon, principalmente de la mucosa y submucosa que es de causa desconocida, y que se

manifiesta clínicamente mediante dolor abdominal por cólicos, sangrado del recto y secreciones sueltas de sangre, pus, y moco con escasas partículas fecales. Las enfermedades relacionadas del intestino incluyen colitis colagenosa, que es un tipo de colitis de etiología desconocida caracterizado por depósitos de material colagenoso por debajo del epitelio del colon, y marcado por dolor abdominal por cólicos con una reducción conspicua de la absorción de fluido y electrolitos que conlleva diarrea acuosa; colitis poliposa, que es colitis ulcerosa asociada a la formación de seudopólipos, es decir, islas edematosas, inflamadas de mucosa entre las zonas de ulceración; y colitis transmural, que es la inflamación del grosor completo del intestino, en lugar de enfermedad de la mucosa y la submucosa, usualmente con formación de granulomas sin caesificación, que clínicamente se parece a la colitis ulcerosa pero en la que la ulceración es a menudo longitudinal o profunda, la enfermedad es a menudo segmentada, la formación de constricción es habitual, 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 cualquier parte del tubo intestinal, pero que habitualmente implica el íleon terminal con cicatrización y engrosamiento de la pared del intestino, que frecuentemente conlleva obstrucción intestinal, y la formación de fístulas y abscesos, y con una alta tasa de recurrencia después del tratamiento. La colitis ulcerosa, la enfermedad de Crohn y las enfermedades relacionadas analizadas anteriormente se denominan colectivamente enfermedad inflamatoria del intestino (IBD). Estas enfermedades son trastornos crónicos, que remiten espontáneamente de causa desconocida que son inmunomediados y cuya patogénesis ha sido establecida a través del uso de modelos animales y técnicas inmunológicas avanzadas. Véase Bickston y Caminelli, "Recent developments in the medical therapy of IBD," *Curr.*

Opin. Gastroenterol. 14 6-10, 1998; y Murthy y cols., "Inflammatory bowel disease: A new wave of therapy," *Exp. Opin. Ther. Patents* 8 (7) 785-818, 1998. Mientras que la incidencia de la colitis ulcerosa ha permanecido relativamente estable, la incidencia de la enfermedad de Crohn ha aumentado significativamente.

La terapia actual para la enfermedad inflamatoria del intestino incluye ácido 5-aminosalicílico, corticoesteroides, e inmunomoduladores tales como azatioprina, 6-mercaptopurina, y metotrexato. Estos agentes tiene un amplio espectro de efectos secundarios adversos y no modifican la enfermedad en sí misma, y por lo tanto existe una necesidad continuada de agentes de tratamiento más efectivos. Los compuestos de Fórmula (1.0.0) son capaces de tratar beneficiosamente las enfermedades inflamatorias del intestino como resultado de su capacidad de inhibir la producción de TNF-α, porque el TNF-α provoca la activación y proliferación de células inmunitarias, y la liberación de mediadores en la enfermedad inflamatoria del intestino. Véase Radford-Smith y Jewel, "Cytokines and inflammatory bowel disease." *Baillieres Clin. Gastroenterol.* 10 151-164, 1996. También se ha detectado el TNF-α en las deposiciones y mucosa intestinal de pacientes con enfermedad inflamatoria del intestino. Además, estudios clínicos tempranos de la enfermedad de Crohn usando anticuerpos monoclonales contra TNF han demostrado ser una esperanza significativa.

Como se ha detallado anteriormente, los inhibidores selectivos de PDE4 tienen un efecto significativo sobre la inhibición de la liberación de TNF-α de mononucleocitos de la sangre periférica después de que esas células han sido estimuladas con una amplia gama de mediadores, tanto *in vitro* como *in vivo*. Se ha demostrado que el inhibidor selectivo de PDE4, arofilina, proporciona efectos beneficiosos cuando se analiza en modelos de colitis en rata. Además, en un modelo de colitis inducida con sulfato de dextrano en la rata, el rolipram y el inhibidor de PDE4

selectivo, LAS31025 han demostrado efectos beneficiosos comparables a la prednisolona. Ambos compuestos de ensayo han demostrado que mejoran el sangrado y los marcadores de inflamación. Véase Puig y cols. "Curative effects of phosphodiesterase 4 inhibitors in dextran sulfate sodium induced colitis in the rat," *Gastroenterology* 114 (4) A 1064, 1998. Otros investigadores han usado modelos adicionales para demostrar la capacidad de los inhibidores selectivos de PDE4 para proporcionar protección gastrointestinal. Por ejemplo, se ha demostrado que una extravasación eritrocítica inducida por lipopolisacáridos en ratas e hipoperfusión intestinal en los perros puede atenuarse con los inhibidores de PDE4 selectivos rolipram y denbufilina. Véase Cardelus y cols., "Inhibiting LPS induced bowel erythrocyte extravasation in rats, and of mesenteric hypoperfusion in dogs, by phosphodiesterase inhibitors," *Eur. J. Pharmacol.* 299 153-159, 1996; y Cardelus y cols., "Protective effects of denbufilina against endotoxin induced bowel hyperplasia", *Metl Find. Exp. Clin. Pharmacol.* 17 (Supl. A) 142, 1995.

8.11 Choque séptico, insuficiencia renal, caquexia, e infección.

El choque séptico es el choque asociado a la infección insuperable, más comúnmente infección con bacterias gram negativas, aunque puede estar producido por otras bacterias, virus, hongos y protozoos. El choque séptico se estima que es el resultado de la acción de endotoxinas u otros productos del agente infeccioso sobre el sistema vascular, provocando que grandes volúmenes de sangre queden secuestrados en los capilares y venas. También está implicada la activación de los sistemas de complemento y quinina y la liberación de histamina, citocinas, prostaglandinas, y otros mediadores.

Se ha demostrado en un modelo de insuficiencia renal agua inducida por endotoxinas en ratas que el inhibidor selectivo de PDE4, Ro-201724, administrado

como tratamiento posterior con 10 μg/kg/min aumenta significativamente la excreción de AMPc en orina, atenúa marcadamente los aumentos inducidos por endotoxinas de la resistencia vascular renal y las disminuciones del flujo sanguíneo renal y velocidad de filtración glomerular. Se ha demostrado que Ro-201724 aumenta las tasas de supervivencia de las ratas tratadas con endotoxina. Véase Carcillo y cols., *Pharmacol. Exp. Ther.* 279 1197, 1996. Se ha estudiado también la pentoxifilina en pacientes que padecen choque séptico. En este estudio se han seleccionado veinticuatro individuos que cumplían los criterios de choque séptico, doce de los cuales han recibido pentoxifilina a 1 mg/kg/h durante un periodo de 24 horas, mientras que los otros doce han servido como grupo control. Después de 24 horas se ha encontrado que los niveles de TNF-α en el grupo de terapia han bajado significativamente, mientras que los niveles de IL-6 han aumentado significativamente.

En otro estudio se ha demostrado que el tratamiento previo con pentoxifilina de 5 a 50 mg/kg i.p. 3X, o con los inhibidores selectivos de PDE4 rolipram de 10 a 30 mg/kg i.p. 3X, y debufilina de 0,1 a 3 mg/kg i.p. 3x, reduce la extravasación intestinal de eritrocitos inducida por lipopolisacáridos en ratas, y que denbufilina es 100 veces más potente que pentoxifilina en la inhibición de la caída del flujo sanguíneo mesentérico inducida por lipopolisacáridos, sin afectar el flujo renal o el índice cardiaco. Véase Cardelus y cols., *Ibid., Eur. J. Pharmacol.*

La insuficiencia renal es la incapacidad del riñón de excretar los metabolitos a niveles plasmáticos normales en condiciones normales de carga, o la incapacidad de retener electrolitos en condiciones de ingesta normales. En la forma aguda, está marcada por uremia y usualmente por oliguria o anuria, con hipercalemia y edema pulmonar. Basándose en las actividades descritas anteriormente de los inhibidores de PDE4 selectivos, se ha demostrado que los inhibidores selectivos de PDE4 son de

utilidad en el tratamiento de la insuficiencia renal, especialmente en la insuficiencia renal aguda. Véase Begany y cols., "Inhibition of Type IV phosphodiesterase by Ro-20-1724 attenuates endotoxin-induced acute renal failure," *J. Pharmacol. Exp. Thera.* **278** 37-41, 1996. Véase también el documento WO 98/00135 cedida a la Universidad de Pittsburg. En consecuencia, los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento de la insuficiencia renal, en particular la insuficiencia renal aguda.

La caquexia es un estado de salud profundo y marcado de trastorno constitucional caracterizado por estado general malo y malnutrición. La caquexia puede ser el resultado final de numerosos factores causantes, por ejemplo, puede ser resultado de infección por uno cualquiera de numerosos organismos o microorganismos unicelulares diferentes incluyendo bacteria, virus, hongos y protozoos. La caquexia por malaria es representativa y comprende un grupo de signos de una naturaleza crónica que son resultado de ataques precedentes de malaria grave, siendo los síntomas principales anemia, piel cetrina, esclerótica amarilla, esplenomegalia, y hepatomegalia. Otra causa de caquexia es la privación o deterioro de funciones humorales o otras funciones orgánicas, por ejemplo, la caquexia hipofisiaria comprende una sucesión de síntomas que resultan de la privación total de la función de la glándula pituitaria, incluyendo ftisis, pérdida de la función sexual, atrofia de las glándulas diana de la pituitaria, bradicardia, hipotermia, apatía, y coma. La caquexia urémica es la caquexia asociada a otros síntomas sistémicos de insuficiencia renal avanzada. La caquexia cardiaca comprende la extenuación debido a la enfermedad cardiaca. La caquexia suprarrenal, o enfermedad de Addison es un trastorno caracterizado por hipotensión, pérdida de peso, anorexia, y debilidad, provocada por deficiencia de la hormona suprarrenal. Es debida a la tuberculosis o a la destrucción autoimnunitaria o inducida por tuberculosis de la

corteza suprarrenal que da como resultado una deficiencia de aldosterona y cortisol.

La caquexia puede ser también el resultado de estados de enfermedad de diversos tipos. La caquexia cancerosa comprende la afección de debilidad y extenuación que se observa en los casos de tumor maligno. La caquexia puede ser también consecuencia de la infección por el virus de inmunodeficiencia humano (VIH), y comprende los síntomas que comúnmente se denominan síndrome de inmunodeficiencia adquirida (SIDA). Los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento de la caquexia de los tipos diferentes descritos anteriormente como resultado de su capacidad de proporcionar regulación por disminución o inhibición de la liberación de TNF-α. Los inhibidores selectivos de PDE4 de la presente invención tienen un efecto marcado sobre la inhibición de la liberación de TNF-α de mononucleocitos de sangre periférica después de que esas células han sido estimuladas con una amplia gama de mediadores. La liberación de TNF-α está implicada o representa un papel mediador en enfermedades o afecciones cuya etiología implica o comprende la liberación mórbida, es decir, insana, excesiva o no regulada de TNF-α.

Los compuestos inhibidores de PDE4 de Fórmula (1.0.0) son útiles además en el tratamiento de infecciones, especialmente infecciones por virus en las que dichos virus aumentan la produción de TNF-α en su hospedador, o en las que dichos virus son sensibles a la regulación al alza de TFN-α en su hospedador de forma que su replicación u otras actividades vitales reciben un impacto adverso. Dichos virus incluyen, por ej. VIH-1, VIH-2 Y VIH-3; citomegalovirus, CMV; gripe; adenovirus, y virus Herpes, especialmente herpes Zoster y Herpes simples.

Los compuestos inhibidores de PDE4 de Fórmula (1.0.0) son de utilidad además en el tratamiento de infecciones por levaduras y hongos en las que dichas levaduras y hongos son sensibles de regulación por aumento por TNF-α o provocan la producción

de TNF-α en su hospedador. Una enfermedad particular que es tratable de esta forma es la meningitis fúngica. Los compuestos de Fórmula (1.0.0) proporcionan también efectos beneficiosos cuando se combinan, es decir, se administran conjuntamente con otros fármacos de elección para el tratamiento de infecciones sistémicas por levaduras y hongos. Tales fármacos de elección incluyen, pero sin limitación polimixinas, por ejemplo polimicina B; imidazoles, por ejemplo clotrimazol, econazol, miconazol, y cetoconazol; triazoles, por ejemplo fluconazol e itranazol; y anfotericinas, por ejemplo, anfotericina B y anfotericina B liposómica. El término "coadministración" según se usa en el presente documento con referencia a los compuestos de Fórmula (1.0.0) y los fármacos de elección para el tratamiento de infecciones sistémicas por levaduras y hongos, se pretende que signifique e incluya *(a)* la administración simultánea de tal(es) compuesto(s) y fármaco(s) a un sujeto cuando se formulan juntos en una sola forma de dosificación farmacéutica; *(b)* administración sustancialmente simultánea de tal(es) compuesto(s) y fármaco(s) a un sujeto cuando se formulan separados los unos de los otros en formas de dosificación farmacéuticas diferentes; y *(c)* administración secuencial de tal(es) compuesto(s) y fármaco(s) a un sujeto cuando se formulan separados los unos de los otros y se administran de forma consecutiva con algún intervalo de tiempo significativo entre ellos.

8.2 Lesión hepática

Además de los efectos adversos del TNF-α descritos anteriormente, también provoca insuficiencia hepática en los humanos, un fenómeno que se ha demostrado en numerosos modelos animales. Por ejemplo, en un modelo agudo de insuficiencia hepática mediada por linfocitos T, rolipram administrado de 0,1 a 10 mg/kg i.p. 30 minutos antes de la provocación con concanavalina A o enterotoxina B de estafilococos, se ha demostrado que reduce significativamente las concentraciones de TNF-α e INF-γ

en plasma, mientras que también eleva significativamente los niveles de IL-10. Véase Gantner y cols., *J. Pharmacol. Exp. Ther.* 280 53, 1997. En este mismo estudio, se demostró también que rolipram suprime la liberación de IL-4 inducida por concanavalina A. En este estudio también se han evaluado las actividades plasmáticas de las enzimas hepáticas específicas ALT, AST y SDH, dado que un aumento de sus niveles indicaría la destrucción masiva de hepatocitos. Se ha observado que en el tratamiento previo de ratones que recibían concanavalina A por primera vez, o en ratones sensibilizados con galactosamina que recibían galactosamina / enterotoxina B de estafilococos, con rolipram de 0,1 a 10 mg/kg i.p., el rolipram ha inhibido de forma dependiente de la dosis las actividades enzimáticas plasmáticas mencionadas anteriormente. En consecuencia, los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento de trastornos de linfocitos T tales como la insuficiencia renal.

8.13 Hipertensión pulmonar

Es sabido que puede aumentarse la actividad de las fosfodiesterasas que hidrolizan los segundos mensajeros AMPc y GMPc vasodilatadores mediante la hipertensión pulmonar inducida por la hipoxia (HPH). La hipoxia es una reducción el aporte de oxígeno a los tejidos por debajo de los niveles fisiológicos a pesar de una perfusión adecuada del tejido por la sangre. La hipertensión pulmonar resultante está caracterizada por una presión aumentada, es decir, superior a 4,0 kPa sistólica y 1,6 kPa diastólica, en la circulación arterial pulmonar. Usando un modelo que utiliza anillos arteriales pulmonares aislados de ratas normales y de ratas con hipertensión pulmonar inducida por hipoxia, se ha demostrado que el inhibidor de PDE4 selectivo rolipram potencia las actividades relajantes de isoproterenol y forskolina. El mismo efecto se ha observado con milrinona, que es un inhibidor selectivo de PDE3, apoyando así la inhibición tanto de PDE3 como de PDE4 para mejorar significativamente la relajación

arterial pulmonar en la hipertensión pulmonar inducida por hipoxia. Véase Wagner y cols., *J. Pharmacol. Exp. Ther.* 282 1650, 1997. En consecuencia, los compuestos de Fórmula (1.0.0) son de utilidad en el tratamiento de hipertensión pulmonar, especialmente en la hipertensión pulmonar inducida por hipoxia.

8.14 Enfermedad de pérdida ósea

La enfermedad de pérdida ósea, más comúnmente denominada osteoporosis, es una afección de baja masa ósea y alteración de la microarquitectura que da como resultado fracturas con traumatismos mínimos. La osteoporosis secundaria es debida a enfermedad sistémica o medicaciones tales como glucocorticoides. La osteoporosis primaria, según se ha acordado, debe verse como que comprende dos afecciones: osteoporosis tipo I que es la pérdida ósea trabecular debida a la deficiencia de estrógenos en la menopausia, y la osteoporosis tipo II que es la pérdida ósea cortical y trabecular debido a una remodelación ineficiente a largo plazo, inadecuación de la dieta, y activación del eje paratiroideo con la edad. Los reguladores primarios de la masa de hueso adulto incluyen la actividad física, el estado endocrino reproductor, y la ingesta de calcio, y el mantenimiento óptimo de los huesos requiere suficiencia en las tres áreas.

Se ha demostrado que los inhibidores selectivos de PDE4 son de utilidad en el tratamiento beneficioso de la enfermedad de pérdida ósea, particularmente osteoporosis. Se ha estudiado el efecto de denbufilina sobre la pérdida ósea en ratas Walker que portan 256/S y sobre la formación de nódulos mineralizados y la formación de células tipo osteoclastos en sistemas de cultivo de médula ósea. Se ha descubierto que las administraciones orales en serie de denbufilina inhiben el descenso de la densidad mineral ósea de los fémures de ratas Walker que portan 256/S, y restauran la masa ósea y el número de osteoclastos y osteoblastos por superficie trabecular en la metáfisis del fémur. También se ha observado que la administración de denbufilina da como

resultado un aumento del número de nódulos mineralizados y un descenso del número de células tipo osteoclasto en el sistema de cultivo de médula ósea *in vitro*. Estos efectos beneficiosos son específicos de la inhibición de PDE4 y son imitados por AMPc de dibutirilo, demostrando que la isozima PDE4 representa un papel importante en el renovación ósea a través del AMPc. Véase Miyamoto y cols., *Biochem Pharmacol.* 54 613, 1997; Waki y cols., "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; y el documento JP 9169665 cedido a Miyamoto (1997). En consecuencia, los inhibidores selectivos de PDE4 de Fórmula (1.0.0) son de utilidad en el tratamiento de enfermedades que implican pérdida ósea, específicamente osteoporosis.

8.15 Trastornos del SNC

El inhibidor selectivo de PDE4 rolipram se desarrolló inicialmente como un antidepresivo y continúa siendo estudiado en ensayos clínicos para esa indicación. Adicionalmente, se ha demostrado que los inhibidores selectivos de PDE4 proporcionan efectos beneficiosos en otros trastornos del sistema nervioso central, incluyendo la enfermedad de Parkinson, Hulley y cols., "Inhibitors of Type IV phosphodiesterases reduce the toxicity of MPTP in substantia nigra neurons *in vivo*," *Eur. J. Neurosci.* 7 2431-2440, 1995; así como deterioros del aprendizaje y memoria, Egawa y cols., "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 y cols., "Ameliorating effects of rolipram on experimentally induced impairments of learning and memory in rodents," *Eur. J. Pharmacol.* 321 273-278, 1997; y Barad y cols., "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.

El uso de inhibidores de PDE4 que tratan la disquinesia tadía y la drogodependencia ha sido también descrita en la técnica, documentos WO 95/28177 y JP 92221423 (1997), ambas a Meiji Seika Kaisha Ltd. Se ha observado que la isozima PDE4 representa un papel principal en el control de la biosíntesis de dopamina en neuronas mesoencefálicas; en consecuencia los inhibidores de PDE4 son de utilidad en el tratamiento de trastornos y enfermedades que se asocian o están mediados por dopamina dentro y alrededor de las neuronas mesoencefálicas, Yamashita y cols., "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.

Los compuestos inhibidores de PDE4 de Fórmula (1.0.0) son adicionalmente de utilidad en el tratamiento de la demencia arteriosclerótica y demencia subcortical. La demencia ateriosclerótica, también denominada demencia vascular y demencia multiinfarto, es una demencia con un curso de deterioro paso a paso en forma de una serie de pequeños infartos, y una distribución irregular de deficiencias neurológicas provocadas por una enfermedad cerebrovascular. Las demencias subcorticales están provocadas por lesiones que afectan las estructuras cerebrales subcorticales y están caracterizadas por pérdida de memoria con lentitud para procesar la información o hacer respuestas intelectuales. Se incluyen las demencias que acompañan al corea de Huntington, la enfermedad de Wilson, parálisis agitante, y atrofias talámicas.

8.16 Otras aplicaciones terapéuticas

Se ha demostrado que los inhibidores de PDE4 son de utilidad en el tratamiento de lesiones por isquemia-reperfusión, Block y cols., "Delayed treatment with rolipram protects against neuronal damage following global ischemia in rats," *NeuroReport* 8

3829-3832, 1997 y Belayev y cols., "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; en el tratamiento de diabetes autoinmunitaria, Liang y cols., "The phosphodiesterase inhibitors pentoxifylline and rolipram prevent diabetes in NOD mice," *Diabetes* 47 570-575, 1998; en el tratamiento de autoinmunidad retiniana, Xu y cols., "Protective effects 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; en el tratamiento de leucemia linfocítica crónica, Kim y Lerner, "Type 4 cyclic adenosine monophosphate phosphodiesterase as a therapeutic agent in chronic lymphocytic leukemia," *Blood* 92 2484-2494, 1998; en el tratamiento de infecciones por VIH, Angel y cols., "Rolipram, a specific Type IV phosphodiesterase inhibitor, is a potent inhibitor of HIV-1 replication," *AIDS* 9, 1137-1144, 1995 y Navarro y cols. "Inhibition of phosphodiesterase Type IV suppresses human immunodeficiency virus Type 1 replication and cytokine production in primary T cells: involvement of N-kappaB and NFAT," *J. Virol.* 72 4712-4720, 1998; en el tratamiento de lupus eritematoso, documento JP 10067682 (1998) cedido a Fujisawa Pharm. Co. Ltd.; en el tratamiento de enfermedades del riñón y uréteres, documento DE 4230755 (1994) cedido a Schering AG; en el tratamiento de trastornos urogenitales y gastrointestinales, documento WO 96/06423 cedido a Schering AG; y en el tratamiento de enfermedades de próstata, documento WO 99/02161 asignado 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 de utilidad en el tratamiento beneficioso de uno cualquiera o más de los miembros seleccionados del grupo constituido por las siguientes enfermedades,

trastornos, y afecciones:

- asma de cualquier tipo, etiología, o patogénesis; o asma que es un miembro seleccionado del grupo constituido por asma atópica; asma no atópica; asma alérgica; asma atópica, bronquial, asma mediada por IgE; asma bronquial; asma idiopática; asma verdadera; asma intrínseca provocada por alteraciones patofisiológicas; asma extrínseca provocada por factores medioambientales; asma idiopática de causa desconocida o no evidente; asma no atópica; asma bronquítica; asma enfisematosa; asma inducida por el ejercicio; asma ocupacional; asma infecciosa provocada por infección bacteriana, fúngica, protozóica, o viral; asma no alérgica; asma incipiente; síndrome de sibilancias en el niño;

- broncoconstricción crónica o agua; bronquitis crónica; obstrucción de las vías respiratorias menores; y enfisema;

- enfermedades obstructivas o inflamatorias de las vías respiratorias de cualquier tipo, etiología, o patogénesis; o una enfermedad obstructiva o inflamatoria de las vías respiratorias que es un miembro seleccionado del grupo constituido por asma; neumoconiosis; neumonía eosinófila crónica; enfermedad pulmonar obstructiva crónica (COPD); COPD que incluye bronquitis crónica, enfisema pulmonar o disnea asociada a los mismos; COPD caracterizada por la obstrucción irreversible, progresiva de las vías respiratorias; síndrome disneico agudo del adulto (ARDS), y exacerbación de la hiperreactividad de las vías respiratorias como consecuencia de otras farmacoterapias;

- neumoconiosis de cualquier tipo, etiología, o patogénesis; o neumoconiosis que es un miembro seleccionado del grupo constituido por aluminosis o enfermedad de los trabajadores de la bauxita; antracosis o asma de los mineros; asbestosis o asma de los montadores de calderas; calicosis o enfermedad del sílex; ptilosis provocada por la inhalación del polvo de las plumas de avestruz; siderosis provocada por la inhalación de

partículas de hierro; silicosis o enfermedad de los amoladores; bisinosis o asma del polvo del algodón; y neumoconiosis del talco;

- bronquitis de cualquier tipo, etiología o patogénesis; o bronquitis que es un miembro seleccionado del grupo constituido por bronquitis aguda; bronquitis laringotraqueal aguda; bronquitis araquídica; bronquitis catarral; bronquitis pseudomembranosa; bronquitis seca; bronquitis asmática infecciosa; bronquitis productiva; bronquitis por estafilococos o estreptococos; y bronquitis vesicular;

- bronquiectasia de cualquier tipo, etiología o patogénesis; o bronquiectasia que es un miembro seleccionado del grupo constituido por bronquiectasia cilíndrica; bronquiectasia saculada; bronquiectasia fusiforme; bronquiectasia capilar; bronquiectasia cística; bronquiectasia seca; y bronquiectasia folicular;

- rinitis alérgica estacional; o rinitis alérgica perenne; o sinusitis de cualquier tipo, etiología o patogénesis; o sinusitis que es un miembro seleccionado del grupo constituido por sinusitis purulenta o no purulenta; sinusitis aguda o crónica; y sinusitis etmoide, frontal, maxilar, o esfenoidal;

- artritis reumatoide de cualquier tipo, etiología o patogénesis; o artritis reumatoide que es un miembro seleccionado del grupo constituido por artritis aguda; artritis gotosa aguda; artritis inflamatoria crónica; artritis degenerativa; artritis infecciosa; artritis de Lyme; artritis proliferativa; artritis soriásica; y artritis vertebral;

- gota, y fiebre y dolor asociados a la inflamación;

- un trastorno relacionado con la eosinofilia de cualquier tipo, etiología o patogénesis; o un trastorno relacionado con la eosinofilia que es un miembro seleccionado del grupo constituido por eosinofilia; eosinofilia en infiltración pulmonar; síndrome de Loffler; neumonía eosinófila crónica; eosinofilia pulmonar tropical; aspergilosis bronconeumónica; aspergiloma; granulomas que contienen eosinófilos;

vasculitis granulomatosa alérgica o síndrome de Churg-Strauss; poliarteritis nodosa (PAN); y vasculitis necrosante sistémica;

- dermatitis atópica; o dermatitis alérgica; o eczema alérgico o atópico;

- urticaria de cualquier tipo, etiología o patogénesis; o urticaria que es un miembro seleccionado del grupo constituido por urticaria inmunomediada; urticaria mediada por complemento; urticaria inducida por materiales urticantes; urticaria inducida por agentes físicos; urticaria inducida por estrés; urticaria idiopática; urticaria aguda; urticaria crónica; angioedema; urticaria colinérgica; criourticaria de la forma de autosoma dominante o de la forma adquirida; urticaria de contacto; megaurticaria; y urticaria papular;

- conjuntivitis de cualquier tipo, etiología o patogénesis; o conjuntivitis que es un miembro seleccionado del grupo constituido por conjuntivitis actínica; conjuntivitis catarral aguda; conjuntivitis contagiosa aguda; conjuntivitis alérgica; conjuntivitis atópica; conjuntivitis catarral crónica; conjuntivitis purulenta; y conjuntivitis primaveral;

- uveítis de cualquier tipo, etiología o patogénesis; o uveítis que es un miembro seleccionado del grupo constituido por inflamación de toda o parte de la úvea; uveítis anterior; iritis; ciclitis; iridociclitis; uveítis granulomatosa; uveítis no granulomatosa; uveítis facoantígena; uveítis posterior; coroiditis; y corioretinitis;

- soriasis;

- esclerosis múltiple de cualquier tipo, etiología o patogénesis; o esclerosis múltiple que es un miembro seleccionado del grupo constituido por esclerosis múltiple progresiva primaria; y esclerosis múltiple recidivante remitente;

- enfermedades autoinmunitarias/inflamatorias de cualquier tipo, etiología o patogénesis; o una enfermedad autoinmunitaria/inflamatoria que es un miembro

seleccionado del grupo constituido por trastornos hematológicos autoinmunitarios; anemia hemolítica; anemia aplásica; eritrocitopenia pura; púrpura trombocitopénica idiopática; lupus eritematoso sistémico; policondritis; escleroderma; granulomatosis de Wegner; dermatomiositis; hepatitis activa crónica; miastenia grave; síndrome de Stevens-Johnson; esprue idiopática; enfermedades inflamatorias del intestino autoinmunitarias; colitis ulcerosa; enfermedad de Crohn; oftalmopatía endocrina; enfermedad de Grave; sarcoidosis; alveolitis; neumonitis por hipersensibilidad crónica; cirrosis biliar primaria; diabetes juvenil o diabetes melitus tipo I; uveítis anterior; uveítis granulomatosa o posterior; queratoconjuntivitis seca; queratoconjuntivitis epidémica; fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial; fibrosis pulmonar idiopática; fibrosis quística; artritis soriásica; glomerulonefritis con y sin síndrome nefrótico; glomerulonefritis aguda; síndrome nefrótico idiopático; nefropatía de cambio mínimo; enfermedades cutáneas inflamatorias/hiperproliferativas; soriasis; dermatitis atópica; dermatitis de contacto; dermatitis alérgica de contacto; pénfigo familiar benigno; pénfigo eritematoso; pénfigo foliáceo; y pénfigo vulgar;

- prevención del rechazo de aloinjertos tras el trasplante de órganos;

- enfermedad inflamatoria del intestino (IBD) de cualquier tipo, etiología, o patogénesis; o enfermedad inflamatoria del intestino que es un miembro seleccionado del grupo constituido por colitis ulcerosa (UC); colitis colágena; colitis poliposa; colitis transparietal; y enfermedad de Crohn (CD);

- choque séptico de cualquier tipo, etiología, o patogénesis; o choque séptico que es un miembro seleccionado del grupo constituido por insuficiencia renal; insuficiencia renal aguda; caquexia; caquexia por malaria; caquexia hipofisiaria; caquexia urémica; caquexia cardiaca; caquexia suprarrenal o enfermedad de Addison; caquexia cancerosa; y caquexia como consecuencia de infección por el virus de inmunodeficiencia humano

(VIH);

- lesión hepática;

- hipertensión pulmonar; e hipertensión pulmonar inducida por hipoxia;

- enfermedades de pérdida ósea; 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 del grupo constituido por depresión; enfermedad de Parkinson; deterioro del aprendizaje y memoria; disquinesia tardía; drogodependencia; demencia arteriosclerótica; y demencias que acompañan el corea de Huntington, enfermedad de Wilson, parálisis agitante, y atrofias talámicas;

- infección, especialmente infección por virus en las que tales virus aumentan la producción de TNF-α en su hospedador, o en las que tales virus son sensibles a la regulación por aumento de TNF-α en su hospedador de forma que su replicación u otras actividades vitales sufren un impacto adverso, incluyendo un virus que es un miembro seleccionado del grupo constituido por VIH-1, VIH-2, y VIH-3; citomegalovirus, CMV; gripe; adenovirus; y virus del Herpes, incluyendo *Herpes zoster* y *Herpes simplex*;

- infecciones por levaduras y hongos en las que dichas levaduras y hongos son sensibles a regulación por aumento mediante TNF-α o provocan la producción de TNF-α en su hospedador, por ejemplo meningitis fúngica; particularmente cuando se administra en conjunción con otros fármacos de elección para el tratamiento de infecciones sistémicas de levaduras y hongos, incluyendo pero sin limitación, polimixinas; por ejemplo, Polimicina B; imidazoles, por ejemplo, clotrimazol, econazol, miconazol, y cetoconazol; triazoles, por ejemplo, fluconazol e itranazol; y anfotericinas, por ejemplo, Amfotericina B y Anfotericina liposómica B.

- lesión por isquemia - reperfusión; diabetes autoinmunitaria; autoinmunidad retiniana; leucemia linfocítica crónica; infecciones por VIH; lupus eritematoso; enfermedad renal y ureteral; trastornos urogenitales y gastrointestinales; y enfermedades de próstata.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

9.0 Combinación con otros fármacos y terapias

La presente invención contempla realizaciones en las que un compuestos de Fórmula (1.0.0) es el único agente terapéutico que se emplea en un procedimiento de tratamiento descrito en el presente documento, ya sea usado sólo o más comúnmente, junto con un vehículo farmacéuticamente aceptable para producir una forma de dosificación adecuada para su administración a un paciente. Otras realizaciones de la presente invención contemplan una combinación de un compuestos de Fórmula (1.0.0) junto con uno o más agentes terapéuticos adicionales para administrarse conjuntamente a un paciente para obtener algún resultado final terapéutico deseado de forma particular. El segundo, etc. agente terapéutico puede ser también uno o más compuestos de Fórmula (1.0.0), o uno o más inhibidores de PDE4 conocidos en la técnica y descritos en detalle en el presente documento. Más típicamente, el segundo, etc. agente terapéutico se seleccionará de una clase diferente de agentes terapéuticos. Estas selecciones se describen en detalle a continuación.

Según se usan en el presente documento, los términos "coadministración", "coadministrado", y "combinado con", en referencia a los compuestos de Fórmula (1.0.0) y uno o más agentes terapéuticos diferentes, se pretende que signifique, y se refiere e incluye lo siguiente: *(a)* administración simultánea de tal combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente que necesite tratamiento, cuando tales componentes se formulan juntos en una sola forma farmacéutica que libera tales

componentes sustancialmente al mismo tiempo a dicho paciente; *(b)* administración sustancialmente simultánea de tal combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente que necesite tratamiento, cuando tales componentes se formulan separados los unos de los otros en formas de dosificación diferentes que son ingeridas sustancialmente al mismo tiempo por dicho paciente, a partir de donde dichos componentes se liberan sustancialmente al mismo tiempo a dicho paciente; *(c)* administración secuencial de tal combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente que necesite tratamiento, cuando tales componentes se formulan separados los unos de los otros en formas de dosificación diferentes que son ingeridas en tiempos consecutivos por dicho paciente con un intervalo de tiempo significativo entre cada ingestión, a partir de la cual dichos componentes son liberados en tiempos sustancialmente diferentes a dicho paciente; y *(d)* administración secuencial de tal combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente que necesite el tratamiento, cuando tales componentes se formulan juntos en una única forma de dosificación que libera dichos componentes de forma controlada a partir de donde se ingieren de forma concurrente, consecutiva, y/o superpuesta a la vez y/o en momentos diferentes por dicho paciente.

9.1 Con inhibidores de la biosíntesis de leucotrienos: inhibidores de 5-lipoxigenasa (5-LO) y antagonistas de proteína activadora de 5-lipoxigenasa (FLAP)

Uno o más compuestos de Fórmula (1.0.0) se usan en combinación con inhibidores de la biosíntesis de leucotrienos, es decir, inhibidores de 5-lipoxigenasa y/o de la proteína activadora de 5-lipoxigenasa, para formar realizaciones de la presente invención. Como ya se ha advertido anteriormente, 5-lipoxigenasa (5-LO) es una de los dos grupos de enzimas que metabolizan el ácido araquidónico, siendo el otro grupo las

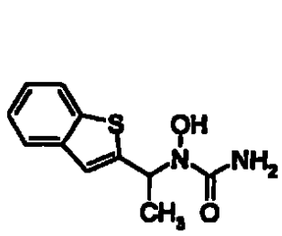
ciclooxigenasas, COX-1 y COX-2. La proteína activadora de 5-lipoxigenasa es una proteína de 18 kD unida a la membrana, que se une al araquidonato que estimula la conversión de ácido araquidónico celular mediante 5-lipoxigenasa. El ácido araquidónico se convierte a acido 5-hidroperoxieicosatetraenóico (5-HPETE), y esta ruta eventualmente lleva a la producción de leucotrienos inflamatorios; en consecuencia, el bloqueo de la proteína activadora de 5-lipoxigenasa o de la enzima 5-lipoxigenasa misma proporciona una diana deseable para interferir de forma beneficiosa con dicha ruta. Un inhibidor tal de 5-lipoxigenasa es zileuton representado por la Fórmula (0.1.14), que puede encontrarse anteriormente y a continuación. Entre las clases de inhibidores de la síntesis de leucotrienos que son de utilidad para formar combinaciones terapéuticas con los compuestos de Fórmula (1.0.0) están los siguientes:

(a) agentes activos de oxidorreducción que incluyen *N*-hidroxiureas; ácidos *N*-alquihidroxámicos; selenita; hidroxibenzofuranos; hidroxilaminas; y catecoles; véase Ford-Hutchinson y cols., "5-Lipoxygenase," *Ann. Rev. Biochem.* 63 383-417, 1994; Weitzel y Wendel, "Selenoenzymes regulate the activity of leukocyte 5-lipoxygenase via the peroxide tone," *J. Biol. Chem.*. 268 6288-92, 1993; Björnstedt y cols. "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 8511-6, 1996; y Stewart y cols., "Structure-activity relationships of N-hydroxyurea 5-lipoxygenase inhibitors," *J. Med. Chem.* 40 1955-68, 1997;

(b) se ha observado que los agentes de alquilación y compuestos que reaccionan con grupos SH inhiben la síntesis de leucotrienos *in vitro*; véase Larsson y cols., "Effects of 1-chloro-2,4,6-trinitrobenzene on 5-lipoxygenase activity and cellular leukotriene synthesis," *Biochem. Pharmacol.* 55 863-71, 1998; y

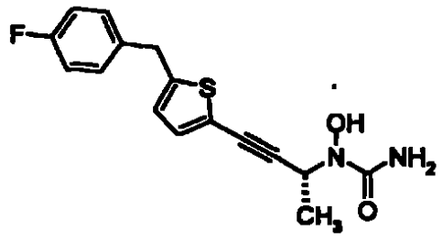
(c) inhibidores competitivos de 5-lipoxigenasa, basados en estructuras de tiopiranoindol y metoxialquiltiazol que pueden actuar como inhibidores no oxidorreductores de 5-lipoxigenasa; véase Ford-Hutchinson y cols., referencia anterior; y Hamel y cols., "Substituted (pyridylmethoxy)naphthalenes as potent and orally active 5-lipoxygenase inhibitors - synthesis, biological profile, and pharmacokinetics of L-739.010," *J. Med. Chem.* 40 2866-75, 1997.

La observación de que el hidroxiamato de araquidonoilo inhibe 5-lipoxigenasa ha llevado al descubrimiento de inhibidores de 5-lipoxigenasa selectivos tales clínicamente útiles como los derivados de *N*-hidroxiurea zileuton y ABT-761, representados por las Fórmulas (0.1.14) y (5.2.1):



Zileuton

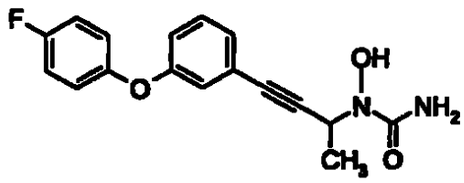
(0.1.14)



ABT-761

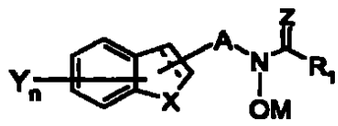
(5.2.1)

Otro compuesto de *N*-hidroxiurea es fenleuton (Abbott-76745) que se representa mediante la Fórmula (5.2.2):



Fenleuton (5.2.2)

El zileuton está cubierto por el documento US 4.873.259 (Summers y cols.) cedido a Abbot Laboratories, que describe compuestos que inhiben lipoxigenasas que contienen indol, benzofurano, y benzotiofeno que pueden representarse con la Fórmula (5.2.3):



(5.2.3)

donde R_1 es H; alquilo C_1-C_4; alquenilo C_2-C_4; o NR_2R_3 donde R_2 y R_3 son H; alquilo C_1-C_4; u OH; X es O; S; SO_2; o NR_4 donde R_4 es H, alquilo C_1-C_6; alcanoílo C_1-C_6; aroílo; o alquilsulfonilo; A es alquileno C_1-C_6, o alquenileno C_2-C_6; 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; aroílo; arilalquilo C_1-C_{12}; arilalquenilo C_2-C_{12}; arilalcoxi C_1-C_{12}; ariltioalcoxi C_1-C_{12}; o derivados sustituidos de arilo; ariloxi; arioílo; arilalquilo C_1-C_{12}; arilalquenilo C_2-C_{12}; arilalcoxi C_1-C_{12}; ariltioalcoxi C_1-C_{12}; donde dicho sustituyente es halo; NO_2; CN; o alquilo C_1-C_{12}-alcoxi C_1-C_{12} y alquilo C_1-C_{12} sustituido con halo; Z es O o S; y M es H; catión farmacéuticamente aceptable; aroílo; o alcanoílo C_1-C_{12}.

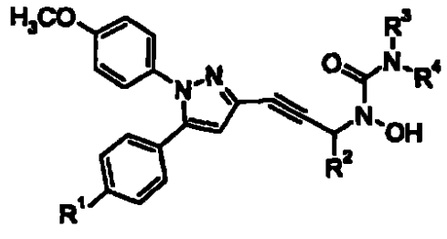
Los compuestos relacionados se describen en los documentos US 4.769.387

(Summers y cols.); US 4.822.811 (Summers); US 4.822.809 (Summers y Stewart); US 4.897.422 (Summers); US 4.992.464 (Summers y cols.); y US 5.250.565 (Brooks y Summers); cada uno de los cuales se incorpora al presente documento como referencia en su totalidad como si se describieran completamente en el presente documento.

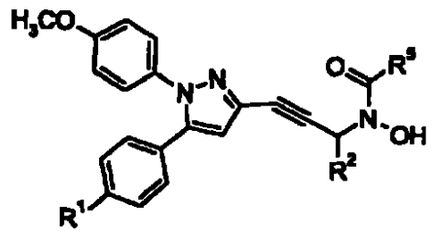
Zileuton o cualquiera de los derivados descritos anteriormente se combinan con los compuestos de Fórmula (1.0.0) para formar realizaciones de la presente invención.

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 5.407.95?, 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; y US 5.506.261; cada uno de los cuales se incorpora al presente documento como referencia en su totalidad como si se describieran completamente en el presente documento. Descripciones adicionales de tal *N*-hidroxiurea e inhibidores relacionados de 5-lipoxigenasa y la síntesis de leucotrienos inflamatorios puede encontrarse 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.

Tepoxalina es un inhibidor de COX/5-LO dual con actividad *in vivo* de corta duración que ha llevado al desarrollo de dos series de compuestos híbridos que son *N*-hidroxiureas y ácidos hidroxámicos de Fórmulas (5.2.4) y (5.2.5), respectivamente:



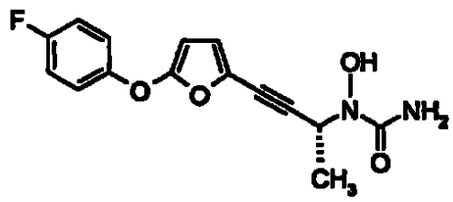
(5.2.4)



(5.2.5)

donde R^1 a R^4 son H; Cl; CH_3; etilo; *iso*-propilo; o *n*-propilo; o R^3 y R^4 juntos son $(CH_2)_5$ o $(CH_2)_2O(CH_2)_2$; y R^5 es metilo; etilo; *iso*-propilo; metoxi; trifluorometilo; clorometilo; etilpropionato; fenilo; 2-furilo; 3-piridilo; o 4-piridilo. Véase Connolly y cols. "N-Hydroxyurea and hydroxamic acid inhibitors of cyclooxygenase and 5-lipoxygenase," *Bioorganic & Medicinal Chemistry Letters* 9 979-984, 1999.

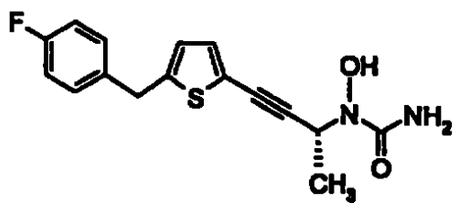
Otro compuesto de *N*-hidroxiurea es Abbott-79175 que se representa mediante la Fórmula (5.26):



Abbott-79175 (5.2.6)

Abbott -79175 tiene una duración de acción mayor que zileuton; Brooks y cols., *J. Pharm. Exp. Therapeut.* 272 724, 1995.

Otro compuesto más de *N*-hidroxiurea es Abbott-85761 que se representa mediante la Fórmula (5.2.7):

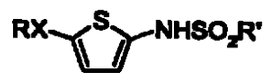


Abbott-85761 (5.2.7)

Abbott - 85761se administra al pulmón mediante administración en aerosol de una formulación homogénea físicamente estable y casi monodispersa; Gupta y cols., "Pulmonary delivery of the 5-lipoxygenase inhibitor, Abbott-85761, in beagle dogs," *Internacional Journal of Pharmaceutics* 147 207-218, 1997.

Fenleuton, Abbott-79175, Abbott-85761 o cualquiera de los derivados de los mismos o de tepoxalina descritos anteriormente, se combinan con los compuestos de Fórmula (1.0.0) para formar las realizaciones de la presente invención.

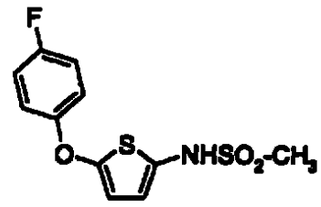
Desde la elucidación de la ruta de biosíntesis de 5-LO, ha existido un debate continuado de si es más ventajoso inhibir la enzima 5-lipoxigenasa o antagonizar los receptores de leucotrieno peptídico o no peptídico. Los inhibidores de 5-lipoxigenasa se cree que son superiores a los antagonistas del receptor LT, debido a que los inhibidores de 5-lipoxigenasa bloquean la acción del todo el espectro de productos 5-LO, mientras que los antagonistas de LT producen efectos menos amplios. Sin embargo, las realizaciones de la presente invención incluyen combinaciones de los compuestos de Fórmula (1.0.0) con antagonistas de LT así como inhibidores de 5-LO, como se describe más adelante. Los inhibidores de 5-lipoxigenasa que tienen estructuras químicas que difieren de las clases de *N*-hidroxiureas y ácidos hidroxámicos descritas anteriormente se usan también en combinación con los compuestos de Fórmula (1.0.0) para formar realizaciones adicionales de la presente invención. Un ejemplo de tal clase diferente son las *N* - (5-sustituido)-tiofeno-2-alquilsulfonamidas de Fórmula (5.2.8):



(5.2.8)

donde X es O o S; R' es metilo, *iso*-propilo, *n*-butilo, *n*-octilo, o fenilo; y R es *n*-

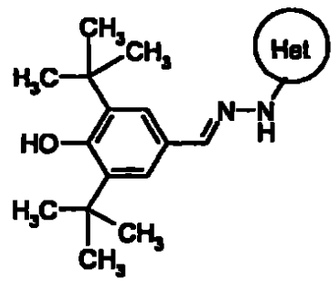
pentilo, ciclohexilo, fenilo, tetrahidro-1-naftilo, 1- ó 2-naftilo, o fenilo mono- o di-sustituido con Cl, F, Br, CH_3, OCH_3, SCH_3, SO_2CH_3, CF_3, o *iso*-propilo. Un compuesto preferido es aquel de Fórmula (5.2.9):



(5.2.9)

Puede encontrarse una descripción adicional de estos compuestos en Beers y cols., "*N*-(5-substituted)tiophene-2-alkylsulfonamides as potent inhibitors of 5-lipoxygenase," *Bioorganic & Medicinal Chemistry* 5(4) 779-786, 1997.

Otra clase aparte de inhibidores de 5-lipoxigenasa es la de 2,6-di-*terc*-butilfenol hidrazonas descritas en Cuadro y cols., "Synthesis and biological evaluation of 2,6-di-*tert*-butylphenol hidrazones as 5-lipoxygenase inhibitors," *Bioorganic & Medicinal Chemistry* 6 173-180, 1998. Los compuestos de este tipo se representan mediante la Fórmula (5.2.10):

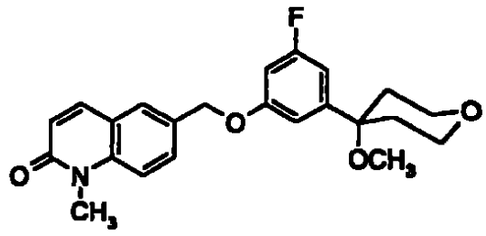


(5.2.10)

donde "Het" es benzoxazol-2-ilo; benzotiazol-2-ilo; piridin-2-ilo; pirazin-2-ilo; pirimidin-2-ilo; 4-fenilpirimidin-2-ilo; 4,6-difenilpirimidin-2-ilo; 4-metilpirimidin-2-ilo; 4,6-dimetilpirimidin-2-ilo; 4-butilpirimidin-2-ilo; 4,6-dibutilpirimidin-2-ilo; y 4-metil-6-fenilpirimidin-2-ilo.

Las *N*-(sustituido en 5)-tiofeno-2-alquilsulfonamidas de Fórmula (5.2.8), o las 2,6-di-*terc*-butilfenol hidrazonas de Fórmula (5.2.10), o cualquiera de los derivados de las mismas descritos anteriormente, se combinan con los compuestos de Fórmula (1.0.0) para formar las realizaciones de la presente invención.

Una clase aparte adicional de inhibidores de 5-lipoxigenasa es la de metoxitetrahidropiranos a los que pertenece Zeneca ZD-2138. ZD-2138 se representa mediante la Fórmula (5.2.11):

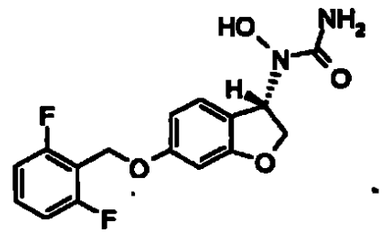


(5.2.11)

ZD-2138 es altamente selectivo y altamente activo oralmente en numerosas especies y se ha evaluado en el tratamiento de asma y artritis reumatoide por administración oral. Se describen características adicionales referentes a ZD-2138 y derivados en Crawley y cols., *J. Med. Chem.*, 35 2600, 1992; y Crawley y cols., *J. Med. Chem.* 36 295, 1993.

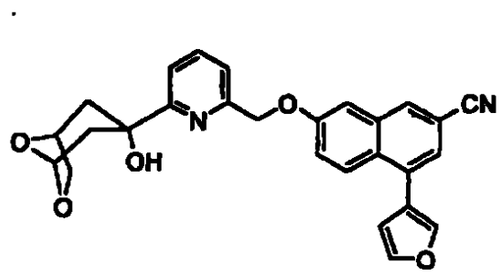
Otra clase aparte de inhibidores de 5-lipoxigenasa es aquella a la que pertenece el compuesto de SmithKline Beecham SB-210661. SB-210661 se representa mediante

la Fórmula (5.2.12):



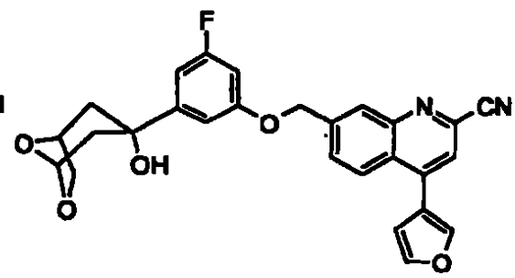
(5.2.12)

Dos clases aparte y relacionadas adicionales de inhibidores de 5-lipoxigenasa comprenden una serie de compuestos de 2-cianonaftaleno sustituidos con piridinilo y una serie de compuestos de 2-cianoquinolina descubiertos por Merck Frosst. Estas dos clases de inhibidores de 5-lipoxigenasa se ejemplifican en 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)

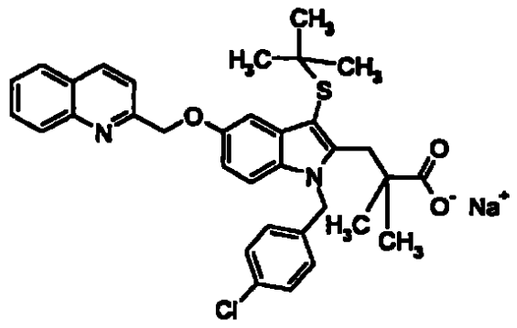
Los detalles concernientes a L-739.010 y L-746.530 se describen en Dubé y cols., "Quinolines as potent 5-lipoxygenase inhibitors: synthesis and biological profile of L-746.530," *Bioorganic & Medicinal Chemistry* 8 1255-1260, 1998; y en el documento WO 95/03309 (Friesen y cols.).

La clase de metoxitetrahidropiranos que incluyen Zeneca ZD-2138 de Fórmula (5.2.11); o el compuesto principal SB-210661 de Fórmula (5.2.12) y la clase a la que pertenece; o la serie de compuesto de 2-cianonaftaleno sustituidos con piridinilo a la que pertenece L-739.010, o la serie de compuestos de 2-cianoquinolina a la que pertenece L-746.530; o cualquiera de los derivados descritos anteriormente de cualquiera de la clases mencionadas anteriormente se combinan con los compuestos de Fórmula (1.0.0) para formar realizaciones de la presente invención.

Además de la enzima 5-lipoxigenasa, el otro agente endógeno que representa un papel significativo en la biosíntesis de leucotrienos es la proteína activadora de 5-lipoxigenasa (FLAP). Este papel es indirecto, al contrario que el papel directo de la enzima 5-lipoxigenasa. Sin embargo, se emplean antagonistas de la proteína activadora de 5-lipoxigenasa para inhibir la síntesis celular de leucotrienos, y como tales se usan también en combinación con los compuestos de Fórmula (1.0.0) para formar realizaciones de la presente invención.

Los compuestos que se unen a la proteína activadora de 5-lipoxigenasa y así bloquean la utilización de la reserva endógena de ácido araquidónico que está presente han sido sintetizados a partir de estructuras de indol y quinolina; véase Ford-Hutchinson y cols., referencia anterior; Rouzer y cols. "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; y Gorenne y cols., "{(R)-2-quinolin-2-yl-metoxy)phenyl)-2-cyclopentyl acetic acid} (BAY X 1005), a potent leukotriene synthesis inhibitor: effects on anti-IgE challenge in human airways," *J. Pharmacol. Exp. Ther.* 268 868-72, 1994.

MK-591, que se ha denominado quiflipon sódico, se representa mediante la Fórmula (5.2.15):



(5.2.15)

Las clases de compuestos de indol y quinolina mencionadas anteriormente y los compuestos específicos MK-591, MK-886, y BAY x 1005 a los que pertenecen, o cualquiera de los derivados descritos anteriormente de cualquiera de las clases mencionadas anteriormente, se combinan con los compuestos de Fórmula (1.0.0) para formar realizaciones de la presente invención.

9.2 Con antagonistas del receptor de leucotrienos LTB_4, LTC_4, LTD_4, y LTE_4

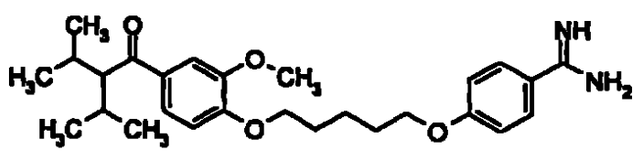
Uno o más compuestos de Fórmula (1.0.0) se usa en combinación con los antagonistas de receptores de los leucotrienos LTB_4, LTC_4, LTD_4, y LTE_4. Los más significativos de estos leucotrienos en lo que se refiere a la respuesta inflamatoria, son LTB_4 y LTD_4. Las clases de antagonistas para los receptores de estos leucotrienos se describen en los párrafos a continuación.

Las 4-bromo-2,7-dimetoxi-3*H*-fenotiazin-3-onas, que incluyen L651.392 son antagonistas potentes del receptor de LTB_4 que se describen en el documento US 4.939.145 (Guidon y cols.) y US 4.845.083 (Lau y cols.). L-651.392 se representa mediante la Fórmula (5.2.16):



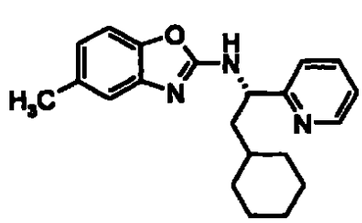
L-851,392 (5.2.16)

Una clase de compuestos de amidino que incluye CGS-25019c se describe en los documentos US 5.451.700 (Morrissey y Suh); US 5.488.160 (Morrissey); y US 5.639.768 (Morrissey y Suh). Estos antagonistas de los receptores de LTB_4 son tipificados por CGS-25019c, que se representa mediante la Fórmula (5.2.17):



CGS-25019c (5.2.17)

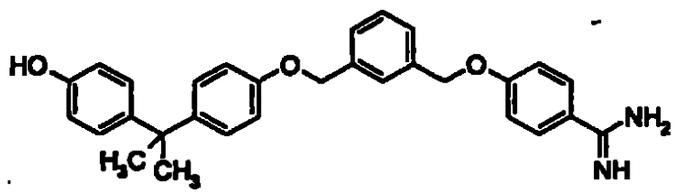
Ontazolast, un miembro de una clase de benzoxazolaminas que son antagonistas del receptor de LTB_4 se describe en EP 535 521 (Anderskewitz y cols.); y se representa mediante la Fórmula (5.2.18):



Ontazolast (5.2.18)

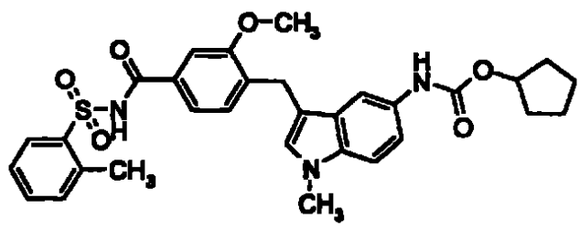
El mismo grupo de investigadores ha descubierto también una clase de

bencenocarboximidamidas que son antagonistas del receptor de LTB_4, que se describe en el documento WO 97/21670 (Anderskewitz y cols.); y WO 98/11119 (Anderskewitz y cols.); que se tipifican mediante BIIL 284/260, representado por la Fórmula (5.2.19):



BIIL 284/260 (5.2.19)

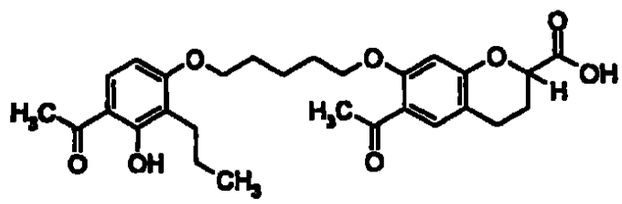
Zafirlukast es un antagonista de los receptores de LTC_4, LTD_4, y LTE_4 que se vende comercialmente con el nombre Accolate®. Pertenece a una clase de derivados de amida heterocíclicos descrita en los documentos US 4.859.692 (Bernstein y cols.); US 5.319.097 (Holohan y Edwards); US 5.294.636 (Edwards y Sherwood); US 5.482.963; US 5.583.152 (Bernstein y cols.); y US 5.612.367 (Timko y cols.). Zafirlukast se representa mediante la Fórmula (5.2.20):



Zafirlukast (5.2.20)

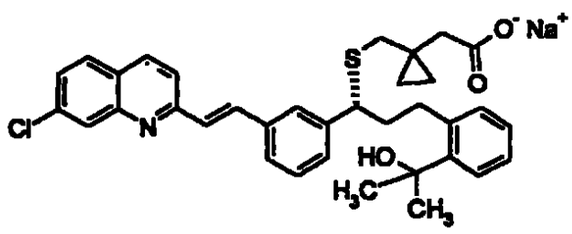
Ablukast es un antagonista del receptor de LTD_4 que se denomina Ro 23-3544/001, y se representa mediante la Fórmula (5.2.21):

372



Ablukast (5.2.21)

Montelukast es un antagonista del receptor de LTD_4 que se vende comercialmente con el nombre Singulair® y se describe en US 5.565.473. Montelukast se representa mediante la Fórmula (5.2.22):



Montelukast (5.2.22)

Otros antagonistas del receptor de 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 mencionada anteriormente, que incluye L-651.392; la clase de compuestos de amidino que incluye CGS-25019c; la clase de benzoxazolaminas que incluye Ontazolast; la clase de bencenocarboximidamidas tipificada por BIIL 284/260; los derivados de amida heterocíclicos que incluyen Zafirlukast; Ablukast y Montelukast y las clases de compuestos a los que pertenecen; o cualquiera de los derivados descritos anteriormente de cualquiera de las clases mencionadas anteriormente, se combinan con los

compuestos de Fórmula (1.0.0) para formar realizaciones de la presente invención.

9.3 Con otros agentes terapéuticos para formar combinaciones adicionales

Uno o más compuestos de Fórmula (1.0.0) se usan junto con otros agentes terapéuticos así como con agentes no terapéuticos para formar combinaciones que son realizaciones adicionales de la presente invención y que son de utilidad en el tratamiento de un número significativo de diferentes enfermedades, trastornos, y afecciones descritas en el presente documento. Dichas realizaciones comprenden uno o más compuestos de Fórmula (1.0.0) junto con uno o más de los siguientes:

(a) Inhibidores de PDE4 incluyendo inhibidores de la isoforma PDE4D;

(b) Inhibidores de 5-lipoxigenasa (5-LO); o antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP);

(c) Inhibidores duales de 5-lipoxigenasa (5-LO) y antagonistas del factor activador de plaquetas (PAF);

(d) Antagonistas de leucotrienos (LTRA) incluyendo antagonistas de LTB_4, LTC_4, LTD_4, y LTE_4;

(e) Antagonistas antihistamínicos del receptor H_1 incluyendo cetirizina, loratadina, desloratadina, fexofenadina, astemizol, azelastina, y clorfeniramina;

(f) Antagonistas gastroprotectores del receptor H_2;

(g) Agentes simpaticomiméticos vasoconstrictores agonistas de los adrenorreceptores α_1 y α_2 administrados oral o tópicamente para uso descongestivo, incluyendo propilhexedrina, fenilefrina, fenilpropanolamina, pseudoefedrina, clorhidrato de nafazolina, clorhidrato de oximetazolina, clorhidrato de tetrahidrozolina; clorhidrato de xilometazolina, y clorhidrato de etilnorepinefrina;

(h) Agonistas de los adrenorreceptores α_1 y α_2 en combinación con

inhibodores de 5-lipoxigenasa (5-LO);

(i) Agentes anticolinérgicos incluyendo bromuro de ipratropio;

(j) Agonistas de los adrenorreceptores β_1 a β_4 incluyendo isoprenalina, albuterol, salbutamol, formoterol, salmeterol, terbutalina, orciprenalina, mesilato de bitolterol, y pirbuterol;

(k) Teofilina y aminofilina;

(l) Cromoglicato sódico;

(m) Antagonistas de los receptores muscarínicos (M1, M2, y M3);

(n) Inhibidores de COX-1 (NSAID); inhibidores selectivos de COX-2 incluyendo rofecoxib; y NSAID de óxido nítrico;

(o) Miméticos del factor de crecimiento insulinoide tipo I (IGF-1);

(p) Ciclesonida;

(q) Glucocorticoides inhalados con efectos secundarios sistémicos reducidos, incluyendo flunisolida, acetonida de triamcinolona, dipropionato de beclometasona, budesonida, propionato de fluticasona, y furoato de mometasona;

(r) Inhibidores de triptasa;

(s) Antagonistas del factor activador de plaquetas (PAF);

(t) Antincuerpos monoclonales contra entidades inflamatorias endógenas;

(u) IPL 576;

(v) Agentes contra el factor necrosante tumoral (TNFα) incluyendo Etanercept, Infliximab, y D2E7;

(w) DMARD incluyendo Leflunomida;

(x) Péptidos TCR;

(y) Inhibidores de la enzima convertidora de interleucina (ICE);

(z) Inhibidores de IMPDH;

(aa) Inhibidores de la molécula de adhesión incluyendo antagonistas de VLA-4;

(bb) Catepsinas;

(cc) Inhibidores de MAP cinasa;

(dd) Inhibidores de glucosa-6-fosfato deshidrogenasa;

(ee) Antagonistas de los receptores de quinina-B_1 y B_2;

(ff) Oro en forma de grupo aurotio junto con diversos grupos hidrófilos;

(gg) Agentes inmunosupresores, por ejemplo, ciclosporina, azatioprina, y metotrexato;

(hh) Agentes contra la gota, por ejemplo colchicina;

(ii) Inhibidores de la xantina oxidasa; por ejemplo alopurinol;

(jj) Agentes uricosúricos, por ejemplo, probenecid, sulfinpirazona, y benzbromarona;

(kk) Agentes antineoplásicos, especialmente fármacos antimitóticos incluyendo los alcaloides de la vinca tales como vinblastina y vincristina;

(ll) Secretagogos de la hormona del crecimiento;

(mm) Inhibidores de las metaloproteasas de matriz (MMP), es decir las estromelisinas, las colagenasas, y las gelatinasas, así como agrecanasas, 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) Factor de crecimiento transformador (TGFβ);

(oo) Factor de crecimiento derivado de plaquetas (PDGF);

(pp) Factor de crecimiento de fibroblastos, por ejemplo el factor de crecimiento de fibroblastos básico (bFGF);

(qq) Factor estimulador de colonias de granulocitos macrófagos (GM-CSF);

(rr) Crema de capsaicina;

(ss) Agentes antieméticos incluyendo antagonistas del receptor NK-1 y D-4418; y

(tt) Antidepresivos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

10.0 Composiciones y formulaciones farmacéuticas

La descripción a continuación concierne a la manera en la que los compuestos de Fórmula (1.0.0), junto con otros agentes terapéuticos o agentes no terapéuticos cuando estos sean deseables, se combinan con lo que son en su mayoría vehículos farmacéuticamente aceptables convencionales para formar formas de dosificación adecuadas para las diferentes vías de administración que se utilizan para cualquier paciente dado, así como apropiadas para la enfermedad, trastorno, o afección por la que se está tratando cualquier paciente dado.

Las vías preferidas de administración para los compuestos de Fórmula (1.0.0) son mediante formulaciones orales y en aerosol preparadas y administradas de modo convencional. A continuación se analiza adicionalmente la información detallada referente a la preparación de tales formulaciones y la forma en la que deben administrarse a un paciente que necesita tratamiento.

Las composiciones farmacéuticas de la presente invención comprenden uno cualquiera o más de los compuestos inhibidores descritos anteriormente de la presente invención, o una sal farmacéuticamente aceptable de los mismos como se describe también anteriormente, junto con un vehículo farmacéuticamente aceptable de acuerdo con las propiedades y funcionamiento esperado de tales vehículos que son bien conocidos en la técnica pertinente.

La cantidad de ingrediente activo que puede combinarse con los materiales

vehículo para producir una única forma de dosificación variará dependiendo del hospedador tratado, y del modo de administración particular. Debe entenderse, sin embargo, que el régimen de dosificación y de tratamiento para un paciente particular dependerá de una diversidad de factores, incluyendo la actividad del compuesto específico empleado, la edad, peso corporal, salud general, sexo, dieta, tiempo de administración, velocidad de excreción, combinación de fármacos, y el juicio del médico que trata y la gravedad de la enfermedad particular que está siendo tratada. La cantidad de ingrediente activo puede depender también del agente terapéutico o profiláctico, si lo hubiera, con el que se coadministra el ingrediente.

Los compuestos descritos anteriormente de la presente invención pueden utilizarse en forma de ácidos, ésteres, u otras clases químicas de compuestos a los que pertenecen los compuestos descritos. También está dentro del alcance de la presente invención utilizar aquellos compuestos en forma de sales farmacéuticamente aceptables derivadas de diversos ácidos y bases orgánicos e inorgánicos de acuerdo con métodos descritos en detalle anteriormente y notorios en la técnica. A menudo se utiliza un ingrediente activo que comprende un compuesto de Fórmula (1.0.0) en forma de sal del mismo, especialmente cuando dicha forma salina confiere a dicho ingrediente activo propiedades farmacocinéticas mejoradas en comparación con la forma libre del ingrediente activo o alguna otra forma salina de dicho ingrediente activo utilizado previamente. La forma salina farmacéuticamente aceptable de dicho ingrediente activo puede conferir también inicialmente una propiedad farmacocinética deseable a dicho ingrediente activo que no poseía previamente, y puede incluso afectar positivamente la farmacocinética de dicho ingrediente activo con respecto a su actividad terapéutica en el cuerpo.

Las propiedades farmacocinéticas de dicho ingrediente activo que puede estar

afectadas favorablemente incluyen, por ejemplo, la forma en la que dicho ingrediente activo se transporta a través de las membranas celulares, que a su vez pueden afectar de forma directa y positiva la absorción, distribución, biotransformación y excreción de dicho ingrediente activo. Aunque la vía de administración de la composición farmacéutica es importante, y diversos factores anatómicos, fisiológicos y patológicos pueden afectar críticamente la biodisponibilidad, la solubilidad de dicho ingrediente activo depende usualmente del carácter de la forma salina particular del mismo que se utiliza. Adicionalmente, como entenderán los expertos en la técnica, una solución acuosa de dicho ingrediente activo proporcionará la absorción más rápida de dicho ingrediente activo al cuerpo de un paciente en tratamiento, mientras que las soluciones y suspensiones lipídicas, así como las formas de dosificación sólidas, darán como resultado una absorción menos lenta de dicho ingrediente activo. La ingestión oral de dicho ingrediente activo es la vía más preferida de administración por razones de seguridad, conveniencia, y economía, pero la absorción de tal forma de dosificación oral puede ser afectada adversamente por características físicas tales como polaridad, emesis provocada por la irritación de la mucosa gastrointestinal, destrucción mediante enzimas digestivas y pH reducido, absorción o propulsión irregular en presencia de alimentos u otros fármacos, y metabolismo por las enzimas de la mucosa, la flora intestinal o el hígado. La formulación de dicho ingrediente activo en formas salinas farmacéuticamente aceptables diferentes puede ser efectiva para superar o aliviar uno o más de los problemas referidos anteriormente que se dan con la absorción de formas de dosificación orales.

Entre las sales farmacéuticas referidas más arriba, las preferidas incluyen, pero sin limitación acetato, besilato, citrato, fumarato, gluconato, hemisuccinato, hipurato, clorhidrato, bromhidrato, isotionato, mandelato, meglumina, nitrato, oleato, fosfonato,

pivalato, fosfato sódico, estearato, sulfato, sulfosalicilato, tatrato, tiomalato, tosilato, y trometamina.

Múltiples formas salinas se incluyen dentro del alcance de la presente invención donde un compuesto de la presente invención contiene más de un grupo capaz de formar tales sales farmacéuticamente aceptables. Los ejemplos de las múltiples formas salinas típicas incluyen, pero sin limitación bitartrato, diacetato, difumarato, dimeglumina, difosfato disódico, y triclorhidrato.

Las composiciones farmacéuticas de la presente invención comprenden uno cualquiera o más de los compuestos inhibidores anteriormente descritos de la presente invención, o una sal farmacéuticamente aceptable de los mismos como también se describió anteriormente, junto con un vehículo farmacéuticamente aceptable con las propiedades y funcionamiento esperado de tales vehículos que son notorios en la técnica pertinente.

El término "vehículo" según se usa en el presente documento incluye diluyentes, excipientes, adyuvantes, vehículos, solubilizantes, modificadores de la viscosidad, conservantes y otros agentes aceptables notorios para los expertos en la técnica porque proporcionan propiedades favorables a la composición farmacéutica final. Para ilustrar tales vehículos, a continuación hay un breve resumen de vehículos farmacéuticamente aceptables que pueden usarse en las composiciones farmacéuticas de la presente invención, y a continuación una descripción más detallada de los diversos tipos de ingredientes. Los vehículos típicos incluyen, pero sin limitación en modo alguno, composiciones de intercambio de iones; alúmina; estearato de aluminio; lecitina; seroproteínas; por ejemplo seroalbúmina humana; fosfatos; glicina; ácido sórbico; sorbato potásico; mezclas de glicéridos parciales de ácidos grasos vegetales saturados; aceites de palma hidrogenados; agua; sales o electrolitos, por ejemplo, sulfato de

prolamina, hidrogenofosfato disódico, hidrogenofosfato potásico; cloruro sódico, y sales de zinc; sílice coloidal; trisilicato magnésico; polivinilpirrolidona; sustancias con base celulósica; por ejemplo carboximetilcelulosa sódica; polietilenglicol; poliacrilatos; ceras; polímeros de bloque de polietileno-polioxipropileno; y lanolina.

Más particularmente, los vehículos usados en las composiciones farmacéuticas de la presente invención comprenden diversas clases y especies de aditivos que son miembros seleccionados independientemente de los grupos constituidos esencialmente por los referidos en los párrafos siguientes.

Los agentes acidificantes y basificantes se añaden para obtener un pH deseado o predeterminado y comprenden agentes acidificantes, por ejemplo, ácido acético, ácido acético glacial, ácido málico, y ácido propiónico. Ácidos más fuertes como ácido clorhídrico, ácido nítrico y ácido sulfúrico pueden usarse pero son menos preferidos. Los agentes basificantes incluyen, por ejemplo, edetol, carbonato potásico, hidróxido potásico, borato sódico, carbonato sódico, e hidróxido sódico. También pueden usarse los agentes basificantes que contienen grupos amina activos, tales como dietanolamina y trolamina.

Cuando las composiciones farmacéuticas se administran en forma de aerosol a una presión significativa son necesarios los propelentes en aerosol. Tales propelentes incluyen, por ejemplo fluoroclorohidrocarburos aceptables tales como diclorodifluorometano, diclorotetrafluoroetano, y tricloromonofluorometano; nitrógeno; o un hidrocarburo volátil tal como butano, propano, isobutano o mezclas de los mismos.

Los agentes antimicrobianos que incluyen los agentes antibacterianos, antifúngicos y antiprotozoos se añaden cuando la composición farmacéutica se aplica localmente a zonas de la piel que es probable que hayan sufrido condiciones adversas o abrasiones mantenidas o cortes que exponen la piel a infecciones por bacterias, hongos

o protozoos. Los agentes antimicrobianos incluyen compuestos tales como alcohol bencílico, clorobutanol, alcohol feniletílico, acetato fenilmercúrico, sorbato potásico, y ácido sórbico. Los agentes antifúngicos incluyen compuestos tales como ácido benzoico, butilparaben, etilparaben, metilparaben, propilparaben, y benzoato sódico.

Se añaden conservantes antimicrobianos a las composiciones farmacéuticas de la presente invención para protegerlas del crecimiento de microorganismos potencialmente dañinos que habitualmente invaden la fase acuosa, pero en algunos casos pueden crecer también en la fase aceitosa de una composición. Por lo tanto son deseables los conservantes con solubilidad acuosa y lipídica. Los conservantes antimicrobianos adecuados incluyen, por ejemplo ésteres de alquilo de ácido *p*-hidroxibenzoico, sales de propionato, fenoxietanol, metilparaben sódico, propilparaben sódico, deshidroacetato sódico, cloruro de benzalconio, cloruro de bencetonio, alcohol bencílico, derivados de hidantoína, compuestos de amonio cuaternario y polímeros catiónicos, imidazolidinilurea, diazolidinilurea, y tetracetato de etilenodiamina trisódica (EDTA). Los conservantes se emplean preferiblemente en cantidades que oscilan desde aproximadamente 0,01% a aproximadamente 2,0% en peso de la composición total.

Los antioxidantes se añaden para proteger todos los ingredientes de la composición farmacéutica de daños o degradación mediante los agentes oxidantes presentes en la composición misma o el entorno de uso, por ejemplo, anoxomer, palmitato de ascorbilo, hidroxianisol butilado, hidroxitolueno butilado, ácido hipofosforoso, metabisulfuro potásico, galato de propilo, octilo y dodecilo, metabisulfito sódico, dióxido de azufre, y tocoferoles.

Los agentes tamponadores se usan para mantener un pH deseado de un composición una vez establecido, de los efectos de agentes exteriores y desplazamiento de equilibrios de los componentes de la composición. El tampón puede elegirse entre

los familiares para los expertos en la técnica en la preparación de composiciones farmacéuticas, por ejemplo, acetato cálcico, metafosfato potásico, fosfato potásico monobásico, y ácido tartárico.

Los agentes quelantes se usan para mantener la fortaleza iónica de la composición farmacéutica y unirse y eliminar de forma efectiva los compuestos destructivos y metales, e incluyen, por ejemplo, edetato dipotásico, edetato disódico, y ácido edético.

Los agentes dermatológicamente activos se añaden a las composiciones farmacéuticas de la presente invención cuando van a aplicarse tópicamente, e incluyen, por ejemplo, agentes para curar heridas tales como derivados peptídicos, levaduras, pantenol, hexilresorcinol, fenol, clorhidrato de tetraciclina, lamina y quinetina; retinoides para tratar el cáncer de piel, por ejemplo, retinol, tretinoína, isotretinoína, etretinato, acitretina, y arotinoide; agentes antibacterianos suaves para tratar infecciones cutáneas , por ejemplo resorcinol, ácido salicílico, peróxido de benzoílo, peróxido de eritromicín-benzoílo, eritromicina, y clindamicina; agentes antifúngicos para tratar tiña corporal, tiña del pie, candidiasis y tiña versicolor, por ejemplo, griseofulvina, azoles tales como miconazol, econazol, itraconzol, fluconazol, y cetoconazol, y alilaminas tales como naftifina y terfinafina; agentes antivirales para tratar el herpes simplex cutáneo, herpes zoster, y varicela, por ejemplo, aciclovir, famciclovir, y valaciclovir; antihistaminas para tratar pruritos, dermatitis atópica y de contacto, por ejemplo difenhidramina, terfenadina, astemizol, loratadina, cetirizina, acrivastina, y temelastina; anestésicos locales para aliviar el dolor, irritación y picor, por ejemplo, benzocaína, lidocaína, dibucaína, y clorhidrato de pramoxina; analgésicos locales para aliviar el dolor y la inflamación, por ejemplo, salicilato metílico, alcanfor, mentol, y resorcinol; antisépticos tópicos para prevenir infecciones, por ejemplo cloruro de benzalconio y

povidona-yodo; y vitaminas y derivados de las mismas tales como tocoferol, acetato de tocoferol, ácido retinoico y retinol.

Los agentes de dispersión y de suspensión se usan como ayudas para la preparación de formulaciones estables e incluyen, por ejemplo, poligenina, povidona, y dióxido de silicio.

Los emolientes son agentes, preferiblemente no aceitosos y solubles en agua, que suavizan y calman la piel, especialmente la piel que se ha vuelto seca debido a la pérdida excesiva de agua. Tales agentes se usan con composiciones farmacéuticas de la presente invención que se prefieren sean de aplicación tópica, e incluyen, por ejemplo aceites hidrocarbonados y ceras, ésteres de triglicéridos, monoglicéridos acetilados, ésteres de ácidos grasos C_{10}-C_{20} de metilo y otros alquilos, ácidos grasos C_{10}-C_{20}, alcoholes grasos C_{10}-C_{20}, lanolina y derivados, ésteres de alcohol polihídrico tales como polietilenglicol (200-600), ésteres de ácidos grasos de polioxietilensorbitan, ésteres de ceras, fosfolípidos, y esteroles; agentes emulsionantes usados para la preparación de emulsiones de aceite en agua; excipientes, por ejemplo laurocapramo y monometiléter de polietilenglicol; humectantes, por ejemplo, sorbitol, glicerina y ácido hialurónico; bases de ungüentos, por ejemplo vaselina, polietilenglicol, lanolina, y poloxámero; potenciadores de la penetración, por ejemplo isosorburo dimetílico, monoetiléter de dietilglicol, 1-dodecilazacicloheptan-2-ona, y dimetilsulfóxido (DMSO); conservantes, por ejemplo, cloruro de benzalconio, cloruro de bencetonio, ésteres alquílicos de ácido *p*-hidroxibenzoico, derivados de hidantoína, cloruro de cetilpiridinio, propilparaben, compuestos de amonio cuaternario tales como benzoato potásico, y timerosal; agentes secuestrantes que comprenden ciclodextrinas; disolventes, por ejemplo, acetona, alcohol, hidrato de amileno, alcohol butílico, aceite de maíz, aceite de semilla de algodón, acetato etílico, glicerina, hexilenglicol, alcohol isopropílico, alcohol de

isoestearilo, alcohol metílico, cloruro de metileno, aceite mineral, aceite de cacahuete, ácido fosfórico, polietilenglicol, 15-estearilléter de polioxipropileno, propilenglicol, diacetato de propilenglicol, aceite de sésamo, y agua purificada; estabilizantes, por ejemplo, sacarato cálcico y timol; tensioactivos, por ejemplo cloruro de lapirio; lauret 4, es decir, α-dodecil-ω-hidroxi-poli(oxi-1,2-etanodiilo) o monododeciléter de polietilenglicol.

Los agentes emulsionantes, incluyendo agentes emulsionantes y endurecedores y adyuvantes de emulsión, se usan para preparar emulsiones de aceite en agua cuando éstas forman la base de las composiciones farmacéuticas de la presente invención. Tales agentes emulsionantes incluyen, por ejemplo, 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 diésteres ácidos grasos C_{10}-C_{20} de etilenglicol, monoglicérido de ácidos grasos C_{10}-C_{20}, dietilenglicol, polietilenglicoles de PM 200-6000, polipropilenglicoles de PM 200-3000, y en particular sorbitol, sorbitan, polioxietilensorbitol, polioxietilensorbitan, ésteres de cera hidrófila, alcohol cetoestearílico, alcohol oleílico, alcoholes de lanolina, colesterol, mono- y di-glicéridos, monoestearato de glicerilo, monoestearato de polietilenglicol, ésters mono- y diesteáricos mixtos de etilenglicol y polioxietilenglicol, monoestearato de propilenglicol, e hidroxipropilcelulosa. Agentes emulsionantes que contienen grupos amina activos pueden usarse también y típicamente incluyen emulsionantes aniónicos tales como jabones de ácidos grasos, por ejemplo, jabones de sodio, potasio y trietanolamina 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_{50})etoxietersulfonatos. Otros agentes emulsionantes adecuados incluyen aceite de

castor y aceite de castor hidrogenado; lecitina; y polímeros de ácido 2-propenoico junto con polímeros de ácido acrílico, tanto entrecruzados con aliléteres de sacarosa y/o pentaeritritol, con viscosidades variables e identificados mediante los nombres de productos carbómero 910, 934, 934P, 940, 941, y 1342. Pueden usarse también los emulsionantes catiónicos que tienen grupos amina activos, incluyendo aquellos basados en compuestos de amonio cuaternario, morfolinio y piridinio. De forma similar, pueden usarse los emulsionantes anfóteros que tienen grupos amina activos, tales como cocobetaínas, óxido de laurildimetilamina y cocoilimidazolina. Los agentes emulsionantes y endurecedores útiles incluyen también alcohol cetílico y estearato sódico; y adyuvantes de la emulsión tales como ácido oléico, ácido esteárico, y alcohol estearílico.

Los excipientes incluyen, por ejemplo laurocapramo y monometiléter de polietilenglicol.

Cuando la composición farmacéutica de la presente invención debe aplicarse tópicamente, pueden usarse potenciadores de la penetración, que incluyen, por ejemplo isosorburo dimetílico, monoetiléter de dietil-glicol, 1-dodecilazacicloheptan-2-ona, y deimetilsulfóxido (DMSO). Tales composiciones incluirán también típicamente bases de ungüentos, por ejemplo, vaselina, polietilenglicol, lanolina, y poloxámero, que es un copolímero de bloque de polioxietileno y polioxipropileno, que puede servir también como agente tensioactivo o emulsionante.

Los conservantes se usan para proteger las composiciones farmacéuticas de la presente invención del ataque degradante de microorganismos ambientales, e incluyen, por ejemplo, cloruro de benzalconio, cloruro de bencetonio, ésteres alquílicos de ácido *p*-hidroxibenzoico, derivados de hidantoína, cloruro de imidazolidinilo, monotioglicerol, fenol, fenoxietanol, metilparaben, imidazolidinilurea, deshidroacetato

sódico, propilparaben, compuestos de amonio cuaternario, especialmente polímeros tales como cloruro de polixetonio, benzoato potásico, formaldehidosulfoxilato sódico, propionato sódico, y timerosal.

Los agentes secuestrantes se usan para mejorar la estabilidad de las composiciones farmacéuticas de la presente invención e incluyen, por ejemplo, las ciclodextrinas que son una familia de oligosacáridos cíclicos naturales capaces de formar complejos de inclusión con una variedad de materiales, y son de tamaños de anillos variables, denominándose comúnmente aquellos que tienen residuos de glucosa en las posiciones 6, 7 y 8 en un anillo α-ciclodextrinas, β-ciclodextrinas, y γ-ciclodextrinas, respectivamente. Las ciclodextrinas adecuadas incluyen, por ejemplo α-ciclodextrina, β-ciclodextrina, γ-ciclodextrinas, δ-ciclodextrina y ciclodextrinas cationizadas.

Los disolventes que pueden usarse para preparar las composiciones farmacéuticas de la presente invención incluyen, por ejemplo acetona, alcohol, hidrato de amileno, alcohol butílico, aceite de maíz, aceite de semilla de algodón, acetato etílico, glicerina, hexilenglicol, alcohol isopropílico, alcohol isoestearílico, alcohol metílico, cloruro de metileno, aceite mineral, aceite de cacahuete, ácido fosfórico, polietilenglicol, 15-estariléter de polioxipropileno, propilenglicol, diacetato de propilenglicol, aceite de sésamo, y agua purificada.

Los estabilizantes que son adecuados para su uso incluyen, por ejemplo, sacarato cálcico y timol.

Los agentes endurecedores se usan típicamente en formulaciones para aplicaciones tópicas para proporcionar una viscosidad y características de manejo deseadas e incluyen, por ejemplo cera de cetilésteres, alcohol de miristilo, parafina, parafina sintética, cera emulsionante, cera microcristalina, cera blanca y cera amarilla.

Los azúcares se usan a menudo para conferir una variedad de características deseadas a las composiciones farmacéuticas de la presente invención y para mejorar los resultados obtenidos, e incluyen, por ejemplo, monosacáridos, disacáridos, y polisacáridos tales como glucosa, xilosa, fructosa, reosa, ribosa, pentosa, arabinosa, alosa, talosa, altrosa, manosa, galactosa, lactosa, sacarosa, eritrosa, gliceraldehído, o cualquier combinación de las mismas.

Los tensioactivos se emplean para proporcionar estabilidad a las composiciones farmacéuticas con multicomponentes de la presente invención, mejoran las propiedades existentes de esas composiciones, y confieren características nuevas deseables a dichas composiciones. Los tensioactivos se unas como agentes humectantes, agentes antiespumantes, para reducir la tensión superficial del agua, y como emulsionantes, agentes dispersantes, y penetrantes, e incluyen, por ejemplo, cloruro de lapirio; lauret 4, es decir, α-dodecil-ω-hidroxi-poli(oxi-1,2-etanodiilo) o monododeciléter de polietilenglicol; lauret 9, es decir una mezcla de monododeciléteres de poletilenglicol con una media de aproximadamente 9 grupos de óxido de etileno por molécula; monoetanolamina; nonoxinol 4, 9 y 10, es decir, mono(*p*-nonilfenil)éter de polietilenglicol; nonoxinol 15, es decir α-(*p*-nonilfenil)-ω-hidroxipenta-deca(oxietileno); nonoxinol 30, es decir α-(*p*-nonilfenil)-ω-hidroxitriaconta(oxietileno); poloxaleno, es decir, polímero no iónico del tipo de polietilen-polipropilenglicol, PM = aprox. 3000; poloxamer, mencionado en el análisis de bases de ungüentos más arriba; estearato 8, 40 y 50 de polioxilo, es decir, poli(oxi-1,2-etanodiilo), α-hidro-ω-hidroxi-; octadecanoato; oleiléter 10 de polioxilo, es decir, poli(oxi-1,2-etanodiilo), α-[(Z)-9-octadecenil-ω-hidroxi-; polisorbato 20, es decir, sorbitan, monododecanoato, poli(oxi-1,2-etanodiilo); polisorbato 40, es decir, sorbitan, monohexadecanoato, poli(oxi-1,2-etnodiilo); polisorbato 60, es decir, sorbitan, monooctadecanoato, poli(oxi-1,2-

etnodiilo); polisorbato 65, es decir, sorbitan, trioctadecanoato, poli(oxi-1,2-etanodiilo); polisorbato 80, es decir, sorbitan,mono-9-monodecenoato, poli(oxi-1,2-etanodiilo); polisorbato 85, es decir, sorbitan, tri-9-octadecenoato, poli(oxi-1,2-etanodiilo); laurilsulfato sódico; monolaurato de sorbitan,; monooleato de sorbitan; monopalmitato de sorbitan; monoestearato de sorbitan, sesquioleato de sorbitan; trioleato de sorbitan; y triestearato de sorbitan.

Las composiciones farmacéuticas de la presente invención pueden prepararse usando metodología muy sencilla que es bien entendida por los expertos habituales en la técnica. Cuando las composiciones farmacéuticas de la presente invención son soluciones acuosas simples y/o soluciones en otros disolventes, los diversos componentes de la composición global se juntan en cualquier orden práctico, que vendrá dictado mayormente por las consideraciones de conveniencia. Aquellos componentes que tengan una solubilidad reducida en agua, pero una solubilidad suficiente en el mismo codisolvente con agua, pueden disolverse todos en dicho codisolvente, después de lo cual la solución de codisolvente se añadirá a la porción de agua del vehículo donde los solutos se disolverán en el agua. Para ayudar a este proceso de dispersión/solución, puede emplearse un tensioactivo.

Cuando las composiciones farmacéuticas de la presente invención deben estar en forma de emulsiones, los componentes de las composiciones farmacéuticas se juntarán de acuerdo con los siguientes métodos generales. La fase acuosa continua se calienta primero a una temperatura en el intervalo de aproximadamente 60° a aproximadamente 95°, preferiblemente de aproximadamente 70° a aproximadamente 85°C, dependiendo la elección de la temperatura de las propiedades físicas y químicas de los componentes que forman la emulsión de aceite en agua. Una vez que la fase acuosa continua ha alcanzado su temperatura seleccionada, los componentes de la composición final a añadir en esta

etapa se mezclan con el agua y se dispersan en ella agitando a gran velocidad. Después, la temperatura del agua se devuelve aproximadamente a su nivel original, después de lo cual los componentes de la composición que comprenden la siguiente etapa se añaden a la mezcla de la composición con agitación moderada y continúa el mezclado desde aproximadamente 5 a aproximadamente 60 minutos, preferiblemente aproximadamente de 10 a aproximadamente 30 minutos, dependiendo de los componentes de las dos primeras etapas. A partir de entonces, la mezcla de la composición se enfría de forma pasiva o activa aproximadamente de 20° a aproximadamente 55°C para la adición de cualquier componente en las etapas que quedan, después de lo cual se añade el agua en cantidad suficiente para alcanzar su concentración predeterminada original en la composición global.

De acuerdo con la presente invención, las composiciones farmacéuticas pueden estar en forma de preparación inyectable estéril, por ejemplo una suspensión estéril inyectable acuosa u oleaginosa. Esta suspensión puede formularse de acuerdo con técnicas conocidas en la técnica usando agentes dispersantes o humectantes adecuados y agentes de suspensión. La preparación estéril inyectable puede ser también una solución o suspensión inyectable estéril en un diluyente o disolvente no tóxico parenteralmente aceptable, por ejemplo en forma de una solución en 1,3-butanodiol. Entre los vehículos y disolventes aceptables que pueden emplearse están el agua, solución de Ringer y solución de cloruro sódico isotónico. Además, se emplean convencionalmente aceites estériles, fijos como disolvente o medio de suspensión. Para este fin puede emplearse cualquier aceite fijo suave incluyendo mono- o di-glicéridos sintéticos. Los ácidos grasos, tales como el ácido oleico y sus derivados glicéridos son de utilidad en la preparación de inyectables, al igual que los aceites naturales farmacéuticamente aceptables, tales como aceite de oliva o aceite de castor, especialmente en sus versiones

polioxietiladas. Estas soluciones o suspensiones en aceite pueden contener también un diluyente o dispersante de alcohol de cadena larga, tal como alcohol *Rh*, HCIX o alcohol similar.

Las composiciones farmacéuticas de la presente invención pueden administrarse oralmente en cualquier forma de dosificación aceptable oralmente incluyendo, pero sin limitación, cápsulas, comprimidos, suspensiones o diluciones acuosas. En el caso de los comprimidos para uso oral, los vehículos que se usan habitualmente incluyen lactosa y almidón de maíz. Los agentes lubricantes, tales como estearato magnésico, se añaden también típicamente. Para la administración oral en forma de cápsula, los diluyentes de utilidad incluyen lactosa y almidón de maíz seco. Cuando se requieren suspensiones acuosas para uso oral, el ingrediente activo se combina con agentes emulsionantes y de suspensión. Si se desea, pueden añadirse también ciertos agentes edulcorantes, aromas o colorantes. De forma alternativa, las composiciones farmacéuticas de esta invención pueden administrarse en forma de supositorios para la administración rectal. Éstos pueden prepararse mezclando el agente con un excipiente adecuado no irritante que es sólido a temperatura ambiente pero líquido a la temperatura rectal y por lo tanto se fundirá en el recto para liberar el fármaco. Tales materiales incluyen manteca de cacao, cera de abeja y polietilenglicoles.

Las composiciones farmacéuticas de la presente invención pueden administrarse también por vía tópica, especialmente cuando la diana de tratamiento incluye áreas u órganos fácilmente accesibles por aplicación tópica, incluyendo enfermedades oculares, cutáneas, o del tubo digestivo inferior. Las formulaciones tópicas adecuadas se preparan fácilmente para cada uno de estos órganos o áreas.

La aplicación tópica para el tubo intestinal inferior puede efectuarse en una formulación de supositorio rectal, como se describe anteriormente, o en una

formulación en enema adecuada. Pueden usarse también los parches transdérmicos activos tópicamente.

Para las aplicaciones tópicas, las composiciones farmacéuticas pueden formularse en un ungüento adecuado que contiene el ingrediente activo suspendido o disuelto en uno o más vehículos. Los vehículos para la administración tópica de los compuestos de esta invención incluyen, pero sin limitación, aceite mineral, vaselina líquida, vaselina blanca, compuestos de propilenglicol, polioxietileno, polioxipropileno, cera emulsionante y agua. De forma alternativa, las composiciones farmacéuticas pueden formularse en una loción o crema adecuada que contiene los componentes activos suspendidos o disueltos en uno o más vehículos farmacéuticamente aceptables. Los vehículos adecuados incluyen, pero sin limitación, aceite mineral, monoestearato de sorbitan, polisorbato, cera de cetilésteres, alcohol cetearílico, 2-octildodecanol, alcohol bencílico y agua.

Las composiciones farmacéuticas dentro del alcance de la presente invención incluyen aquellas en las que la cantidad terapéuticamente efectiva de un ingrediente activo que comprende un compuesto de la presente invención requerido para tratar o prevenir enfermedades, trastornos, y afecciones mediadas o asociadas a la modulación de PDE4, especialmente la actividad de PDE4D según se describe en el presente documento, se proporciona en una forma de dosificación adecuada para la administración sistémica. Tal composición farmacéutica contendrá dicho ingrediente activo en forma líquida adecuada para la administración mediante: (1) inyección o con infusión con que es intraarterial, intra o transdérmica, subcutánea, intramuscular, intraespinal, intratecal, o intravenosa, en la que dicho ingrediente activo: (a) está contenido en solución en forma de soluto; (b) está contenido en la fase discontinua de una emulsión o la fase discontinua de una emulsión inversa que se invierte al inyectar o

infundir, conteniendo dichas emulsiones agentes emulsionantes adecuados; o (c) está contenido en una suspensión en forma de sólido suspendido en forma coloidal o microparticulada, conteniendo dicha suspensión agentes de suspensión adecuados; (2) inyección o infusión en tejidos o cavidades corporales adecuados en forma de depósito, en la que dicha composición proporciona el almacenamiento de dicho ingrediente activo y después la liberación retardada, mantenida, y/o controlada de dicho ingrediente activo para su distribución sistémica; (3) instilación, inhalación o insuflación en tejidos o cavidades corporales adecuadas de dicha composición farmacéutica en forma sólida adecuada, donde dicho ingrediente activo: (a) está contenido en una composición implantada sólida que proporciona la liberación retardada, mantenida y/o controlada de dicho ingrediente activo; (b) está contenida en una composición de partículas para ser inhalada a los pulmones; o (c) está contenida en una composición de partículas para ser sopladas en tejidos o cavidades corporales adecuados, proporcionando dicha composición liberación retardada, mantenida y/o controlada de dicho ingrediente activo; o (4) ingestión de dicha composición farmacéutica en una forma sólida o líquida adecuada para la administración peroral de dicho ingrediente activo, donde dicho ingrediente activo está contenido en una forma de dosificación sólida; o (b) está contendido en una forma de dosificación líquida.

Las formas de dosificación particulares de las composiciones farmacéuticas descritas anteriormente incluyen (1) supositorios como un tipo especial de implante, que comprenden bases que son sólidas a temperatura ambiente pero que se funden a la temperatura corporal, liberando lentamente el ingrediente activo con el que están impregnados al tejido corporal que los rodea, donde el ingrediente activo se absorbe y se transporta para efectuar una administración sistémica; (2) formas de dosificación perorales sólidas seleccionadas del grupo constituido por (a) comprimidos cápsulas,

comprimidos oblongos, pastillas, tabletas, y multipartículas orales de liberación retardada; (b) comprimidos de recubrimiento entérico y cápsulas que evitan la liberación y absorción en el estómago para facilitar la administración distal al estómago del paciente en tratamiento; (c) comprimidos, cápsulas y micropartículas orales de liberación mantenida, que proporcionan la administración sistémica del ingrediente activo de forma controlada hasta un periodo de 24 horas; (d) comprimidos de disolución rápida; (e) soluciones encapsuladas; (f) una pasta oral; (g) una forma granular incorporada o para ser incorporada a la comida de un paciente en tratamiento; y (h) formas de dosificación perorales líquidas seleccionadas del grupo constituido por soluciones, suspensiones, emulsiones, emulsiones inversas, elixires, extractos, tinturas, y concentrados.

Las composiciones farmacéuticas dentro del alcance de la presente invención incluyen aquellas en las que la cantidad terapéuticamente efectiva de un ingrediente activo que comprende un compuesto de la presente invención requerido para tratar o prevenir enfermedades, trastornos, y afecciones medidas o asociadas a la modulación de PDE4, especialmente la actividad de PDE4D como se describe en el presente documento se proporciona en una forma de dosificación adecuada para la administración local a un paciente en tratamiento, en la que dicha composición farmacéutica contiene dicho ingrediente activo en forma líquida adecuada para administrar dicho ingrediente activo mediante: (1) inyección o infusión en un sitio local que es intraarterial, intraarticular, intracondrial, intracostal, intracística, intra o transdérmica, intrafasicular, intraligamentosa, intramedular, intramuscular, intranasal, intraneural, intraocular, es decir, administración oftálmica, intraosteal, intrapélvica, intrapericárdica, intraespinal, intraesternal, intrasinovial, intratarsiano, o intratecal; incluyendo componentes que proporcionan liberación retardada, liberación controlada,

y/o liberación mantenida de dicho ingrediente activo en dicho sitio local; donde se contiene dicho ingrediente activo: (a) en solución un como soluto; (b) en la fase discontinua de una emulsión, o la fase discontinua de una emulsión inversa que se invierte al inyectar o infundir, conteniendo dichas emulsiones agentes emulsionantes adecuados; o (c) en una suspensión en forma de sólido suspendido en forma coloidal o de micropartícula, conteniendo dicha suspensión agentes de suspensión adecuados; o (2) inyección o infusión en forma de depósito para administrar dicho ingrediente activo a dicho sitio local; en la que dicha composición proporciona el almacenamiento de dicho ingrediente activo y después la liberación retardada, mantenida y/o controlada de dicho ingrediente activo a dicho sitio local, y en la que dicha composición también incluye componentes que aseguran que dicho ingrediente activo tiene predominantemente un actividad local, con poca actividad sistémica transferida; o en la que dicha composición farmacéutica contiene dicho ingrediente activo en forma sólida adecuada para administrar dicho inhibidor por: (3) instilación, inhalación o insuflación a dicho sitio local, donde está contenido dicho ingrediente activo: (a) en una composición implantada sólida que se instala en dicho sitio local, proporcionando opcionalmente dicha composición liberación retardada, mantenida y/o controlada de dicho ingrediente activo a dicho sitio local; (b) en una composición en partículas que se inhala a un sitio local que comprende los pulmones; o (c) en una composición en partículas que se sopla a un sitio local, donde dicha composición incluye componentes que aseguran que dicho ingrediente activo tiene predominantemente actividad local, con una actividad sistémica transferida insignificante, y que opcionalmente proporciona una liberación retardada, mantenida y/o controlada de dicho ingrediente activo a dicho sitio local. Para el uso oftálmico, las composiciones farmacéuticas pueden formularse en forma de suspensión micronizada en solución salina isotónica con pH ajustado estéril, o, preferiblemente, en

forma de soluciones en solución salina estéril con pH ajustado, con o sin un conservante tal como cloruro de bencilalconio. De forma alternativa, para el uso oftálmico, las composiciones farmacéuticas pueden formularse en un ungüento como vaselina.

Las composiciones farmacéuticas de la presente invención pueden administrarse también mediante aerosol nasal o inhalación a través del uso de un nebulizador, un inhalador de polvo seco o un inhalador dosificador. Tales composiciones se preparan de acuerdo con técnicas notorias en la técnica de la formulación farmacéutica y pueden prepararse en forma de soluciones en solución salino, empleando alcohol bencílico u otros conservantes adecuados, promotores de la absorción para potenciar la biodisponibilidad, hidrofluorocarbonos, y/o otros agentes convencionales solubilizantes o dispersantes.

Como ya se ha mencionado, los ingredientes activos de Fórmula (1.0.0) de la presente invención pueden administrarse sistémicamente a un paciente a tratar en forma de composición farmacéutica en forma líquida adecuada mediante inyección o infusión. Hay numerosos sitios y sistemas de órganos en el cuerpo de un paciente que permitirán que la composición farmacéutica formulada adecuadamente, una vez inyectada o infundida, se distribuya por todo el cuerpo y todos los sistemas de órganos del paciente tratado. Una inyección es una dosis única de la composición farmacéutica que se fuerza, habitualmente con una jeringuilla, al tejido implicado. Los tipos más comunes de inyecciones son intramuscular, intravenosa, y subcutánea. Por el contrario, una infusión es la introducción gradual de la composición farmacéutica al tejido implicado. El tipo más común de infusión es la intravenosa. Otros tipos de inyección o infusión comprenden la intraarterial, intra o transdérmica (incluyendo subcutánea), o intraespinal especialmente intratecal. En estas composiciones farmacéuticas líquidas, el ingrediente activo puede estar contenido en solución como el soluto. Este es el tipo más común y

más preferido de cada composición, pero requiere un ingrediente activo en forma salina que tenga una solubilidad acuosa razonablemente buena. Agua (o solución salina) es, con mucho, el disolvente preferido para tales composiciones. Ocasionalmente pueden utilizarse soluciones supersaturadas, pero éstas presentan problemas de estabilidad que las hacen poco prácticas para su uso diario.

Si no es posible obtener una forma de algún compuesto de Fórmula (1.0.0) que cumpla el grado de solubilidad acuosa requerido, como puede suceder a veces, está dentro de la técnica del experto preparar una emulsión, que es una dispersión de glóbulos pequeños 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 mediante el uso de emulsionantes que son farmacéuticamente aceptables Así, si el ingrediente activo es un aceite insoluble en agua, puede administrarse en una emulsión de la que es la fase discontinua. También puede usarse una emulsión cuando el ingrediente activo es insoluble en agua pero puede disolverse en un disolvente que es inmiscible en agua. Aunque el ingrediente activo se usaría más habitualmente como fase discontinua o interna de lo que se denomina emulsión de aceite en agua, puede usarse también como fase discontinua o interna de una emulsión inversa, que se denomina comúnmente emulsión de agua en aceite. Aquí el ingrediente activo es soluble en agua y podría administrarse como solución acuosa simple. Sin embargo, las emulsiones inversas se invierten al inyectar o infundir en un medio acuoso tal como la sangre, y ofrecen la ventaja de proporcionar una dispersión más rápida y eficiente del ingrediente activo en ese medio acuoso que puede obtenerse usando una solución acuosa. Las emulsiones inversas se preparan usando agentes emulsionantes adecuados, farmacéuticamente aceptables, notorios en la técnica. Cuando el ingrediente activo tiene una solubilidad en agua limitada, puede administrarse

también como sólido suspendido en forma coloidal o de micropartículas en una suspensión preparada usando agentes de suspensión adecuados, farmacéuticamente aceptables. Los sólidos suspendidos que contienen el ingrediente activo pueden formularse también como composiciones de liberación retardada, mantenida y/o controlada.

Aunque la administración sistémica se realizará más frecuentemente mediante inyección o infusión de un líquido, hay muchas situaciones en las que será ventajoso o incluso necesario administrar el ingrediente activo en forma de sólido. La administración sistémica de los sólidos se realiza por instilación inhalación o insuflación de una composición farmacéutica en una forma sólida adecuada que contenga el ingrediente activo. La instalación del ingrediente activo puede suponer la instalación de una composición sólida implantada en tejidos o cavidades corporales adecuadas. El implante puede comprender una matriz de materiales biocompatibles y bioerosionables en los que las partículas de un ingrediente activo sólido se dispersan, o en el que, posiblemente, están atrapados glóbulos o células aisladas de un ingrediente activo líquido. De forma deseable, la matriz se desintegrará y será absorbida por el cuerpo. La composición de la matriz se selecciona también preferiblemente para proporcionar una liberación retardada, mantenida y/o controlada del ingrediente activo durante periodos de tiempo prolongados, incluso hasta varios meses.

El término "implante" más a menudo denota una composición farmacéutica sólida que contiene el ingrediente activo, mientras que el término "depósito" habitualmente implica una composición farmacéutica líquida que contiene el ingrediente activo, que se deposita en cualquier tejido o cavidad corporal adecuado para formar un almacen o reserva que lentamente migra hacia los tejidos y órganos que lo rodean y eventualmente se distribuye sistémicamente. Sin embargo, estas distinciones

son se siguen estrictamente en la técnica, y en consecuencia se contempla que se incluyen dentro del alcance de la presente invención los implantes líquidos y los depósitos sólidos, e incluso formas sólidas y líquidas mixtas de ambos. Los supositorios pueden considerarse un tipo de implante, dado que comprenden bases que son sólidas a temperatura ambiente pero que se funden a la temperatura corporal del paciente, liberando lentamente el ingrediente activo con el que están impregnados al tejido corporal del paciente, donde el ingrediente activo se absorbe y se transporta para efectuar una administración sistémica.

La administración sistémica puede lograrse también mediante inhalación o insuflación de un polvo, es decir, una composición en partículas que contiene el ingrediente activo. Por ejemplo, el ingrediente activo en forma de polvo puede inhalarse a los pulmones usando dispositivos convencionales para formar aerosoles de formulaciones con partículas. El ingrediente activo como formulación de partículas puede administrarse también por insuflación, es decir, soplada o dispersada de otro modo en tejidos o cavidades corporales adecuadas por simple espolvoreado o usando dispositivos convencionales para formar aerosoles con formulaciones de partículas. Estas composiciones de partículas pueden formularse también para proporcionar una liberación retardada, mantenida y/o controlada de dicho ingrediente activo de acuerdo con principios bien entendidos y materiales conocidos.

Otros medios de administración sistémica que pueden utilizar los ingrediente activos de la presente invención en forma líquida o sólida incluyen las vías transdérmica, intranasal, y oftálmica. En particular, pueden prepararse parches transdérmicos de acuerdo con tecnología de administración de fármacos notoria y aplicarse a la piel de un paciente a tratar, y a partir de ese momento el agente activo debido a sus características de solubilidad formulada migra a través de la epidermis a

las capas dérmicas de la piel del paciente donde se absorbe como parte de la circulación general del paciente, finalmente proporcionando una distribución sistémica del ingrediente activo durante un periodo de tiempo extenso deseado. También se incluyen los implantes que se colocan por debajo de la capa de la epidermis de la piel, es decir, entre la epidermis y la dermis de la piel del paciente tratado. Un implante así se formulará de acuerdo con principios y materiales usados bien conocidos comúnmente en esta tecnología de administración, y pueden prepararse de tal forma que proporcionen una liberación controlada, mantenida, y/o retardada del ingrediente activo a la circulación sistémica del paciente. Tales implantes subepidérmicos (subcuticulares) proporcionan la misma facilidad de instalación y eficacia de administración que los parches transdérmicos, pero sin la limitación de estar sujetos a degradación, deterioro o retirada accidental como consecuencia de estar expuesto sobre la capa superior de la piel del paciente.

En la descripción anterior de composiciones farmacéuticas que contienen un ingrediente activo de Fórmula (1.0.0), se han usado las expresiones equivalentes: "administración", "administración de", "administrando", y "administrando una" con respecto a dichas composiciones farmacéuticas. Empleadas como tal, se pretende que estas expresiones signifiquen proporcionar a un paciente que necesite tratamiento una composición farmacéutica de la presente invención mediante cualquiera de las vías de administración descritas en el presente documento, en la que el ingrediente activo es un compuesto de Fórmula (1.0.0) o un profármaco, derivado, o metabolito del mismo que es de utilidad en el tratamiento de una enfermedad, trastorno, o afección mediada o asociada a la modulación de la actividad de la PDE4, especialmente de la actividad de la PDE4D en dicho paciente. En consecuencia, se incluye en el alcance de la presente invención cualquier otro compuesto que, al ser administrado a un paciente, puede

directa o indirectamente proporcionar un compuesto de Fórmula (1.0.0). Tales compuestos se reconocen como profármacos, y hay disponibles numerosos métodos establecidos para preparar tales formas de profármacos de los compuestos de Fórmula (1.0.0).

La dosificación y la posología de los compuestos de Fórmula (1.0.0) efectivas para tratar o prevenir una enfermedad, trastorno, o afección mediada o asociada a la modulación de la actividad de la PDE4, especialmente de la PDE4D dependerá de varios factores, tales como la naturaleza del inhibidor, el tamaño del paciente, el objetivo del tratamiento, la naturaleza de la patología a tratar, la composición farmacéutica específica usada, y las observaciones y conclusiones del médico que trata.

Por ejemplo, cuando la forma de dosificación es oral, por ejemplo un comprimido o cápsula, los niveles de dosificación adecuados de los compuestos de Fórmula (1.0.0) estarán entre aproximadamente 0,1 μg/kg y aproximadamente 50,0 mg/kg de peso corporal al día, preferiblemente entre aproximadamente 5,0 μg/kg y aproximadamente 5,0 mg/kg de peso corporal al día, más preferiblemente entre aproximadamente 10,0 μg/kg y aproximadamente 1,0 mg/kg de peso corporal al día, y más preferiblemente entre aproximadamente 20,0 μg/kg y aproximadamente 0,5 mg/kg de peso corporal al día del ingrediente activo.

Cuando la forma de dosificación se administra tópicamente a los bronquios y pulmones, por ejemplo mediante un inhalador de polvo o nebulizador, los niveles de dosificación adecuados de los compuestos de Fórmula (1.0.0) estarán entre aproximadamente 0,001 μg/kg y aproximadamente 10,0 mg/kg de peso corporal al día, preferiblemente entre aproximadamente 0,5 μg/kg y aproximadamente 0,5 mg/kg de peso corporal al día, más preferiblemente entre aproximadamente 1,0 μg/kg y aproximadamente 0,1 mg/kg de peso corporal al día, y más preferiblemente entre

aproximadamente 2,0 μg/kg y aproximadamente 0,05 mg/kg de peso corporal al día del ingrediente activo.

Usando los pesos corporales representativos de 10 kg y 100 kg para ilustrar el intervalo de dosificaciones tópicas en aerosol diarias que pueden usarse como se describe anteriormente, los niveles de dosificación adecuados de los compuestos de Fórmula (1.0.0) estarán entre aproximadamente 1,0 - 10,0 μg y 500,0 - 5000,0 mg al día, preferiblemente entre aproximadamente 5,0 - 50,0 μg y 5,0 - 50, 0 mg al día, más preferiblemente entre aproximadamente 100,0 - 1000,0 μg y 10,0 - 100,0 mg al día, y más preferiblemente entre aproximadamente 200,0 - 2000,0 μg y aproximadamente 5,0 - 50,0 mg al día de ingrediente activo que comprende un compuesto de Fórmula (1.0.0). Estos intervalos de cantidades de dosificación representan las cantidades de dosificación totales del ingrediente activo al día para un paciente dado. El número de veces al día que se administra una dosis dependerá de factores farmacológicos y farmacocinéticos tales como la semivida del ingrediente activo, que refleja su velocidad de catabolismo y eliminación, así como los niveles mínimo y óptimo en plasma sanguíneo u otros fluidos corporales de dicho ingrediente activo logrados en el paciente que son necesarios para la eficacia terapéutica.

Deben considerarse otros numerosos factores para decidir el número de dosis al día y la cantidad de ingrediente activo por dosis que se administrará. No siendo el factor menos importante de esos otros factores la respuesta del paciente tratado. Así, por ejemplo, cuando el ingrediente activo se usa para tratar o prevenir el asma, y se administra por vía tópica mediante inhalación del aerosol a los pulmones, se administrarán de una a cuatro dosis que consisten en activaciones de un dispositivo de administración, es decir, "puffs" de un inhalador al día, conteniendo cada dosis de aproximadamente 50,0 μg a aproximadamente 10,0 mg de ingrediente activo.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

11.0 Preparaciones y Ejemplos de trabajo

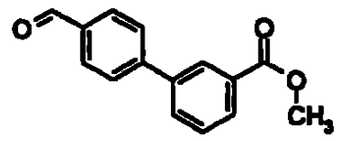
A continuación se incluye una descripción de numerosas preparaciones por las que se hacen intermedios usados para preparar compuestos específicos de Fórmula (1.0.0). También se incluyen numerosos ejemplos que muestran la preparación de compuestos específicos de Fórmula (1.0.0). Se pretende que estas Preparaciones y Ejemplos ilustren adicionalmente los compuestos y procesos de la presente invención de acuerdo con los que pueden ser preparados fácilmente por los expertos en la técnica. Los expertos en la técnica serán conscientes de muchos otros procesos adecuados que hay disponibles también, así como de variaciones aceptables en los procesos descritos a continuación.

La descripción a continuación tiene el fin de ilustrar la presente invención y no se pretende en modo alguno que cree limitaciones, expresas o implicadas, sobre el alcance de la presente invención. Las reivindicaciones anexas al presente documento tienen el fin de referir la presente invención, de expresar el alcance contemplado de la misma, y de señalar los particulares de la misma.

En las siguientes preparaciones, se hicieron caracterizaciones analíticas de los compuestos preparados mediante análisis por espectroscopia de masas determinadas por EMCG, IPMA, IQPA o termopulverización. Todos los espectros de RMN ^1H se obtuvieron con un instrumento a 400 MHz.

Preparación 1

Éster metílico del ácido 4'-formilbifenil-3-carboxílico de Fórmula (9.0.1):



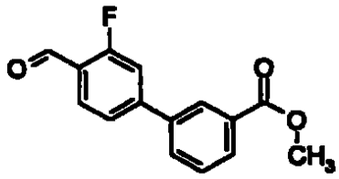
(9.0.1)

Se calentó a 80°C durante 4 horas una mezcla de 2,0 g (9,3 mmol) 3-bromobenzoato de metilo, 1,5 g (10,2 mmol) de ácido 4-formilbencenobórico y 537 mg (0,47 mmol) de tetrakis(trifenilfosfina)paladio en 14 ml (27,9 mmol) de Na_2CO_3 2 M y 15 ml de dimetoxietano. La mezcla se vertió en agua y se extrajo con acetato de etilo. Se combinaron los extractos de acetato de etilo después se lavaron sucesivamente con NaOH 1 N, HCl 1 N, agua, salmuera y después se secaron ($MgSO_4$) y concentraron a vacío para dar un aceite. La cromatografía en gel de sílice eluyendo con acetato de etilo/hexanos (1:5) dio 1,6 g de éster metílico del ácido 4'-formilbifenil-3-carboxílico en forma de aceite.

EM (m/z): 240 (M^+, 100).

Preparación 2

Éster metílico del ácido 3'-fluoro-4'-formil-bifenil-3-carboxílico de Fórmula (9.0.2):



(9.0.2)

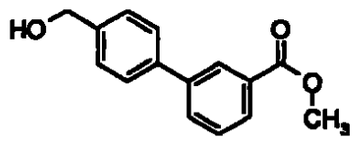
Se calentó a 80°C durante 4 horas una mezcla de 2,0 g (9,85 mmol) de 4-bromo-2-fluorobenzaldehído, 2,8 g (10,8 mmol de bis(pinacolato)diboro, 2,9 g (29,6 mmol) de

acetato potásico y 216 mg (0,3 mmol) de dicloruro de bis(difenilfosfino)ferroceno paladio en 60 ml de dimetilformamida. La mezcla se enfrió y se añadieron 4,2 g (19,7 mmol) de 3-bromobenzoato metílico y 216 mg (0,3 mmol) de dicloruro de bis(difenilfosfino)ferroceno paladio y la mezcla se calentó a 80°C durante 18 horas. La mezcla se vertió en agua y se extrajo con acetato de etilo. Se combinaron los extractos de acetato de etilo después se lavaron sucesivamente con NaOH 1 N, HCl 1 N, agua, salmuera y después se secaron ($MgSO_4$) y concentraron a vacío para dar un aceite. La cromatografía en gel de sílice eluyendo con acetato de etilo/hexanos (1:5) dio 1,4 g de éster metílico del ácido 3'-fluoro-4'-formilbifenil-3-carboxílico en forma de aceite.

EM (m/z): 258 (M^+, 100).

Preparación 3

Éster metílico del ácido 4'-hidroximetilbifenil-3-carboxílico de Fórmula (9.0.3):



(5.0.3)

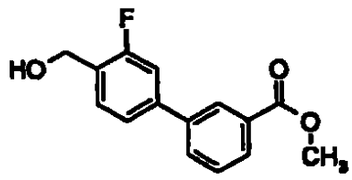
A una mezcla en agitación de 1,56 g (6,5 mmol) de éster metílico del ácido 4'-formilbifenil-3-carboxílico en 30 ml de metanol a 0°C se añadieron 307 mg (8,1 mmol) de borohidruro sódico. La mezcla se agitó a 0°C durante 1 hora, después se inactivó con solución de cloruro amónico saturado. La mezcla se vertió en agua y se extrajo con acetato de etilo. Se combinaron los extractos de acetato de etilo después se lavaron sucesivamente con agua, salmuera y después se secaron ($MgSO_4$) y concentraron a vacío para dar un aceite. La cromatografía en gel de sílice eluyendo con acetato de etilo/hexanos (1:5) dio 1,5 g de éster metílico del ácido 4'-hidroximetil-bifenil-3-

carboxílico en forma de aceite.

RMN ^{1}H ($CDCl_3$) δ 8,3 (dd, 1H, J = 2, 3 Hz), 8,0 (ddd, 1 H, J = 1, 3, 8 Hz), 7,8 (m, 1 H), 7,6 (ddd, 2 H, J = 2, 4, 8 Hz), 7,5 (m, 3 H), 4,7 (d, 2 H, J = 6 Hz), 3,9 (s, 3 H).

Preparación 4

Éster metílico del ácido 3'-fluoro-4'-hidroximetil-bifenil-3-carboxílico de Fórmula (9.0.4):

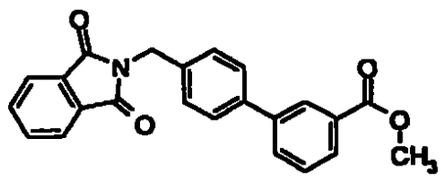


(9.0.4)

Este compuesto se preparó a partir de éster metílico del ácido 3'-fluoro-4'-formilbifenil-3-carboxílico de forma análoga a la Preparación 3.

Preparación 5

Éster metílico del ácido 4'-[1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil]-bifenil-3-carboxílico de Fórmula (9.0.5):



(9.0.5)

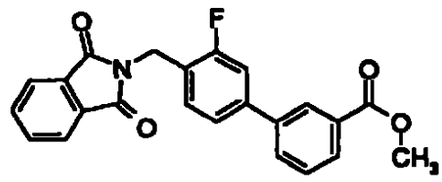
A una mezcla en agitación de 1,4 g (5,8 mmol) de éster metílico del ácido 4'-hidroximetilbifenil-3-carboxílico, 1,0 g (6,9 mmol) de ftalimida y 1,8 g (6,9 mmol) de

trifenilfosfina en 25 ml de tetrahidrofurano a 0°C se añadió 1,2 ml (7,5 mmol) de dietilazodicarboxilato. La mezcla se calentó a temperatura ambiente y se agitó durante 18 horas. La mezcla se vertió en agua y se extrajo con acetato de etilo. Se combinaron los extractos de acetato de etilo después se lavaron sucesivamente con NaOH 1 N, HCl 1 N, agua, salmuera y después se secaron ($MgSO_4$) y concentraron a vacío para dar un solido. La trituración con éter dietílico dio 3,0g. éster metílico del ácido 4'-[1,3-dioxo-1,3-dihidro-isoindol-2-ilmetil]-bifenil-3-carboxílico en forma de un sólido.

EM (m/z): 371 (M^+, 100).

Preparación 6

Éster metílico del ácido 4'-[1,3-dioxo-1,3-dihidroisoindol-2-ilmetil]-3'-fluorobifenil-3-carboxílico de Fórmula (9.0.6):



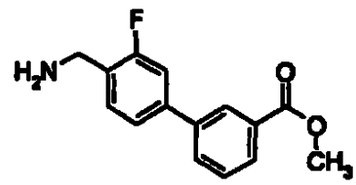
(9.0.6)

Este compuesto se preparó a partir de éster metílico del ácido 3'-fluoro-4'-hidroximetilbifenil-3-carboxílico de forma análoga a la Preparación 5.

EM (m/z): 389 (M^+, 100).

Preparación 7

Éster metílico del ácido 4'-aminometil-3'-fluorobifenil-3-carboxílico de Fórmula (9.0.7):



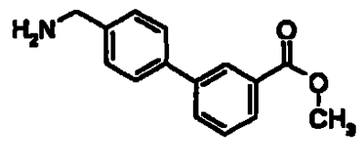
(9.0.7)

A una mezcla en agitación de 832 mg (2,14 mmol) de éster metílico del ácido 4'-[1,3-dioxo-1,3-dihidroisoindol-2-ilmetil]3'fluoro-bifenil-3-carboxílico en 20 ml de metanol y 10 ml de tetrahidrofurano a temperatura ambiente se añadieron 0,2 ml (6,42 mmol) de hidrato de hidracina. La mezcla se agitó durante 18 horas y se filtró el precipitado resultante. El volumen de filtrado se redujo a vacío y se vertió sobre HCl 0,5 N y se lavó con éter dietílico. El extracto acuoso se basificó con NaOH 6 H a pH 10 y después se extraio con acetato de etilo. Se combinaron los extractos de acetato de etilo después se lavaron sucesivamente con agua, salmuera y después se secaron ($MgSO_4$) y concentraron a vacío para dar 400 mg de de éster metílico del ácido 4'-aminometil-3'-fluorobifenil-3-carboxílico en forma de aceite.

EM (m/z): 258 (M^+, 100).

Preparación 8

Éster metílico del ácido 4'-aminometilbifenil-3-carboxílico de Fórmula (9.0.8):



(9.0.8)

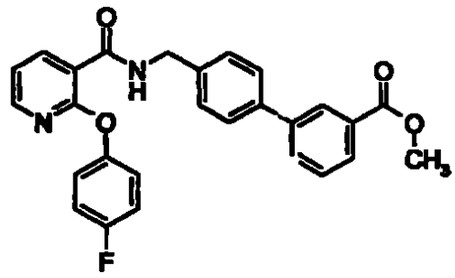
Este compuesto se preparó a partir de éster metílico del ácido 4'-[1,3-dioxo-1,3-

dihidroisoindol-2-ilmetil]bifenil-3-carboxílico de forma análoga a la Preparación 7.

EM (m/z): 241 (M^+, 60), 240(100).

Preparación 9

Éster metílico del ácido 4'-[[[2-[4-fluorofenoxi]piridin-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (9.0.9):



(9.0.9)

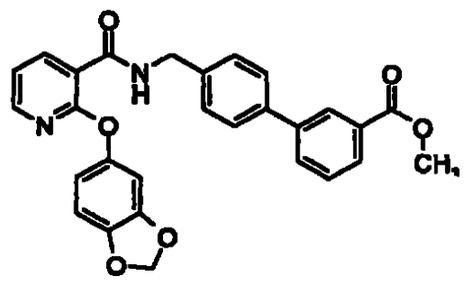
A una solución en agitación de 290 mg (1,24 mmol) de ácido 2-[4-fluorofenoxi]-nicotínico, 300 mg (1,24 mmol) de éster metílico del ácido 4'-aminometil-bifenil-3-carboxílico y 184 mg (1,36 mmol) de hidrato de 1-hidroxibenzotriazol en 10 ml de dimetilformamida a temperatura ambiente se añadieron 285 mg (1,49 mmol) de clorhidrato de 1-[3-[dimetilamino]propil]-3-etilcarbodiimida. La mezcla se agitó temperatura ambiente durante 18 horas, después se vertió en agua y se extrajo con acetato de etilo. Se combinaron los extractos de acetato de etilo después se lavaron sucesivamente con NaOH 1 N, agua, salmuera y después se secaron ($MgSO_4$) y concentraron a vacío para dar un aceite. La cromatografía en gel de sílice eluyendo con acetato de etilo/hexanos (1:1) dio 310 mg de éster metílico del ácido 4'-[[[2-[4-fluorofenoxi]piridin-3-carbonil]amino]metil]bifenil-3-carboxílico en forma de aceite.

RMN ^1H ($CDCl_3$) δ 8,6 (dd, 1H, J = 2, 8 Hz), 8,2 (m, 3 H), 8,0 (ddd, 1 H, J = 1, 3, 8 Hz), 7,7 (dd, 1 H, J = 1, 3, 8 Hz), 7,6 (dd, 2 H , J = 2, 6 Hz), 7,4 (m, 3H), 7,2 (m, 1

H), 7,1 (d, 4 H, J = 7 Hz), 3,9 (s, 3 H).

Preparación 10

Éster metílico del ácido 4'-[[[2-benzo[1,3]dioxol-5-iloxi]-piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (9.0.10):



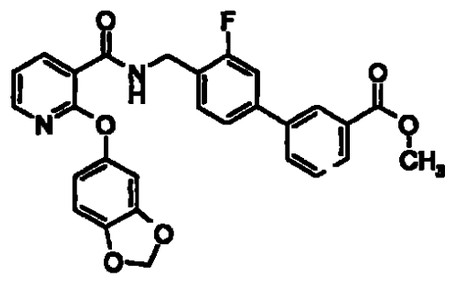
(9.0.10)

Este compuesto se preparó a partir del ácido 2-[benzo[1,3]dioxol-5-iloxi]nicotínico y el éster metílico del ácido 4'-aminometilbifenil-3-carboxílico de forma análoga a la Preparación 9.

EM (m/z): 483 (M^+, 100).

Preparación 11

Éster metílico del ácido 4'[[[2-benzo[1,3]dioxol-5-iloxi]-piridina-3-carbonil]amino]metil]3'-fluorobifenil-3-carboxílico de Fórmula (9.0.11):



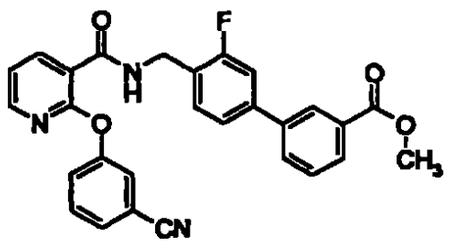
(9.0.11)

Este compuesto se preparó a partir de ácido 2-[benzo[1,3]dioxol-5-iloxi]nicotínico y éster metílico del ácido 4'-aminometil-3'-fluorobifenil-3-carboxílico de forma análoga a la Preparación 9.

EM (m/z): 501 (M^+, 100).

Preparación 12

Éster metílico del ácido 4'-[[[2-[3-cianofenoxi]-piridina-3-carbonil]amino]metil]-3'-fluorobifenil-3-carboxílico de Fórmula (9.0.12):



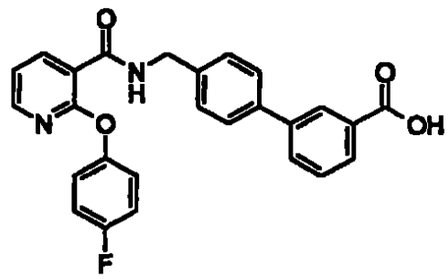
(9.0.12)

Este compuesto se preparó a partir de ácido 2-[3-cianofenoxi]nicotínico y éster metílico del ácido 4'-aminometil-3'-fluorobifenil-3-carboxílico de forma análoga a la Preparación 9.

EM (m/z): 482 (M^+, 100).

Ejemplo 1

Ácido 4'-[[[2-[4-fluorofenoxi]piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (8.5.1):



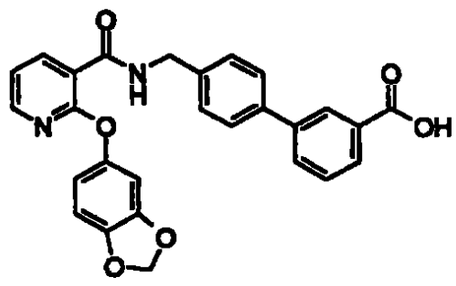
(8.5.1)

Se sometió a reflujo durante 4 horas una mezcla de 300 mg (0,66 mmol) de éster metílico del ácido 4-[[[2-[4-fluorofenoxi]piridin-3-carbonil]amino]metil]bifenil-3-carboxílico y 1,6 ml de NaOH 1,0 N en 10 ml de *t*-butanol y 3 ml de agua. La mezcla se vertió en agua, se acidificó a pH 1 con HCl 2 N, después se extrajo con acetato de etilo. Se combinaron los extractos de acetato de etilo, se lavaron sucesivamente con agua, salmuera y después se secaron ($MgSO_4$) y concentraron para dar un aceite. La cromatografía en gel de sílice eluyendo con metanol/diclorometano (1:40) dio una espuma. La recristalización de acetato de etilo/hexanos dio 151 mg de ácido 4'-[[[2-[4-fluorofenoxi]piridina-3-carbonil]amino]metil]bifenil-3-carboxílico en forma de sólido, pf 184-6°C.

Análisis calculado para $C_{26}H_{19}N_2O_4F$: C, 70,58 H, 4,33; N, 6,33. Encontrado: C, 70,06; H, 4,25; N, 6,25.

Ejemplo 2

Ácido 4'-[[[2-benzo[1,3]dioxol-5-iloxi]-piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (8.5.2):



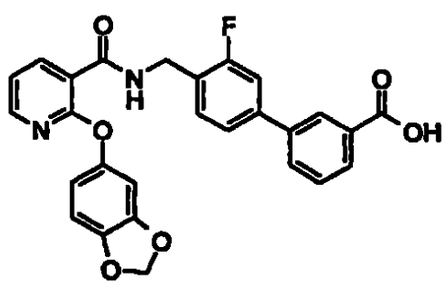
(8.5.2))

Este compuesto se preparó a partir de éster metílico del ácido 4'-[[[2-benzo[1,3]dioxol-5-iloxi]-piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de forma análoga a la del Ejemplo 1, pf 175-7°C.

Anal. calc. para $C_{27}H_{20}N_2O_6$; C, 69,23; H, 4,30; N, 5,98. Hallada: C, 69,60; H, 4,59; N, 5,99.

Ejemplo 3

Ácido 4'-[[[2-benzo[1,3]dioxol-5-iloxi]-piridina-3-carbonil]amino]metil]-3'-fluorobifenil-3-carboxílico de Fórmula (8.5.3):



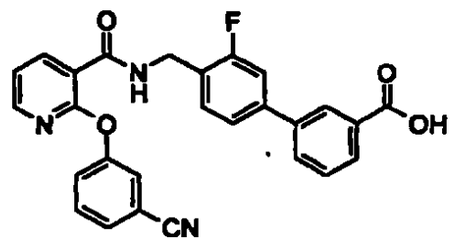
(8.5.3)

Este compuesto se preparó a partir de éster metílico del ácido 4'-[[[2-benzo[1,3]dioxol-5-iloxi]piridina-3-carbonil]amino]metil]-3'-fluorobifenil-3-carboxílico de forma análoga a la del Ejemplo 1, pf 190-2°C.

Anal. calc. para $C_{27}H_{19}N_2O_6F$: C, 66,67; H, 3,94; N, 5,76. Hallada: C, 66,68; H, 4,02; N, 5,95.

Ejemplo 4

Ácido 4'-[[[2-[3-cianofenoxi]-piridina-3-carbonil]amino]metil]-bifenil-3'-fluorobifenil-3-carboxílico de Fórmula (8.5.4):



(8.5.4)

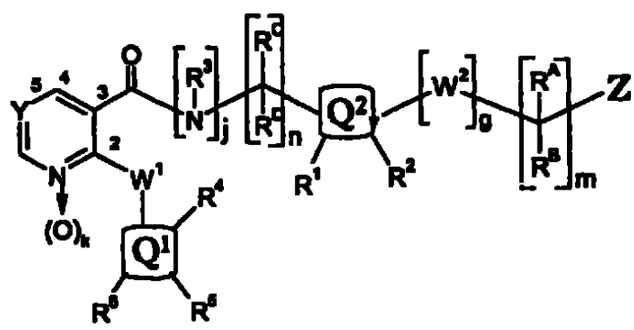
Se agitó a temperatura ambiente durante 18 horas una mezcla de 336 mg (0,7 mmol) de éster metílico del ácido 4'-[[[2-[3-cianofenoxi]piridina-3-carbonil]amino]metil]-3'-fluorobifenil-3-carboxílico y 0,8 ml (0,8 mmol) de LiOH 1,0 N en 20 ml de tetrahidrofurano y 2 ml de agua. La mezcla se vertió en agua, se acidificó a pH 1 con HCl 1 N, después se extrajo con acetato de etilo. Se combinaron los extractos de acetato de etilo, se lavaron sucesivamente con agua, salmuera y después se secaron ($MgSO_4$) y concentraron a vacío para dar un sólido. La cromatografía en gel de sílice eluyendo con metanol/diclorometano (1:20) dio un sólido. La recristalización de acetato de etilo/hexano dio 280 mg de ácido 4'-[[[2-[3-cianofenoxi]-piridina-3-carbonil]amino]metil]-3'-fluorobifenil-3-carboxílico en forma de sólido, pf 200-2°C.

Anal. calc. para $C_{27}H_{18}N_3O_4F$; C, 69,38; H, 3,88; N, 8,99. Hallada: C, 68,44; H, 3,97; N, 8,91.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de Fórmula (1.0.0):



(1.0.0)

en el que

- g es 0 ó 1;
- 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 0, 1, ó 2;
- n es 1 ó 2;
- W^1 es -O-; o $-S(=O)_t-$, donde t es 0, 1, ó 2; o $-N(R^3)-$ donde R^3 tiene el mismo significado que se define más adelante:
- W^2 es -O-; $-S(=O)_t-$, donde t es 0, 1, ó 2; $-N(R^3)-$ donde R^3 tiene el mismo significado que se define más adelante, o $-CR^{29}R^{30}-$;

donde

- $-R^{29}$ y R^{30} son cada uno un miembro seleccionado independientemente del grupo

constituido por -H; -F; -CF_3; -alquilo C_1-C_3; -cicloalquilo C_3-C_6; fenilo; bencilo; y piridilo; en el que dichos restos alquilo, cicloalquilo, fenilo, bencilo y piridilo están cada uno sustituidos independientemente con 0 a 3 sustituyentes R^{10}, donde R^{10} tiene el mismo significado que se define más adelante;

- Y es $=C(R^1_a)-$, donde R^1_a tiene el mismo significado que se define más adelante; o $-[N \rightarrow (O)_k]-$ donde k es 0 ó 1;

donde

- R^1_a es un miembro seleccionado del grupo constituido por -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}; y $-C(=O)NR^{22}_aR^{22}_b$;

donde

-R^{22}_a y R^{22}_b son cada uno 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;

- R^A y R^B son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -F; -CF_3; alquilo C_1-C_4; cicloalquilo C_3-C_7; fenilo; y bencilo; en el que dichos restos cicloalquilo, fenilo, y bencilo están cada uno sustituido independientemente con 0 a 3 sustituyentes R^{10};

donde

- R^{10} es un miembro seleccionado del grupo constituido por fenilo; piridilo; -F; -Cl; CF_3; oxo (=O); $-OR_{16}$; -NO_2; -CN; $-C(=O)OR^{16}$; $-O-C(=O)R^{16}$; $-C(=O)NR^{16}R^{17}$; $-O-C(=O)NR^{16}R^{17}$; $-NR^{16}R^{17}$; $-NR^{16}C(=O)R^{17}$; $-NR^{16}C(=O)OR^{17}$; $-NR^{16}S(=O)_2R^{17}$; y $-S(=O)_2NR^{16}R^{17}$; donde dicho fenilo o piridilo está sustituido con 0 a 3 R^{11};

donde

- R^{11} es -F; -Cl; -CF_3; -CN; -NO_2; -OH; -alcoxi C_1-C_3; alquilo C_1-C_3; o -

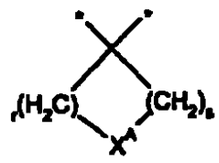
$NR^{16}R^{17}$;

y

$-R^{16}$ y R^{17} son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -alquilo C_1-C_4; -alquenilo C_2-C_4; -cicloalquilo C_3-C_6; fenilo; bencilo; y piridilo; en el que dicho alquilo, alquenilo, cicloalquilo, fenilo, bencilo, o piridilo está sustituido por 0 a 3 sustituyentes seleccionados del grupo constituido por -F, -Cl, $-CF_3$, -CN, y -alquilo C_1-C_3;

o

- R^A y R^B se toman conjuntamente, pero únicamente en el caso en que m es 1, para formar un resto espiro de Fórmula (1.2.0):



(1.2.0)

donde

r y s son independientemente 0 a 4 siempre que la suma de r + s sea al menos 1 pero no mayor que 5;

y

X^A se selecciona de $-CH_2$-, $-CH(R^{11})$-, o $C(R^{11})_2$-, donde cada R^{11} se selecciona independientemente de los demás y cada uno tiene el mismo significado que se define anteriormente; $-NR^{15}$-, donde R^{15} tiene el mismo significado que se define más adelante; -O-; y $-S(=O)_t$-, donde t es 0, 1, ó 2;

y

dicho resto espiro de Fórmula parcial (1.2.0) está sustituido en lo que se refiere a uno cualquiera o más de sus átomos de carbono, excepto el que define a X^A, con 0 a 3

sustituyentes R^{14}, donde R^{14} tiene el mismo significado que se define más adelante; en lo que se refiere a un átomo de nitrógeno del mismo con 0 ó 1 sustituyente R^{15}, donde R^{15} tiene el mismo significado que se define más adelante; y en lo que se refiere a un átomo de azufre del mismo con 0 o 2 átomos de oxígeno;

- R^C y R^D tienen el mismo significado definido anteriormente para R^A y R^B pero uno de ellos debe ser -H, y se seleccionan independientemente el uno del otro y de R^A y R^B;

- R^1 y R^2 pueden aparecer de forma individual o juntos en cualquier anillo o anillos que comprenden un significado del resto Q^2 como se define más adelante; y R^1 y R^2 son cada uno un miembro seleccionado independientemente del grupo constituido por -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 $-C(=O)NR^{22}{}_aR^{22}{}_b$; donde R^{16}, $R^{22}{}_a$, y $R^{22}{}_b$ tienen los mismos significados que se definen anteriormente;

- R^3 es -H; -alquilo C_1-C_3; fenilo; bencilo; o $-OR^{16}$, donde R^{16} tiene el mismo significado definido anteriormente;

- R^4, R^5 y R^6 pueden aparecer individualmente o juntos en cualquier anillo o anillos que comprenden un significado del resto Q^1 como se define más adelante; y R^4, R^5 y R^6 son cada uno un miembro seleccionado independientemente del grupo constituido por

los siguientes:

- *(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; $-NO_2$; $-C(=O)NR^{16}R^{17}$; $-OC(=O)NR^{16}R^{17}$; $-NR^{22}{}_aC(=O)NR^{16}R^{17}$; $-NR^{22}{}_aC(=NR^{12})NR^{16}R^{17}$; $-NR^{22}{}_aC(=NCN)NR^{16}R^{17}$; $-NR^{22}{}_aC(=N-NO_2)NR^{16}R^{17}$; $-C(=NR^{22}{}_a)NR^{16}R^{17}$; $-CH_2C(=NR^{22}{}_a)NR^{16}R^{17}$; $-OC(=NR^{22}{}_a)NR^{16}R^{17}$; $-OC(=N-NO_2)NR^{16}R^{17}$; $-NR^{16}R^{17}$; $-CH_2NR^{16}R^{17}$; $-NR^{22}{}_aC(=O)R^{16}$; $-NR^{22}{}_aC(=O)OR^{16}$;

$=NOR^{16}$; $-NR^{22}{}_aS(=O)_pR^{17}$; $-S(=O)_pNR^{16}R^{17}$; y $-CH_2C(=NR^{22})NR^{16}R^{17}$;

donde

- p es 0, 1, ó 2; y $R^{22}{}_a$, R^{16}, y R^{17} tienen los mismos significados definidos anteriormente;

- *(b)* -alquilo C_1-C_4; y alcoxi C_1-C_4 en el caso en que uno o más de R^4, R^5, o R^6 tiene el significado de $-OR^{16}$ en *(a)* anteriormente y R^{16} se define como -alquilo C_1-C_4; donde dicho alquilo y -alcoxi se sustituyen cada uno independientemente con 0 a 3 sustituyentes -F o -Cl; o 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 del grupo constituido por 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-dihidrobenzofuranilo; 2-*H*-cromenilo; cromanilo; benzotienilo; 1-*H*-indazolilo; bencimidazolilo; benzoxazolilo; benzoisoxazolilo; benzotiazolilo; quinolinilo; isoquinolinilo; ftalazinilo; quinazolinilo; quinoxalinilo; y purinilo; donde dichos restos arilo y heterociclilo están cada uno sustituido independientemente con 0 a 2 sustituyentes R^{14}.

donde

-- R^{14} es un miembro seleccionado del grupo constituido por -alquilo C_1-C_4; -cicloalquilo C_3-C_7; fenilo; bencilo; piridilo; y quinolinilo; donde 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, o -$NR^{16}R^{17}$; y dicho grupo R^{14} está constituido adicionalmente por -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-$C(=O)NR^{16}R^{17}$; -$NR^{16}R^{17}$; -$NR^{16}C(=O)R^{17}$; -$NR^{16}C(=O)OR^{17}$; -$NR^{16}S(=O)_2R^{17}$; o -$S(=O)_2NR^{16}R^{17}$; donde R^{16} y R^{17} tienen los mismos significados definidos anteriormente;

y además donde

—R^{15} es un miembro seleccionado independientemente del grupo constituido por -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 donde u es 0, 1, ó 2; fenilo; bencilo; piridilo; y quinolinilo; donde dicho alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, bencilo, piridilo o quinolinilo está sustituido con 0 a 3 sustituyentes R^{12}; donde R^{16} y R^{17} tienen los mismos significados definidos anteriormente; y

donde

——R^{12} es un miembro seleccionado independientemente del grupo constituido por -F; -Cl; -CO_2R^{18}; -OR^{16}; -CN; -$C(=O)NR^{18}R^{19}$; -$NR^{18}R^{19}$; -$NR^{18}C(=O)R^{19}$; -$NR^{18}C(=O)OR^{19}$; -$NR^{18}S(=O)_pR^{19}$; -$S(=O)_pNR^{18}R^{19}$, donde p es 1 ó 2; -alquilo C_1-C_4; y -alcoxi C_1-C_4 en el caso en que R^{12} tiene el significado de -OR^{16} anterior y R^{16} se define como -alquilo C_1-C_4; donde dicho alquilo y alcoxi están cada uno independientemente sustituidos con 0 a 3 sustituyentes seleccionados independientemente de -F; -Cl; -alcoxi (C_1-C_2)carbonilo; -alquil (C_1-C_2)carbonilo; y alquil (C_1-C_2)carboniloxi; donde R^{16} tiene el mismo significado definido anteriormente; y

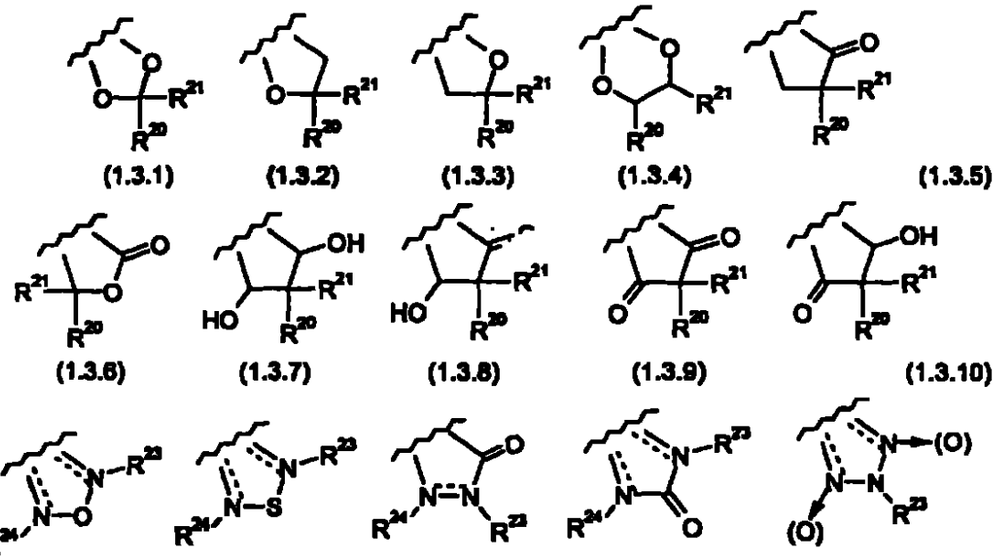
donde

------R^{18} y R^{19} se seleccionan independientemente del grupo constituido por -H; -

alquilo C_1-C_4; y fenilo; donde dicho alquilo o fenilo está sustituido por 0-3 de -F; o -Cl;

o en el caso en que Q^1 es fenilo

- *(d)* R^5 y R^6 se toman conjuntamente para formar un resto que es un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.3.1) a (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 los que

– R^{20} y R^{21} son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -F; -Cl; $-CH_3$; $-CH_2F$; $-CHF_2$; $-CF_3$; $-OCH_3$; y $-OCF_3$;

– R^{23} y R^{24} son cada uno 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 discontinua ---- representa un enlace doble;

- Q^1 es un resto que comprende un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3 a 7 miembros, o que es un policiclo condensado de 7 a 12 miembros; siempre que Q^1 no sea un resto biarilo discontinuo o restringido

como se define en Q^2 más adelante; y en el que opcionalmente un átomo de carbono de dicho sistema de anillos de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo pueden reemplazarse por N;

en el que

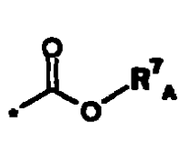
dicho resto que define Q^1 está sustituido en cualquier anillo o anillos del mismo con R^4, R^5, R^6, que tienen los mismos significados definidos anteriormente;

- Q^2 es un resto biarilo discontinuo o restringido que consiste en un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3- a 7- miembros, o que es un policiclo condensado de 7 a 12 miembros; en el que opcionalmente un átomo de carbono de dicho sistema de anillos de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo pueden reemplazarse por N;

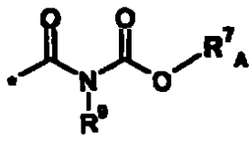
- **Z** es un miembro seleccionado independientemente del grupo constituido por

los siguientes

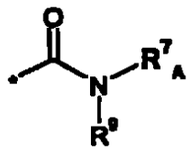
-*(a)* el grupo constituido por las Fórmulas parciales (1.1.1) a (1.1.15):



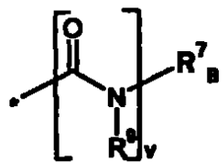
(1.1.1)



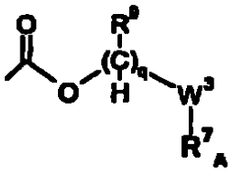
(1.1.2)



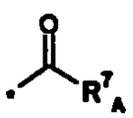
(1.1.3)



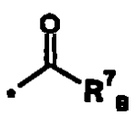
(1.1.4)



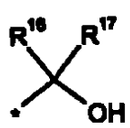
(1.1.5)



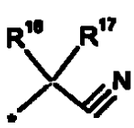
(1.1.6)



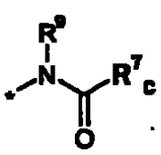
(1.1.7)



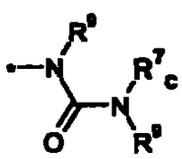
(1.1.8)



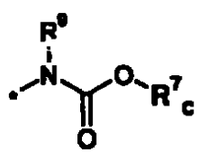
(1.1.9)



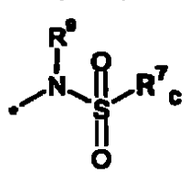
(1.1.10)



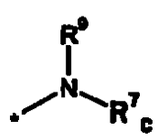
(1.1.11)



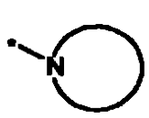
(1.1.12)



(1.1.13)



(1.1.14)



(1.1.15)

en las que

donde R^{16} y R^{17} tienen los mismos significados definidos anteriormente; y R^9 tiene el mismo significado definido más adelante;

-- "*" indica el punto de unión de cada Fórmula parcial (1.1.1) a (1.1.15) a la porción restante de la Fórmula (1.0.0);

– q es 1, 2, ó 3, siempre que cuando q sea 2 ó 3, R^9 tiene el significado de -H al menos en un caso, o en dos casos, respectivamente;

-- v 0 ó 1;

-- W^3 es -O-; -N(R^9)-, donde R^9 tiene el mismo significado definido más adelante; o -OC(=O)-;

- R^7_A es un miembro seleccionado independientemente del grupo constituido por los siguientes:

– *(1)* -H;

– *(2)* -alquilo C_1-C_6; -alquenilo C_2-C_6; o -alquinilo C_2-C_6; donde dicho alquilo, alquenilo o alquinilo está sustituido con 0 a 3 sustituyentes R^{10}, donde R^{10} tiene el mismo significado definido anteriormente;

– *(3)* -$(CH_2)_u$-cicloalquilo C_3-C_7 donde u es 0, 1, ó 2; y adicionalmente donde dicho cicloalquilo C_3-C_7 está sustituido con 0 a 3 sustituyentes R^{10} donde R^{10} tiene el mismo significado definido anteriormente;

y

– *(4)* fenilo o bencilo, donde dicho fenilo o bencilo está sustituido independientemente con 0 a 3 sustituyentes R^{10} donde R^{10} tiene el mismo significado definido anteriormente;

– R^7_B es un miembro seleccionado independientemente del grupo constituido por

los siguientes:

– *(1)* 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; pirrolidonilo; 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; 1*H*-indazolilo; bencimidazolilo; benzoxazolilo; benzosoxazolilo; 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;

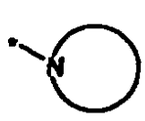
donde

cualquier resto referido en *(1)* o *(2)* anteriormente está opcionalmente sustituido con respecto a *(i)* cualesquiera uno o más átomos de carbono del mismo opcionalmente con un sustituyente R^{14} donde R^{14} tiene el mismo significado definido anteriormente; *(ii)* cualesquiera uno o más átomos de nitrógeno del mismo que no es un punto de unión de dicho resto, opcionalmente con un sustituyente R^{15} donde R^{15} tiene el mismo significado definido anteriormente, y todas las formas tautómeras del mismo; y *(iii)* cualquier átomo de azufre del mismo que no es un punto de unión de dicho resto, con 0, 1, ó 2 átomos de oxígeno;

-- R^9 es un miembro seleccionado del grupo constituido por -H; -alquilo C_1-C_4; -cicloalquilo C_3-C_7; fenilo; bencilo; piridilo; -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}; donde R^{16} tiene el mismo significado definido anteriormente;

– $R^7{}_C$ es un miembro seleccionado independientemente del grupo constituido por los significados de $R^7{}_A$ y los significados de $R^7{}_B$ definidos anteriormente;

y adicionalmente en el que



(1.1.15)

-- comprende un sistema de anillos carbocíclico saturado o insaturado monocíclico de 4 a 8 miembros, o bicíclico condensado o abierto, de 5 a 10 miembros que contiene un heteroátomo de nitrógeno como se muestra en la Fórmula parcial (1.1.15); en el que opcionalmente de 1 a 3 átomos de carbono de dicho sistema de anillos carbocíclico puede ser reemplazado individualmente por un heteroátomo de nitrógeno; u opcionalmente 1 átomo de carbono del mismo puede ser reemplazado por un heteroátomo de oxígeno o por un heteroátomo de azufre; u opcionalmente 2 átomos de carbono del mismo pueden ser reemplazados individualmente por un heteroátomo de nitrógeno y un heteroátomo de oxígeno, o por un heteroátomo de nitrógeno y un heteroátomo de azufre;

donde

cualquier resto de Fórmula parcial (1.1.15) mencionado anteriormente está opcionalmente sustituido con respecto a *(1)* cualesquiera uno o más átomos de carbono del mismo, con un sustituyente R^{14} donde R^{14} tiene el mismo significado definido anteriormente; *(2)* cualesquiera uno o más átomos de nitrógeno del mismo, con un sustituyente R^{15} donde R^{15} tiene el mismo significado definido anteriormente, y todas las formas tautómeras, y opcionalmente las formas de N-óxido del mismo; o *(3)* cualquier átomo de azufre del mismo con 0, 1, ó 2 átomos de oxígeno;

y **Z** se selecciona adicionalmente de

- *(b)* un resto que comprende un miembro seleccionado del grupo constituido por -O-P(=O)$(OH)_2$ (fosfórico); -PH(=O)OH (fosfínico); -P(=O)$(OH)_2$ (fosfónico); -[P(=O)(OH)-O-alquilo (C_1-C_4)] (alquilfosfono); -P(=O)(OH)-O-alquilo (C_1-C_4) (alquilfosfinilo); -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)$_2NHR^{26}$ o -NHS(=O)$_2R^{26}$ (sulfonamido) donde R^{26} es $-CH_3$, $-CF_3$, u

o-tolilo; y acilsulfonamido seleccionado del grupo consituido por -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)NHalquilo 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};

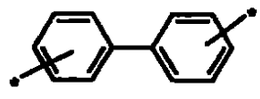
donde

– R^{25} es -H; -alquilo C$_1$-C$_4$; fenilo; u -OR^{18}, donde R^{18} tiene el mismo significado definido anteriormente;

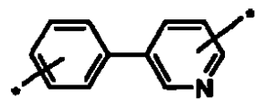
o

una sal farmacéuticamente aceptable del mismo.

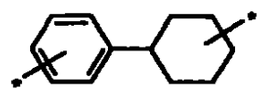
2. Un compuesto de acuerdo con la reivindicación 1 en el que el grupo Q^2 comprende un miembro seleccionado del grupo constituido por los siguientes restos representados por las Fórmulas parciales (1.2.1) a (1.2.32):



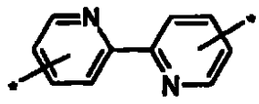
(1.2.1)



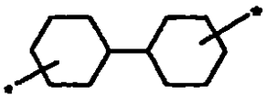
(1.2.2)



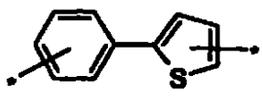
(1.2.3)



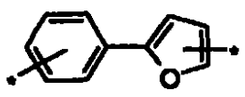
(1.2.4)



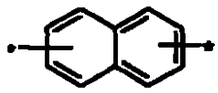
(1.2.5)



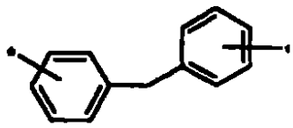
(1.2.6)



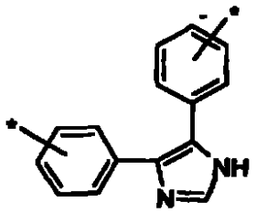
(1.2.7)



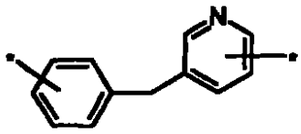
(1.2.8)



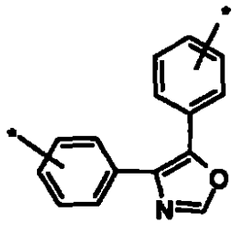
(1.2.9)



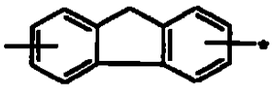
(1.2.10)



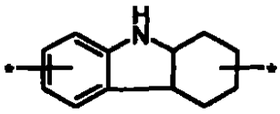
(1.2.11)



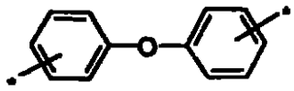
(1.2.12)



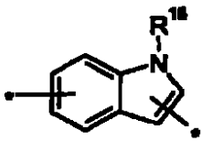
(1.2.13)



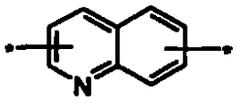
(1.2.14)



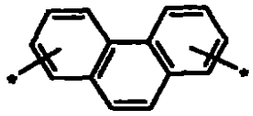
(1.2.15)



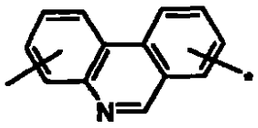
(1.2.16)



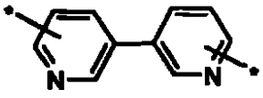
(1.2.17)



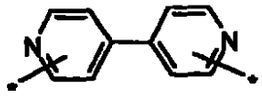
(1.2.18)



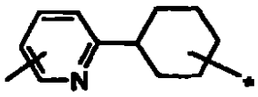
(1.2.19)



(1.2.20)



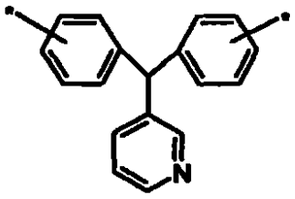
(1.2.21)



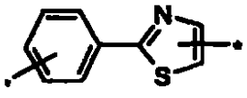
(1.2.22)



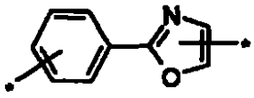
(1.2.23)



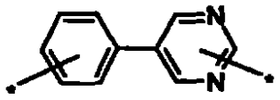
(1.2.24)



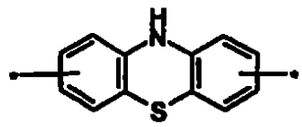
(1.2.25)



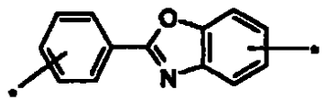
(1.2.26)



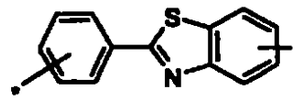
(1.2.27)



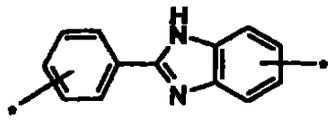
(1.2.28)



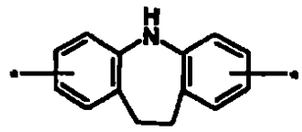
(1.2.29)



(1.2.30)



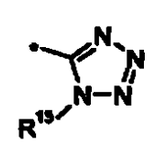
(1.2.31)



(1.2.32)

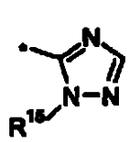
donde "*" es un símbolo que indica los dos puntos de unión de dicho grupo Q^2 a los componentes restantes de la Fórmula (1.0.0).

3. Un compuesto de acuerdo con la reivindicación 1 en el que Z comprende las Fórmulas parciales (1.1.4) y (1.1.10) a (1.1.14), y el significado de R^7_B de Fórmula parcial (1.1.4) donde v es 0 ó 1, o el significado de R^7_C de Fórmulas parciales (1.1.10) a (1.1.14) se define como un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.4.1) a (1.4.28):



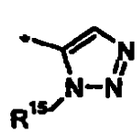
tetrazol-5-ilo

(1.4.1)



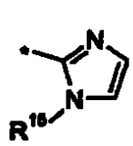
1,2,4-triazol-3-ilo

(1.4.2)



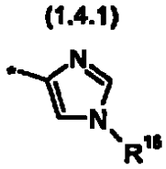
1,2,3-triazol-5-ilo

(1.4.3)



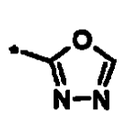
imidazol-2-ilo

(1.4.4)



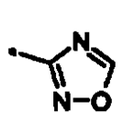
imidazol-4-ilo

(1.4.5)



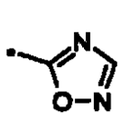
1,3,4-oxadiazolilo

(1.4.6)



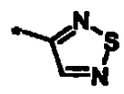
1,2,4-oxadiazol-3-ilo

(1.4.7)



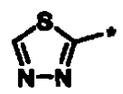
1,2,4-oxadiazol-5-ilo

(1.4.8)



1,2,5-tiadiazol-2-ilo

(1.4.9)



1,3,4-tiadiazolilo

(1.4.10)



oxazolilo

(1.4.11)



isoxazolilo

(1.4.12)



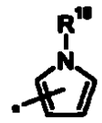
tiazolilo

(1.4.13)



isotiazolilo

(1.4.14)



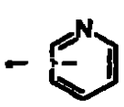
pirrolilo

(1.4.15)



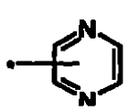
pirazolilo

(1.4.16)



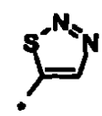
piridilo

(1.4.17)



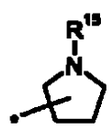
pirazinilo

(1.4.18)



1,2,3-tiadiazol-5-ilo

(1.4.19)



pirrolidinilo

(1.4.20)



furanilo

(1.4.21)



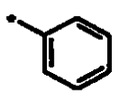
tetrahidrofuranilo

(1.4.22)



tienilo

(1.4.23)



fenilo

(1.4.24)



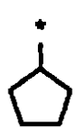
ciclopropilo

(1.4.25)



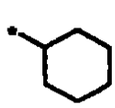
ciclobutilo

(1.4.26)



ciclopentilo

(1.4.27)



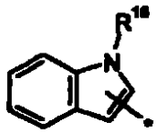
ciclohexilo

(1.4.28)

donde "*" indica el punto de unión a la porción restante de la Fórmula (1.0.0); y donde cada átomo de carbono está sustituido opcionalmente con un sustituyente R^{14}; y donde R^{14} y R^{15} tienen el mismo significado definido en la reivindicación 1; y todas las formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

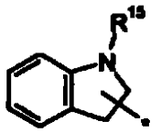
4. Un compuesto de acuerdo con la reivindicación 1 en el que Z comprende las Fórmulas parciales (1.1.4) y (1.1.10) a (1.1.14), y los preferidos de R^7_B y R^7_C en dichas Fórmulas parciales son cada uno independientemente un miembro seleccionado del

grupo constituido por las Fórmulas parciales (1.5.1) a (1.5.29):



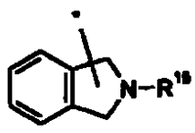
indolilo

(1.5.1)



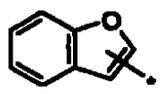
indolinilo

(1.5.2)



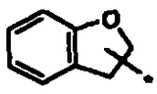
isoindolinilo

(1.5.3)



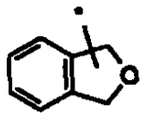
benzo[*b*]furanilo

(1.5.4)



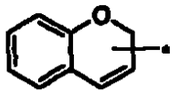
2,3-dihidrobenzo-furanilo

(1.5.5)



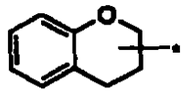
1,3-dihidroisobenzo-furanilo; ftalanilo

(1.5.6)



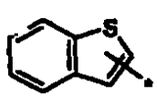
2*H*-1-benzopiranilo

(1.5.7)



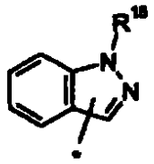
cromanilo

(1.5.8)



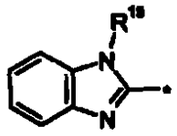
benzotienilo

(1.5.9)



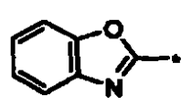
1*H*-indazolilo

(1.5.10)



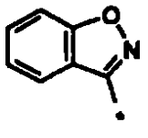
bencimidazolilo

(1.5.11)



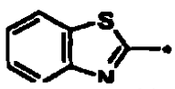
benzoxazolilo

(1.5.12)



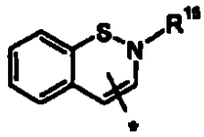
bencisoxazolilo

(1.5.13)



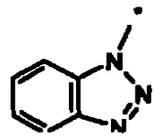
benzotiazolilo

(1.5.14)



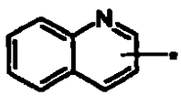
2*H*-1,2-benzotiazinilo

(1.5.15)



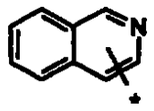
benzotriazolilo

(1.5.16)



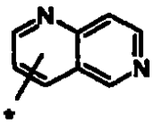
quinolinilo

(1.5.17)



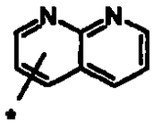
isoquinolinilo

(1.5.18)



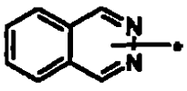
1,6-naftiridinilo

(1.5.19)



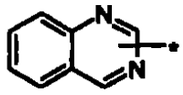
1,8-naftiridinilo

(1.5.20)



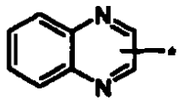
ftalazinilo

(1.5.21)



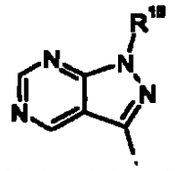
quinazolinilo

(1.5.22)



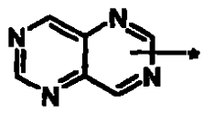
quinoxalinilo

(1.5.23)



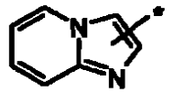
1*H*-pirazolo[3,4-*d*]-pirimidinilo

(1.5.24)



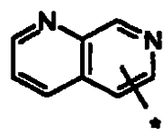
pirimido [5,4-*d*]-pirimidinilo

(1.5.25)



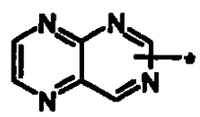
imidazo- [1,2-*a*]-piridinilo

(1.5.26)



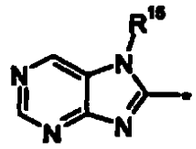
1,7-naftiridinilo

(1.5.27)



pteridinilo

(1.5.28)

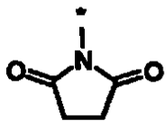


1*H*-purinilo

(1.5.29)

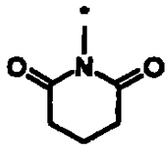
donde "*" indica el punto de unión a la porción restante de la Fórmula (1.0.0); y donde cada átomo de carbono está sustituido opcionalmente con un sustituyente R^{14}; y donde R^{14} y R^{15} tienen el mismo significado definido en la reivindicación 1, y todas las formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

5. Un compuesto de acuerdo con la reivindicación 1 en el que Z comprende un miembro seleccionado del grupo constituido por las Fórmulas parciales (1.7.1) a (1.7.46):



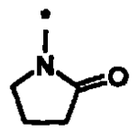
succinimid-1-ilo

(1.7.1)



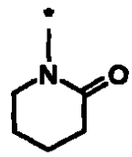
glutarimid-1-ilo

(1.7.2)



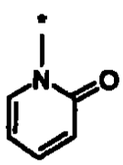
pirrolidin-2-on-1-ilo

(1.7.3)



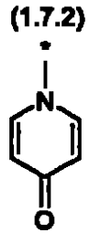
piperid-2-on-1-ilo

(1.7.4)



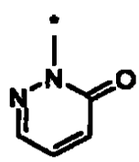
pirid-2-on-1-ilo

(1.7.5)



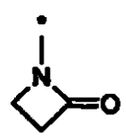
pirid-4-on-1-ilo

(1.7.6)



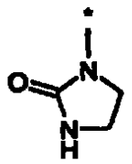
piridazin-3-on-2-ilo

(1.7.7)



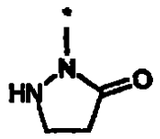
azetidin-2-on-1-ilo

(1.7.8)



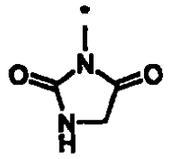
imidazolidin-2-on-1-ilo

(1.7.9)



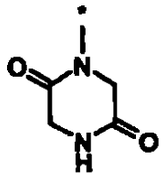
pirazol-5-on-1-ilo

(1.7.10)



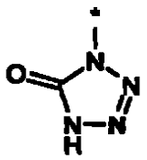
imidazolidin-2,4-dion-1-ilo

(1.7.11)



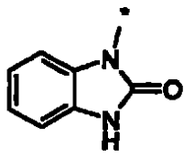
piperazin-2,5-dion-1-ilo

(1.7.12)



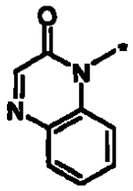
4,5-dihidro-5-oxo 1*H*-tetrazol-1-ilo

(1.7.13)



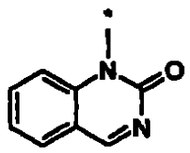
bencimidazolin-2-on-1-ilo

(1.7.14)



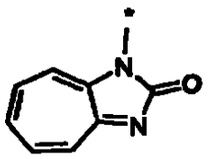
1*H*-quinoxalin-2-on-1-ilo

(1.7.15)



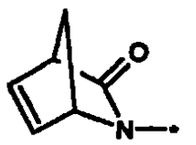
1*H*-quinazolin-2-on-1-ilo

(1.7.16)



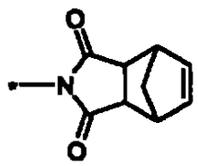
1*H*-cicloheptimidazol-2-on-1-ilo

(1.7.17)



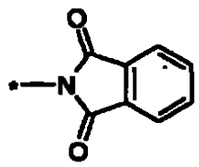
2-azabiciclo[2.2.1]-hept-5-en-3-on-1-ilo

(1.7.18)



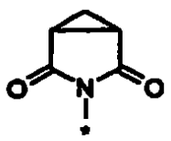
norborn-5-en-2,3-dicarboximid-1-ilo

(1.7.19)



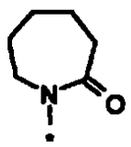
ftalimid-1-ilo; 1*H*-isoindol-1,3(2*H*)-dion-1-ilo

(1.7.20)



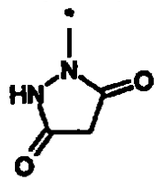
3-azabiciclo[3.1.0]-hexano-2,4-dion-3-ilo

(1.7.21)



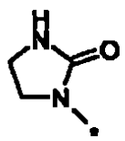
2*H*-azepin- 2-on-1-ilo

(1.7.22)



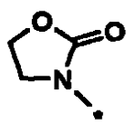
pirazolidin-3,5-dion-1-ilo

(1.7.23)



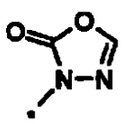
imidazolidin-2-on-1-ilo

(1.7.24)



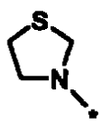
oxazolidin- 2-on-1-ilo

(1.7.25)



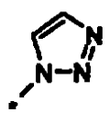
1,3,4-oxadiazol-2(3*H*)-on-3-ilo

(1.7.26)



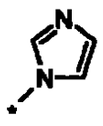
tiazolidin-3-ilo

(1.7.27)



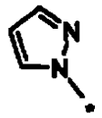
1*H*-1,2,3-triazol-1-ilo

(1.7.28)



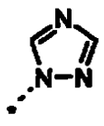
imidazol-1-ilo

(1.7.29)



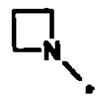
pirazol-1-ilo

(1.7.30)



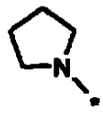
1*H*-1,2,4-triazol-1-ilo

(1.7.31)



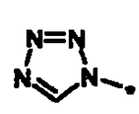
azetidin-1-ilo

(1.7.32)



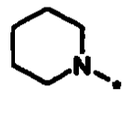
pirrolidin-1-ilo

(1.7.33)



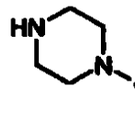
tetrazol -1-ilo

(1.7.34)



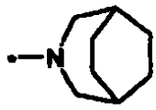
piperidin-1-ilo

(1.7.35)



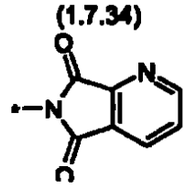
piperazin-1-ilo

(1.7.36)



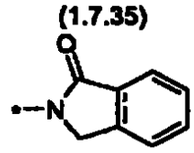
3-azabiciclo[3.2.2]-non-3-ilo

(1.7.37)



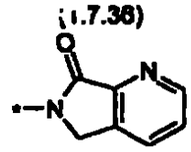
pirrolo[3,4-*b*]piridin-5,7-dion-6-ilo

(1.7.38)



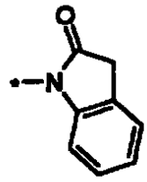
2,3-dihidro-*1,3*-indol-1-on-2-ilo

(1.7.39)



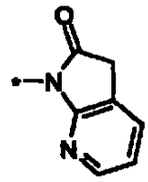
pirrolo[3,4-*b*]piridin-7-on-6-ilo

(1.7.40)



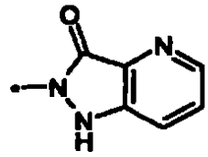
1,3-dihidro-indol-2-on-1-ilo

(1.7.41)



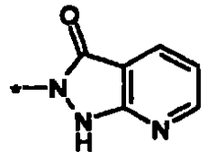
pirrolo[4,5-*b*]piridin-3-on-2-ilo

(1.7.42)



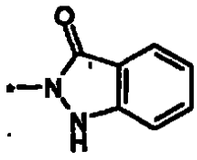
1*H*-pirazolo[4,5-*e*]piridin-7-on-2-ilo

(1.7.43)



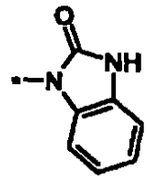
1*H*-pirazolo[4,5-*b*]piridin-4-on-2-ilo

(1.7.44)



1*H*-indazol-3-on-2-ilo

(1.7.45)



1*H*-bencimidazol-2-on-3-ilo

(1.7.46)

donde "*" indica el punto de unión a la porción restante de la Fórmula (1.0.0); y donde cada átomo de carbono está sustituido opcionalmente con un sustituyente R^{14}; y

donde cada átomo de nitrógeno está sustituido opcionalmente con un sustituyente R^{15}; donde R^{14} y R^{15} tienen el mismo significado definido en la reivindicación 1; y todas las formas tautómeras, y opcionalmente formas de N-óxido de las mismas.

6. Un compuesto de acuerdo con la reivindicación 1 en el que dicho compuesto es un miembro seleccionado del grupo constituido por los siguientes:

Ácido 4'-[[[2-[4-fluorofenoxil]piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (8.5.1);

Ácido 4'-[[[2-benzo[1,3]dioxol-5-iloxi]piridina-3-carbonil]amino]metil]bifenil-3-carboxílico de Fórmula (8.5.2);

Ácido 4'-[[[2-benzo[1,3]dioxol-5-iloxi]piridina-3-carbonil]amino]metil]-3'-fluorobifenil-3-carboxílico de Fórmula (8.5.3);

Ácido 4'-[[[2-[3-cianofenoxi]piridina-3-carbonil]amino]metil]bifenil-3'-fluorobifenil-3-carboxílico de Fórmula (8.5.4);

Ácido [4'-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]acético de Fórmula (8.5.5);

Ácido [4'-({[2-(benzo[2,1,3]oxadiazol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]acético de Fórmula (8.5.6);

Ácido [4'-({[2-(benzo[1,3]dioxol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]acético de Fórmula (8.5.7);

Ácido (±)-2-[4'-({[2-(benzo[1,3]dioxol-5-iloxi]piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-iloxi]propiónico de Fórmula (8.5.8);

(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-(2'-fluoro-4'-[1-(1H-tetrazol-5-il)etoxi]bifenil-4-ilmetil)nicotinamida de Fórmula (8.5.9);

Ácido (±)-2-[4'-({[2-(benzo[1,3]dioxol-5-iloxi]piridina-3-

carbonil]amino}metil)-3'-fluorobifenil-2-iloxi]propiónico de Fórmula (8.5.10);

(±)-2-(Benzo[1,3]dioxol-5-iloxi)-N-(2'-fluoro-4'-[1-(5-metil-4H-[1,2,4]triazol-3-il)-etoxi]-bifenil-4-ilmetil)nicotinamida de Fórmula (8.5.11);

(±)-N-[4'-(1-Carbamoiletoxi)-2'-fluorobifenil-4-ilmetil]-2-(3-cianofenoxi)nicotinamida de Fórmula (8.5.12);

Ácido (±)-2-[2,3'-difluoro-4'-({[2-(3-metoxifenoxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]propiónico de Fórmula (8.5.13);

2-(Benzo[1,3]dioxol-5-iloxi)-N-(4'-carbamoilmetil-3-fluorobifenil-4-ilmetil)nicotinamida de Fórmula (8.5.14);

Ácido [4'-({[2-(3-cianofenoxi)-3-carbonil]amino}metil)-3'-fluorobifenil-4-il]acético de Fórmula (8.5.15);

2-(Benzo[1,3]dioxol-5-iloxi)-N-(4'-[(2-cianobenzoilamino)metil]-2'-fluorobifenil-4-ilmetil)-5-fluoronicotinamida de Fórmula (8.5.16);

Ácido piridin-2-carboxílico (3'-fluoro-4'-{[2-(4-fluorofenoxi)nicotinamida]metil}bifenil-4-ilmetil)amida de Fórmula (8.5.17);

2-(Benzo[1,3]dioxol-5-iloxi)-N-{2'-fluoro-4'-[1-metil-1-(1H-tetrazol-5-il)etil]bifenil-4-ilmetil}nicotinamida de Fórmula (8.5.18);

5-Fluoro-N-(3-fluoro-4'-{[(5-metil-4H-[1,2,4]triazol-3-carbonil)amino]metil}bifenil-4-ilmetil)-2-(3-metoxifenoxi)nicotinamida de Fórmula (8.5.19);

2-(Benzo[1,3]dioxol-5-iloxi)-N-{2'-fluoro-4'-[(2-metoxibenzoilamino)metil]bifenil-4-ilmetil}nicotinamida de Fórmula (8.5.20);

N-[4'-(1,3-Dioxo-1,3-dihidroisoindol-2-ilmetil)-2'-fluorobifenil-4-ilmetil]-2-(4-fluorofenoxi)nicotinamida de Fórmula (8.5.21);

N-(2'-Fluoro-4'-{[(3H-imidazol-4-carbonil)amino]metil}bifenil-4-ilmetil)-2-(3-

nitrofenoxi)nicotinamida de Fórmula (8.5.22);

Ácido (±)-3-[4'-({[2-(3-cloro-4-fluorofenoxi)piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-iloxi]butírico de Fórmula (8.5.23);

Ácido 2-[4'-({[2-(benzo[2,1,3]tiadiazol-5-iloxi)piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-il]-2-metilpropiónico de Fórmula (8.5.24);

Ácido (±)-2-[4'-({[2-(benzo[2,1,3]oxadizol-5-iloxi)piridina-3-carbonil]amino}metil)-2-fluorobifenil-4-iloxi]propiónico de Fórmula (8.5.25);

Ácido (±)-2-[3'-fluoro-4'-({[2-(2-metil-2H-benzotriazol-5-iloxi)piridina-3-carbonil]amino}metil)bifenil-4-iloxi]propiónico de Fórmula (8.5.26);

2-(3-Cianofenoxi)-N-{2'-fluoro-4'-[(piridin-2-ilmetil)carbamoil]bifenil-4-ilmetil}nicotinamida de Fórmula (8.5.27);

2-(Benzo[1,3]dioxol-5-iloxi)-N-(2'-fluoro-4'-[(quinolin-2-ilmetil)carbamoil]bifenil-4-ilmetil)nicotinamida de Fórmula (8.5.28);

5-Fluoro-2-(4-fluorofenoxi)-N-[3-fluoro-3'-(1H-tetrazol-5-il)bifenil-4-ilmetil]nicotinamida de Fórmula (8.5.29);

N-{3-Fluoro-4'-[(1-hidroxipiridin-2-ilmetil)carbamoil]bifenil-4-ilmetil}-2-(3-metoxifenoxi)nicotinamida de Fórmula (8.5.30);

(±)-N-[3-Fluoro-4'-(2-hidroxi-1,2-dimetilpropoxi)bifenil-4-ilmetil]-2-(4-fluorofenoxi)nicotinamida de Fórmula (8.5.31);

N-[2'-Fluoro-4'-(1-hidroxi-1-metiletil)bifenil-4-ilmetil]-2-(4-fluorofenoxi)nicotinamida de Fórmula (8.5.32); y

2-(3-Cloro-4-fluorofenoxi)-N-[4'-(piridin-2-ilmetoxi)bifenil-4-ilmetil]nicotinamida de Fórmula (8.5.33).

7. Un procedimiento para tratar a un sujeto que sufre una enfermedad, trastorno o

afección mediada por la isozima PDE4, incluyendo el subtipo D de la misma, por la que regula la activación y desgranulación de eosinófilos, que comprende la administración a dicho sujeto que necesita dicho tratamiento de una cantidad terapéuticamente efectiva de un compuesto de Fórmula (1.0.0) como se define en la reivindicación 1.

8. Una composición farmacéutica para usarse en el tratamiento de un sujeto que sufre una enfermedad, trastorno o afección mediada por la isozima PDE4, incluyendo el subtipo D de la misma, por la que regula la activación y desgranulación de eosinófilos, que comprende una cantidad terapéuticamente efectiva de un compuesto de Fórmula (1.0.0) como se define en la reivindicación 1, junto con un vehículo farmacéuticamente aceptable para el mismo.

9. Un procedimiento de acuerdo con la reivindicación 8 en el que dicha enfermedad, trastorno o afección comprende uno o más miembros seleccionados del grupo constituido por:

- asma de cualquier tipo, etiología, o patogénesis; o asma que es un miembro seleccionado del grupo constituido por asma atópica; asma no atópica; asma alérgica; asma atópica, bronquial, mediada por IgE; asma bronquial; asma idiopática; asma verdadera; asma intrínseca provocada por alteraciones patofisiológicas; asma extrínseca provocada por factores medioambientales; asma idiopática de causa desconocida o no evidente; asma no atópica; asma bronquítica; asma enfisematosa; asma inducida por el ejercicio; asma ocupacional; asma infecciosa provocada por infección bacteriana, fúngica, protozóica, o viral; asma no alérgica; asma incipiente; síndrome de sibilancias en el niño;

- broncoconstricción crónica o agua; bronquitis crónica; obstrucción de las vías respiratorias menores; y enfisema;

- enfermedades obstructivas o inflamatorias de las vías respiratorias de cualquier tipo, etiología, o patogénesis; o una enfermedad obstructiva o inflamatoria de las vías respiratorias que es un miembro seleccionado del grupo constituido por asma; neumoconiosis; neumonía eosinófila crónica; enfermedad pulmonar obstructiva crónica (COPD); COPD que incluye bronquitis crónica, enfisema pulmonar o disnea asociada a los mismos; COPD caracterizada por la obstrucción irreversible, progresiva de las vías respiratorias; síndrome disneico agudo del adulto (ARDS), y exacerbación de la hiperreactividad de las vías respiratorias como consecuencia de otras farmacoterapias;

- neumoconiosis de cualquier tipo, etiología, o patogénesis; o neumoconiosis que es un miembro seleccionado del grupo constituido por aluminosis o enfermedad de los trabajadores de la bauxita; antracosis o asma de los mineros; asbestosis o asma de los montadores de calderas; calicosis o enfermedad del sílex; ptilosis provocada por la inhalación del polvo de las plumas de avestruz; siderosis provocada por la inhalación de partículas de hierro; silicosis o enfermedad de los amoladores; bisinosis o asma del polvo del algodón; y neumoconiosis del talco;

- bronquitis de cualquier tipo, etiología o patogénesis; o bronquitis que es un miembro seleccionado del grupo constituido por bronquitis aguda; bronquitis laringotraqueal aguda; bronquitis araquídica; bronquitis catarral; bronquitis pseudomembranosa; bronquitis seca; bronquitis asmática infecciosa; bronquitis productiva; bronquitis por estafilococos o estreptococos; y bronquitis vesicular;

- bronquiectasia de cualquier tipo, etiología o patogénesis; o bronquiectasia que es un miembro seleccionado del grupo constituido por bronquiectasia cilíndrica; bronquiectasia saculada; bronquiectasia fusiforme; bronquiectasia capilar;

bronquiectasia cística; bronquiectasia seca; y bronquiectasia folicular;

- rinitis alérgica estacional; o rinitis alérgica perenne; o sinusitis de cualquier tipo, etiología o patogénesis; o sinusitis que es un miembro seleccionado del grupo constituido por sinusitis purulenta o no purulenta; sinusitis aguda o crónica; y sinusitis etmoide, frontal, maxilar, o esfenoidal;

- artritis reumatoide de cualquier tipo, etiología o patogénesis; o artritis reumatoide que es un miembro seleccionado del grupo constituido por artritis aguda; artritis gotosa aguda; artritis inflamatoria crónica; artritis degenerativa; artritis infecciosa; artritis de Lyme; artritis proliferativa; artritis psoriásica; y artritis vertebral;

- gota, y fiebre y dolor asociado a la inflamación;

- un trastorno relacionado con la eosinofilia de cualquier tipo, etiología o patogénesis; o un trastorno relacionado con la eosinofilia que es un miembro seleccionado del grupo constituido por eosinofilia; eosinofilia en infiltración pulmonar; síndrome de Loffler; neumonía eosinófila crónica; eosinofilia pulmonar tropical; aspergilosis bronconeumónica; aspergiloma; granulomas que contienen eosinófilos; angitis granulomatosa alérgica o síndrome de Churg-Strauss; poliarteritis nodosa (PAN); y vasculitis necrosante sistémica;

- dermatitis atópica; o dermatitis alérgica; o eczema alérgico o atópico;

- urticaria de cualquier tipo, etiología o patogénesis; o urticaria que es un miembro seleccionado del grupo constituido por urticaria inmunomediada; urticaria mediada por complemento; urticaria inducida por materiales urticantes; urticaria inducida por agentes físicos; urticaria inducida por estrés; urticaria idiopática; urticaria aguda; urticaria crónica; angioedema; urticaria colinérgica; criourticaria de la forma de autosoma dominante o de la forma adquirida; urticaria de contacto; megaurticaria; y urticaria papular;

- conjuntivitis de cualquier tipo, etiología o patogénesis; o conjuntivitis que es un miembro seleccionado del grupo constituido por conjuntivitis actínica; conjuntivitis catarral aguda; conjuntivitis contagiosa aguda; conjuntivitis alérgica; conjuntivitis atópica; conjuntivitis catarral crónica; conjuntivitis purulenta; y conjuntivitis primaveral;

- uveítis de cualquier tipo, etiología o patogénesis; o uveítis que es un miembro seleccionado del grupo constituido por inflamación de toda o parte de la úvea; uveítis anterior; iritis; ciclitis; iridociclitis; uveítis granulomatosa; uveítis no granulomatosa; uveítis facoantígena; uveítis posterior; coroiditis; y corioretinitis;

- soriasis;

- esclerosis múltiple de cualquier tipo, etiología o patogénesis; o esclerosis múltiple que es un miembro seleccionado del grupo constituido por esclerosis múltiple progresiva primaria; y esclerosis múltiple recidivante remitente;

- enfermedades autoinmunitarias/inflamatorias de cualquier tipo, etiología o patogénesis; o una enfermedad autoinmunitaria/inflamatoria que es un miembro seleccionado del grupo constituido por trastornos hematológicos autoinmunitarios; anemia hemolítica; anemia aplásica; eritrocitopenia pura; púrpura trombocitopénica idiopática; lupus eritematoso sistémico; policondritis; escleroderma; granulomatosis de Wegner; dermatomiositis; hepatitis activa crónica; miastenia grave; síndrome de Stevens-Johnson; esprue idiopática; enfermedades inflamatorias del intestino autoinmunitarias; colitis ulcerosa; enfermedad de Crohn; oftalmopatía endocrina; enfermedad de Grave; sarcoidosis; alveolitis; neumonitis por hipersensibilidad crónica; cirrosis biliar primaria; diabetes juvenil o diabetes melitus tipo I; uveítis anterior; uveítis granulomatosa o posterior; queratoconjuntivitis seca; queratoconjuntivitis epidémica; fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial; fibrosis pulmonar

idiopática; fibrosis quística; artritis soriásica; glomerulonefritis con y sin síndrome nefrótico; glomerulonefritis aguda; síndrome nefrótico idiopático; nefropatía de cambio mínimo; enfermedades cutáneas inflamatorias/hiperproliferativas; soriasis; dermatitis atópica; dermatitis de contacto; dermatitis alérgica de contacto; pénfigo familiar benigno; pénfigo eritematoso; pénfigo foliáceo; y pénfigo vulgar;

- prevención del rechazo de aloinjertos tras el trasplante de órganos;

- enfermedad inflamatoria del intestino (IBD) de cualquier tipo, etiología, o patogénesis; o enfermedad inflamatoria del intestino que es un miembro seleccionado del grupo constituido por colitis ulcerosa (UC); colitis colágena; colitis poliposa; colitis transparietal; y enfermedad de Crohn (CD);

- choque séptico de cualquier tipo, etiología, o patogénesis; o choque séptico que es un miembro seleccionado del grupo constituido por insuficiencia renal; insuficiencia renal aguda; caquexia; caquexia por malaria; caquexia hipofisiaria; caquexia urémica; caquexia cardiaca; caquexia suprarrenal o enfermedad de Addison; caquexia cancerosa; y caquexia como consecuencia de infección por el virus de inmunodeficiencia humano (VIH);

- lesión hepática;

- hipetensión pulmonar; e hipertensión pulmonar inducida por hipoxia;

- enfermedades de pérdida ósea; 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 del grupo constituido por depresión; enfermedad de Parkinson; deterioro del aprendizaje y memoria; disquinesia tardía; drogodependencia; demencia ateriosclerótica; y demencias que acompañan el corea de Huntington, enfermedad de

Wilson, parálisis agitante, y atrofias talámicas;

- infección, especialmente infección por virus en las que tales virus aumentan la producción de TNF-α en su huésped, o en las que tales virus son sensibles a la regulación por aumento de TNF-α en su huésped de forma que su replicación u otras actividades vitales sufren un impacto adverso, incluyendo un virus que es un miembro seleccionado del grupo constituido por VIH-1, VIH-2, y VIH-3; citomegalovirus, CMV; gripe; adenovirus; y virus del Herpes, incluyendo *Herpes zoster* y *Herpes simplex*;

- infecciones por levaduras y hongos en las que dichas levaduras y hongos son sensibles a regulación por aumento mediante TNF-α o provocan la producción de TNF-α en su huésped, cuando se administra junto con otros fármacos de elección para el tratamiento de infecciones sistémicas de levaduras y hongos, incluyendo pero sin limitación, polimixinas; Polimicina B; imidazoles, clotrimazol, econazol, miconazol, y cetoconazol; triazoles, fluconazol e itranazol; y anfotericinas, por ejemplo, Amfotericina B y Anfotericina B liposómica.

- lesión por isquemia - reperfusión; diabetes autoinmunitaria; autoinmunidad retiniana; leucemia linfocítica crónica; infecciones por VIH; lupus eritematoso; enfermedad renal y ureteral; trastornos urogenitales y gastrointestinales; y enfermedades de próstata.

10. La combinación de un compuesto de Fórmula (1.0.0) como se define en la reivindicación 1 junto con uno o más miembros seleccionados del grupo constituido por los siguientes:

(a) Inhibidores de la biosíntesis de leucotrienos: inhibidores de 5-lipoxigenasa (5-LO) y antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP) seleccionados del grupo constituido por zileuton; ABT-761; fenleuton; tepoxalin;

Abbott-79175; Abbott-85761; *N*-(sustituido en 5)-tiofeno-2-alquilsulfonamidas de Fórmula (5.2.8); 2,6-di-*terc*-butilfenolhidrazonas de Fórmula (5.2.10); la clase de metoxitetrahidropiranos que incluye Zeneca ZD-2138 de Fórmula (5.2.11); el compuesto SB-210661 de Fórmula (5.2.12) y la clase a la que pertenece; la clase de compuestos de 2-cianonaftaleno sustituido con piridilo a la que pertenece L-739.010; la clase de compuestos de 2-cianoquinolina a la que pertenece L-746.530; las clases de compuestos de indol y quinolina a la que pertenecen MK-591, MK-886, y BAY x 1005;

(b) Antagonistas de los receptores de leucotrienos, LTB_4, LTC_4, LTD_4, y LTE_4 seleccionados del grupo constituido por la clase de compuestos fenotiazin-3-ona a la que pertenece L-651.392; la clase de compuestos de amidino a la que pertenece CGS-25019c; la clase de benzoxaolaminas a la que pertenece ontazolast; la clase de bencenocarboximidamidas a la que pertenece BIIL 284/260; y las clases de compuestos a las que pertencen zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913; iralukast (CGP 45715A), y BAY x 7195;

(c) Inhibidores de PDE4 incluyendo inhibidores de la isoforma PDE4D;

(d) Inhibidores de 5-lipoxigenasa (5-LO); o antagonistas de la proteína activadora de 5-lipoxigenasa (FLAP);

(e) Inhibidotes duales de 5-lipoxigenasa (5-LO) y antagonistas del factor activador de plaquetas (PAF);

(f) Antagonistas de leucotrienos (LTRA) incluyendo antagonistas de LTB_4, LTC_4, LTD_4, y LTE_4;

(g) Antagonistas antihistamínicos del receptor H_1 incluyendo cetirizina, loratadina, desloratadina, fexofenadina, astemizol, azelastina, y clorfeniramina;

(h) Antagonistas gastroprotectores del receptor H_2;

(i) Agentes simpaticomiméticos vasoconstrictores agonistas de los

adrenorreceptores α_1 y α_2 administrados oral o tópicamente para uso descongestivo, incluyendo propilhexedrina, fenilefrina, fenilpropanolamina, pseudoefedrina, clorhidrato de nafazolina, clorhidrato de oximetazolina, clorhidrato de tetrahidrozolina; clorhidrato de xilometazolina, y clorhidrato de etilnorepinefrina;

(j) Agonistas de los adrenorreceptores α_1 y α_2 en combinación con inhibidores de 5-lipoxigenasa (5-LO);

(k) Agentes anticolinérgicos incluyendo bromuro de ipratropio;

(l) Agonistas de los adrenorreceptores β_1 a β_4 incluyendo isoprenalina, albuterol, salbutamol, formoterol, salmeterol, terbutalina, orciprenalina, mesilato de bitolterol, y pirbuterol;

(m) Teofilina y aminofilina;

(n) Cromoglicato sódico;

(o) Antagonistas de los receptores muscarínicos (M1, M2, y M3);

(p) Inhibidores de COX-1 (NSAID); inhibidores selectivos de COX-2 incluyendo rofecoxib; y NSAID de óxido nítrico;

(q) Miméticos del factor de crecimiento insulinoide tipo I (IGF-1);

(r) Ciclesonida;

(s) Glucocorticoides inhalados con efectos secundarios sistémicos reducidos, incluyendo flunisolida, acetonida de triamcinolona, dipropionato de beclometasona, budesonida, propionato de fluticasona, y furoato de mometasona;

(t) Inhibidores de triptasa;

(u) Antagonistas del factor activador de plaquetas (PAF);

(v) Antincuerpos monoclonales contra entidades inflamatorias endógenas;

(w) IPL 576;

(x) Agentes contra el factor necrosante tumoral (TNFα) incluyendo

Etanercept, Infliximab, y D2E7;

(y) DMARD incluyendo Leflunomida;

(z) Péptidos TCR;

(aa) Inhibidores de la enzima convertidora de interleucina (ICE);

(bb) Inhibidores de IMPDH;

(cc) Inhibidores de la molécula de adhesión incluyendo antagonistas de VLA-4;

(dd) Catepsinas;

(ee) Inhibidores de MAP cinasa;

(ff) Inhibidores de glucosa-6-fosfato deshidrogenasa;

(gg) Antagonistas de los receptores de quinina-B_1 y B_2;

(hh) Oro en forma de grupo aurotio junto con diversos grupos hidrófilos;

(ii) Agentes inmunosupresores, por ejemplo, ciclosporina, azatioprina, y metotrexato;

(jj) Agentes contra la gota, por ejemplo colchicina;

(kk) Inhibidores de la xantina oxidasa; por ejemplo alopurinol;

(ll) Agentes uricosúricos, por ejemplo, probenecid, sulfinpirazona, y benzobromarona;

(mm) Agentes antineoplásicos, especialmente fármacos antimitóticos incluyendo los alcaloides de la vinca tales como vinblastina y vincristina;

(nn) Secretagogos de la hormona del crecimiento;

(oo) Inhibidores de las metaloproteasas de matriz (MMP), es decir las estromelisinas, las colagenasas, y las gelatinasas, así como agrecanasas, 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);

(pp) Factor de crecimiento transformador (TGFβ);

(qq) Factor de crecimiento derivado de plaquetas (PDGF);

(rr) Factor de crecimiento de fibroblastos, por ejemplo el factor de crecimiento de fibroblastos básico (bFGF);

(ss) Factor estimulador de colonias de granulocitos macrófagos (GM-CSF);

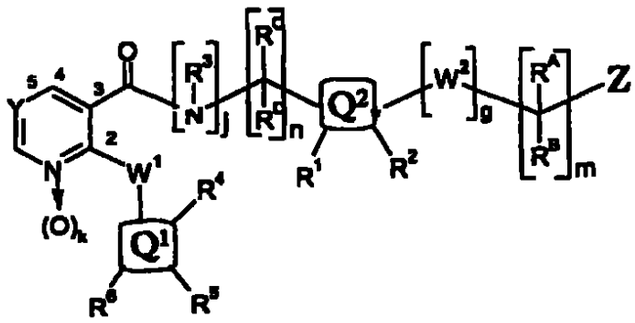
(tt) Crema de capsaicina;

(uu) Agentes antieméticos incluyendo antagonistas del receptor NK-1 y D-4418; y

(vv) Antidepresivos.

RESUMEN DE LA DESCRIPCIÓN

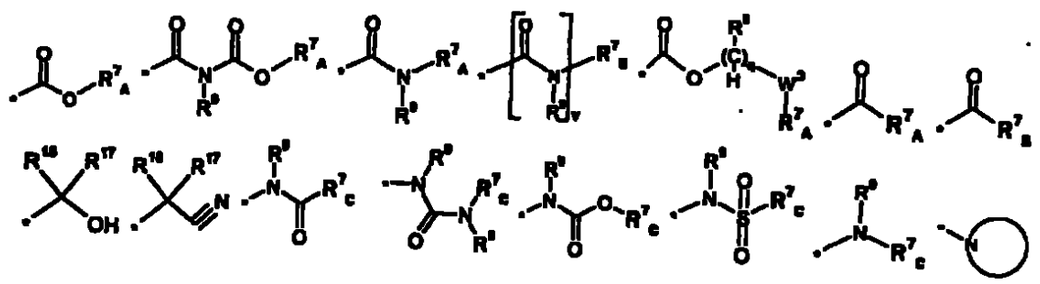
Compuestos de utilidad como inhibidores de PDE4 en el tratamiento de enfermedades reguladas por la activación y desgranulación de eosinófilos, especialmente asma, bronquitis crónica, y enfermedad pulmonar obstructiva crónica de fórmula:



donde 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 0, 1, ó 2; n es 1 ó 2; W^1 es -O-; o -S(=O)$_t$-, donde t es 0, 1, ó 2; o -N(R^3)-; W^2 es -O-C$R^A R^B$-, o está ausente; Y es =C($R^1{}_a$)- o [N ⇨(O)$_k$]- donde k es 0 ó 1; 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 a 3 sustituyentes R^{10}; o R^A y R^B se toman conjuntamente, pero únicamente en el caso en que m es 1, para formar un resto espiro; R^C y R^D tienen el mismo significado que R^A y R^B pero 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}; y -C(=O)N$R^{22}{}_a R^{22}{}_b$; R^3 es -H; -alquilo C_1-C_3; fenilo; bencilo; o -OR^{16}; R^4, R^5 y R^6 además de otros significados pueden tomarse conjuntamente para formar, por ejemplo



Q^1 es un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3 a 7 miembros, o que es un policiclo condensado de 7 a 12 miembros; con la condición de que Q^1 no es un resto biarilo discontinuo o restringido como se define en Q^2; donde opcionalmente un átomo de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo pueden reemplazarse por N; Q^2 es un resto biarilo discontinuo o restringido constituido por un sistema de anillos de carbono saturados o insaturados que es un monociclo de 3- a 7- miembros, o que es un policiclo condensado de 7 a 12 miembros; donde opcionalmente un átomo de carbono de dicho sistema de anillos de carbono puede reemplazarse por un heteroátomo seleccionado de N, O, y S; donde opcionalmente un segundo átomo de carbono del mismo, y de forma adicional opcionalmente un tercer átomo de carbono del mismo pueden reemplazarse por N; Z se selecciona de:



PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT JUN 18 2003

To:
Lumb, J. Trevor
PFIZER INC.
201 Tabor Road
Morris Plains, New Jersey 07950
ETATS-UNIS D'AMERIQUE

RECEIVED
JUN 7 2003
MP PATENT DEPT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	11/06/2003

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
PC11897ARMS	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IB 01/02341	06/12/2001	31/01/2001

Applicant

PFIZER PRODUCTORS INC.

1. The applicant is hereby notified that this 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
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	CHURCHER G Tel. (+49-89) 2399 2828

Form PCT/IPEA/416 (August 2002) P20473

5D1

450

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PC11897ARMS		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 01/ 02341	06/12/2001	31/01/2001
International Patent Classification (IPC) or national classification and IPC		
C07D213/82		
Applicant		
PFIZER PRODUCTORS INC.		

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	05/06/2003
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	GELLIE B R Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.PCT/ IB 01/ 02341

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

Ir ernal Application No
PCT/IB 01/02341

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/82 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, PAJ, WPI Data, 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

-/--

[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)

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

INTERNATI NAL SEARCH REPORT

Information on patent family members

In nal Application No
PCT/IB 01/02341

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	

International Application No. PCT/IB 01 /02341

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5 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-; Q1 is an optionally substituted phenyl or benzofused ring; Q2 is two optionally substituted phenyl rings which are directly linked to one another. 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.

454

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.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03065415 00000000 Folios: 505
Fecha: Fecha (AMD): 2003-07-31 16:56:11
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

207
455

2020
Bogotá, D.C.,

Doctor:
CARLOS R. OLARTE
Apoderado
PFIZER PRODUCTS INC.

Oficio N° 89529

ASUNTO:		
	Radicación N°	03-65415
	Solicitud Internacional	PCT/IB2001/02341
	Fecha inicio fase nacional	31/08/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ Los dibujos adjuntos no son legibles o copiables para trámites posteriores de publicación y título.
- ☐ El número de la prioridad invocada en la solicitud nacional difiere del de la prioridad invocada en la solicitud internacional .
- ☐ El solicitante relacionado en el petitorio de la solicitud nacional difiere del relacionado en la solicitud internacional.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

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

El anterior requerimiento fue notificado por fijación en lista de fecha 31 OCT. 2003.

202058