03/6541

# Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

## SOLICITUD
# PATENTE DE INVENCIÓN

EXPEDIENTE No. 03-6541

TÍTULO Derivados amida de ácido tiazolilico, oxazolilico, pirrolilico e imidazolilico utiles como inhibidores de las isoenzimas pde4

CLASIFICACIÓN INTERNACIONAL A61K 423 ; C07D 417/12

SOLICITANTE Pfizer Products Inc Eastern Point Road, Estado de

DOMICILIO Connecticut, Estados Unidos de America

APODERADO Carlos M Olarte.

BOGOTÁ, D.C., Julio 31, 2003

PETITORIO

1

Industria y Comercio
SUPERINTENDENCIA

03 065412 00

SUPERINTENDENCIA Y COMERCIO
Radicacion : 03065412 00000000 Folios: 432
Fecha (AMD): 2003-07-31 16:54:27
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTACIÓN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

# FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
# PCT
## ENTRADA EN FASE NACIONAL

**(1) SOLICITUD DE :**

| | | | |
|---|---|---|---|
| [X] | Patente de Invención | [ ] | Patente de Modelo de Utilidad |
| [ ] | Capítulo I | [X] | Capítulo II |

**(2) SOLICITANTE (71)**

Nombre: PFIZER PRODUCTS INC.

Dirección: Eastern Point Road, Estado de Connecticut, Estados Unidos de America.

Nacionalidad o Domicilio

Lugar de Constitución: Connecticut; Estados Unidos de América.

Teléfono: Fax:

E-Mail:

IDENTIFICACION

C C [ ] NIT [ ]

C E [ ] Otro [ ]

Cual: _____

Número: _____

**(3) REPRESENTANTE O APODERADO**

Nombre: CARLOS R OLARTE

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

Teléfono: 6386200 Fax: 6386201

E-Mail: filings@olarteraisbeck com

IDENTIFICACION

C C [X] NIT [ ]

C E [ ] Otro [ ]

Cual: _____

Número: 79 782.747 Bta TP 74.295

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

Nombre: ANTHONY MARFAT, MICHAEL WILLIAM MCKECHNEY

Dirección: Eastern Point Road, Groton, Connecticut 06340, Estados Unidos de América.
1 Canon Ridge, Fairport, New York 14450, Estados Unidos de América.

Nacionalidad o Domicilio: ESTADOUNIDENSE

**(5) PCT (85)**

Solicitud Internacional No: PCT/IB01/02728 Fecha: Diciembre 24, 2001

Publicación Internacional No: WO 02/060898 Fecha: Agosto 8, 2002

**(6) Título (54):** DERIVADOS AMIDA DE ACIDO TIAZOLILICO, OXALILICO, PIRROLILICO E IMIDAZOLILICO UTILES COMO INHIBIDORES DE LAS ISOZIMAS PDE4.

**(7) Clasificación Internacional (51)** A61K31/427 ; C07D417/12

| (8) Prioridad | (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|---|
| SI [X] NO [ ] | US | Enero 31, 2001 | 60/265,486 |
| | | | |
| | | | |

**(9) Comprobante de pago No** 52672 **Fecha** 28-0703

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

## (10) ANEXOS

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [X] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] *Arte final* 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional
- [X] Otros BUSQUEDA INTERNACIONAL

## (11) FIGURA CARATERISTICA

## (12) Solicito la concesión de la patente,

NOMBRE CARLOS R OLARTE

FIRMA

C C 74.782 747 de Btá. T P 74.295

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

# *Tabla de Contenido*


| | |
|---|---|
| 1 | 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***

My M

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03065412 00000000 Folios: 032
Fecha (MMD): 2003-07-31 16:54:27
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 52.672
FECHA : JULIO 28 DE 2003

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| OLARTE RAISBECK | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 13594221 | 28/07/2003 | 1.700,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 400,000.00 |
| | | TOTAL : $ | 400.000.00 |

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

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 convencion de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país

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

Marlen Neira C.

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Ingles - Español Ingles
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,

domiciled in

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

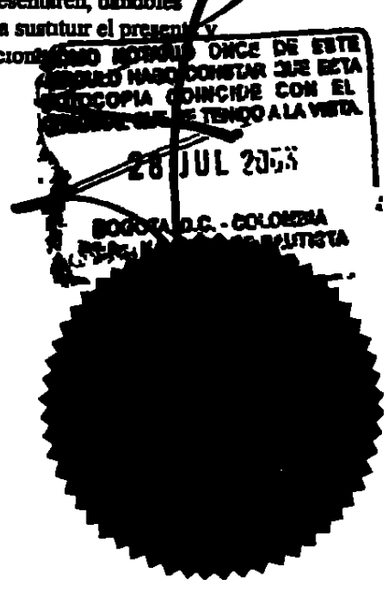
Eastern Point Road, Groton, Connecticut 06340 USA

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 motivos de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones

Signature/Firma _____

Date/Fecha July 14, 2003

City,Country/Ciudad,País New York, USA



# 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)

## Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica

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

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

4 Que
con sede principal ubicada en

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

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

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

NOTARIO NOVENTA ONCE DE ESTE CIRCULO HACE CONSTAR QUE ESTA COPIA COINCIDE CON EL DOCUMENTO QUE TENGO A LA VISTA
28 JUL 2003
BOGOTA, D.C. - COLOMBIA
JUAN NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

NOTARY PUBLIC (Signature)

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

**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

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

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 Margaret Heard
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 20 de mayo de 2003
7. Por el Secretario de Estado de Columbia
8. No 81985
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 AMIDO ACIDOS DE TIAZOLIL-, OXAZOLIL-, PIRROLIL E IMIDAZOLIL 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.

Marlen Neira C

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

42 12
10

En testimonio de lo anterior, firmamos en estas fechas.

| Firma | Lugar y fecha |
|---|---|
| Anthony Marfat | 14 de mayo 2003 - Groton, Connecticut |
| Michael William Mckechney | |

Sello al reverso·

Por el presente se certifica que este documento es original

- Sami Swadek - 5 - 20- 2003 -

Suscrito y legalizado ante notario el 20 de mayo de 2003

Firma y sello de Margaret Heard- Notario público, Distrito de Columbia, sus funciones vencen el 7- 14- 2006. Sello en alto relieve de Notario

---

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

Marlen Neira C

MARLEN NEIRA CASTR
Traductor e Intérprete C
Inglés - Español Ing
Resolución No 2117 del 7 C

102 13
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 MARGARET HEARD

3 acting in the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA

4 bears the seal/stamp of MARGARET HEARD, NOTARY PUBLIC, D.C.

## CERTIFIED

5 at Washington, D C

6 the 20TH day of MAY 2003

7 by *Secretary of the District of Columbia*

8 No 61985

9 Seal/Stamp



10 Signature

SHERRYL H. NEWMAN

PC11894ARMS

CO-1

14
12

# 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 **THIAZOLYL-, OXAZOLYL-, PYRROLYL-, AND IMIDAZOLYL-ACID AMIDE 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

14 May 2003 Groton, Connecticut

Place, date and signature - Anthony MARFAT

Place, date and signature - Michael William MCKECHNEY

I HEREBY CERTIFY THAT
THIS IS THE ORIGINAL
DOCUMENT
SAMI SWADE/C
5.20.03

Subscribed and sworn to before me this
20th day of May 2003
Notary Public

Margaret Heard
Notary Public, District of Columbia
My Commission Expires 07-14-2006

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 Margaret Heard
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 27 de mayo de 2003

7. Por el Secretario de Estado de Columbia

8 No. 110022

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 AMIDO ACIDOS DE TIAZOLIL-, OXAZOLIL-, PIRROLIL E IMIDAZOLIL 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

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No 2117 del 7 Oct 198/

En testimonio de lo anterior, firmamos en estas fechas:

Firma Lugar y fecha

Anthony Marfat

Michael William Mckechney Fairpot, NY, Estados Unidos, mayo 19, 2003

Sello al reverso·

Por el presente se certifica que este documento es original

- Sami Swadek - 5 - 27- 2003 -

Suscrito y legalizado ante notario el 27 de mayo de 2003

Firma y sello de Margaret Heard- Notario público, Distrito de Columbia, sus funciones vencen el 7- 14- 2006. Sello en alto 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 Ofici
Inglés Español Ingl
Resolución No 2117 del 7 Oct 1987

102 15 17

# APOSTILLE

*(Convention de La Haye du 5 octobre 1961)*

1 *District of Columbia*
*United States of America*

MARGARET HEARD

2 This public document has been signed by NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA

3. acting in the capacity of MARGARET HEARD, NOTARY PUBLIC IN AND FOR THE

4. bears the seal/stamp of DISTRICT OF COLUMBIA

## CERTIFIED

5 at Washington, D C

6 the 27 day of MAY 2003

7 by *Secretary of the District of Columbia*

8 No 110022

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 **THIAZOLYL-, OXAZOLYL-, PYRROLYL-, AND IMIDAZOLYL-ACID AMIDE DERIVATIVES USEFUL AS INHIBITORS OF PDE4 ISOZYMES** so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER PRODUCTS INC** in accordance with this assignment.

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

Place, date and signature - Anthony MARFAT

Fairport, NY USA May 19, 2003

Place, date and signature - Michael William MCKECHNEY

I HEREBY CERTIFY THAT THIS
IS THE ORIGINAL DOCUMENT

SAMI SWADEK
5.27.03

Subscribed and sworn to before me this
27th day of May 2003
Notary Public

Margaret Heard
Notary Public, District of Columbia
My Commission Expires 07-14-2008

(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 02/060898 A1

(51) International Patent Classification[7] C07D 417/12, A61P 11/06 29/00, C07D 277/56, A61K 31/427

(21) International Application Number PCT/IB01/02728

(22) International Filing Date
24 December 2001 (24.12.2001)

(25) Filing Language English

(26) Publication Language English

(30) Priority Data.
60/265,486 31 January 2001 (31.01.2001) US

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

(72) Inventors, and
(75) Inventors/Applicants *(for US only)* MARFAT, Anthony [US/US], Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). MCKECHNEY, Michael, William [US/US], 1 Canon Ridge, Fairport, NY 14450 (US).

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

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

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

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

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

(54) Title: THIAZOLYL-, OXAZOLYL-, PYRROLYL-, AND IMIDAZOLYL-ACID AMIDE DERIVATIVES USEFUL AS INHIBITORS OF PDE4 ISOZYMES

(57) Abstract: Compounds useful as inhibitors or 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, k is 0 or 1, m is 0, 1, 2 or 3, n is 1 or 2, $W^1$ is -O-, or -S(=O)$_t$-, where t is 0, 1 or 2, or -N($R^J$)-, $W^2$ is -O-$CR^A R^B$- or is absent, Y is =C($R^1$)$_n$- 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 $R^{10}$, 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, -$NO_2$, -($C_1$-$C_4$) alkyl, -($C_2$-$C_4$) alkynyl, fluorinated -($C_1$-$C_3$) alkyl, -$OR^{16}$, and -C(=O)$NR^{22}{}_a R^{22}{}_b$, $R^3$ 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 formula (II), $G^1$ is a saturated or unsaturated carbon ring system, where optionally one carbon atom may be replaced by a heteroatom selected from N, O, and S, -$G^2$ is a saturated or unsaturated carbon ring system, wherein one carbon atom of may be replaced by a heteroatom selected from N, O, and S, and E is selected from formula (III).

WO 02/060898 A1

# THIAZOLYL-, OXAZOLYL-, PYRROLYL-, AND IMIDAZOLYL-ACID AMIDE DERIVATIVES USEFUL AS INHIBITORS OF PDE4 ISOZYMES

## 10 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, PC11895, PC11896, and PC11897, which involve other classes of nicotinamide derivatives useful as inhibitors of PDE4 isozymes The disclosures of all of said copending applications are incorporated herein by reference in their entireties

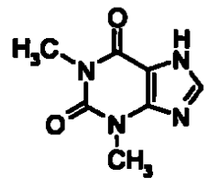
## 20 BACKGROUND OF THE INVENTION

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

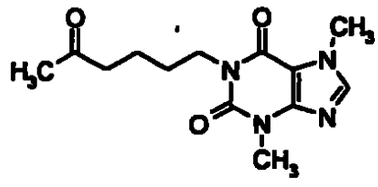
The PDE4s are characterized by selective, high affinity hydrolytic degradation of the second messenger cyclic nucleotide, adenosine 3',5'-cyclic monophosphate (cAMP), and by sensitivity to inhibition by rolipram A number of selective inhibitors of the PDE4s have been discovered in recent years, and beneficial 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



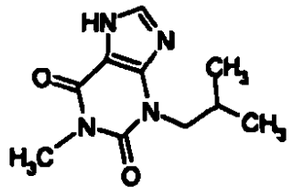
Theophylline

(0 0 1)



Pentoxifylline

(0 0 2)

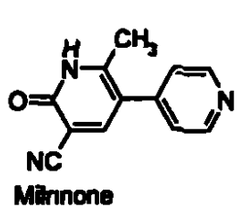


IBMX

(0 0 3)

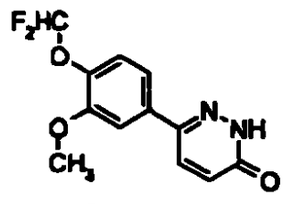
Theophylline, which has the PDEs as one of its biochemical targets, in addition to its well characterized bronchodilatory activity, affects the vasculature of patients with increased pulmonary artery pressure, suppresses inflammatory cell responses, and induces apoptosis of eosinophils Theophylline's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



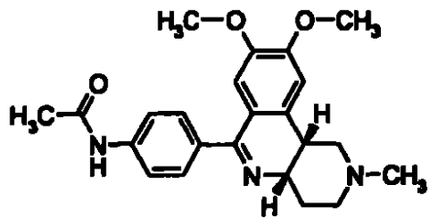
Milrinone

(0 0 4)



Zardaverine

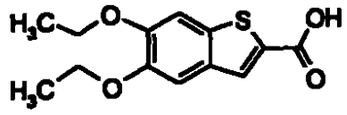
(0 0 5)



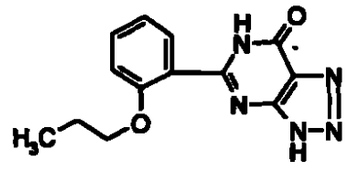
Benafentrine

(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)



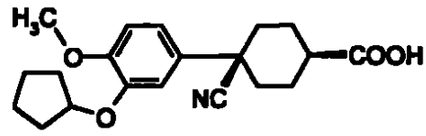
Zaprinast
(0 0 8)

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

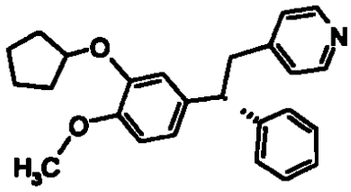
chronic inflammation, and are further implicated in the pathology of conditions such as emphysema

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)

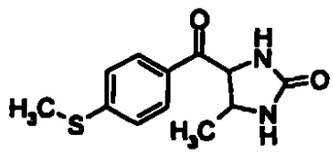
SB-207,499, administered orally at dosages of 5, 10, and 15 mg *b.i.d.*, has produced significant increases in trough $FEV_1$ (forced expiratory volume in 1 second) from placebo at week 2 of a study involving a large number of patients Another potent, selective PDE4 inhibitor, CDP840, has shown suppression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



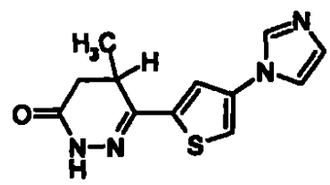
CDP840 (0 0 9)

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 Arifio (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 inhibiton by zaprinast, it has been shown that combined inhibition of PDE 3 and 5 exerts a relaxation of pulmonary artery rings which corresponds broadly to the pattern of PDE isozymes found in the pulmonary artery smooth muscle See Rabe *et al*, *Am J Physiol* 266 (LCMP 10) L536-L543, 1994 The structures of milrinone and zaprinast are shown above as Formulas (0 0.4) and (0 0 8), respectively

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

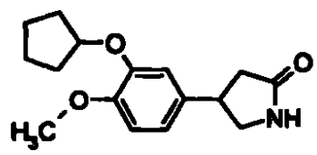


Enoximone
(0 0 10)

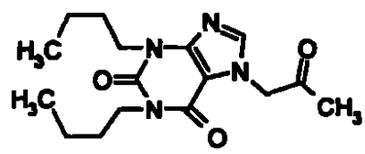


Motapizone
(0 0 11)

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

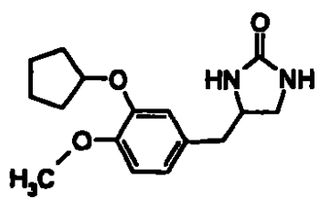


Rolipram
(0 0 12)



Denbufylline
(0 0 13)

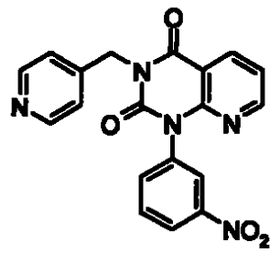
The mechanism(s) by which PDE4 inhibitors may potentially induce emesis is/are uncertain, but a study of the PDE4 inhibitor Ro-20-1724 suggests that nausea and vomiting are at least partially mediated by the emesis centers in the brain Gastrointestinal adverse events may be caused by local effects, *e g* , rolipram is a very potent stimulator of acid secretion from gastric parietal cells, and the resulting excess acid, by producing local irritation, may exacerbate gastrointestinal disturbances Ro-20-1724 may be represented by Formula (0 0 14)



Ro-20-1724
(0 0 14)

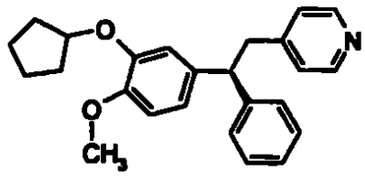
Efforts to minimize or eliminate the above-mentioned adverse events sometimes associated with PDE4 inhibitors have included creating inhibitors which do not penetrate the central nervous system, and administering PDE4 inhibitors by inhalation rather than orally

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



RS-25,344 (0 0 15)

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

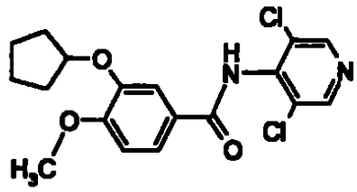


CT-1731 (0 0 16)

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

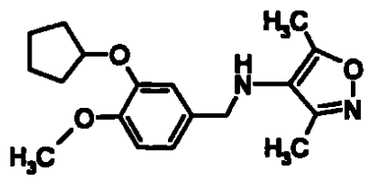
The impact of residues on inhibitor binding is also significant A single amino acid substitution (alanine for aspartate) in the catalytic region of PDE4B has been shown to be critical for inhibition by rolipram, and this appears to be a class effect because related inhibitors RP-73,401 and Ro-20-1724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

RP-73,401, in guinea-pig studies, has been found to be active in (1) the inhibition of antigen-induced lung eosinophilia and eosinophil peroxidase (EPO), Banner, K H , "The effect of selective phosphodiesterase inhibitors in comparison with other anti-asthma drugs on allergen-induced eosinophilia in guinea-pig airways," *Pulm Pharmacol* 8 37-42, 1995, (2) antigen-induced bronchoalveolar lavage (BAL) eosinophilia, Raeburn *et al*, "Anti-inflammatory and bronchodilator properties of RP73401, a novel and selective phosphodiesterase Type IV inhibitor," *Br J Pharmacol.* 113 1423-1431, 1994, (3) antigen-induced airway eosinophilia and platelet activating factor- (PAF)- and ozone-induced airway hyper-responsiveness (AHR), Karlsson *et al*, "Anti-inflammatory effects of the novel phosphodiesterase IV inhibitor RP73401," *Int. Arch Allergy Immunol* 107 425-426, 1995, and (4) IL-5 induced pleural eosinophilia Development of RP-73,401, piclamilast, has been discontinued Piclamilast may be represented by Formula (0 0 17)



Piclamilast (RP-73,401) (0 0 17)

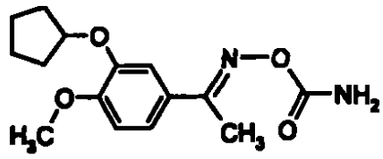
A related series of compounds is represented by RPR-132294 and RPR-132703, which have been demonstrated in rat studies to have activity in the inhibition of antigen-induced bronchospasm, Escott *et al*, "Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic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

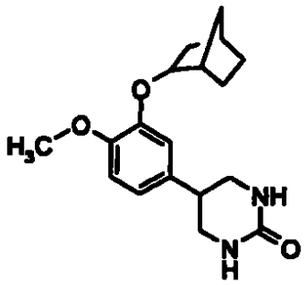
Another compound whose development has been discontinued is WAY-PDA-641, filaminast, which in studies in the dog, has been found to be active in the inhibition of seratonin-induced bronchoconstriction Filaminast may be represented by Formula (0 0 19)



Filaminast (WAY-PDA-641)

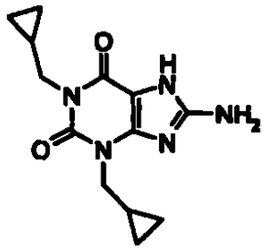
(0 0 19)

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)

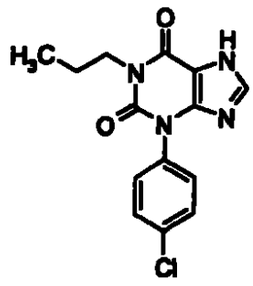
(0 0 20)



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 A511, 1999

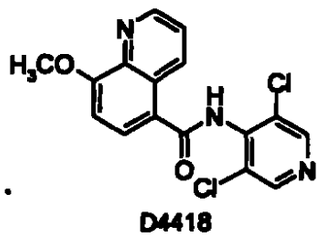
The compound D4418 has been administered to healthy volunteers in a single escalating dose, randomized, placebo-controlled Phase I study; Montana *et al*, "Activity of D4418, a novel phosphodiesterase 4 (PDE4) inhibitor, effects in cellular and animal models of asthma and early clinical studies," *Am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

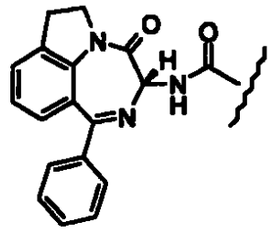
(0 0.22)



D4418

(0 0.23)

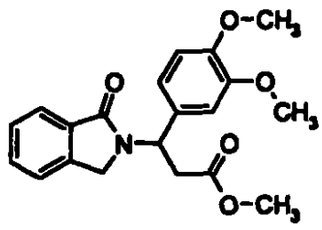
Another compound, CI-1018, has been evaluated in 54 subjects and no adverse events were reported at doses up to 400 mg, Pruniaux *et al.*, "The novel phosphodiesterase inhibitor CI-1018 inhibits antigen-induced lung eosinophilia in sensitized brown-norway rats - comparison with rolipram," *Inflammation* 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)



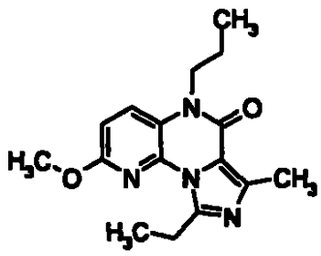
(0 0.24)

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

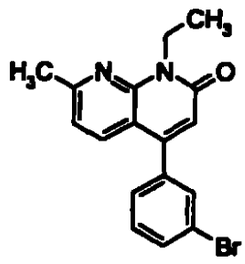


CDC-3052
(0 0.27)

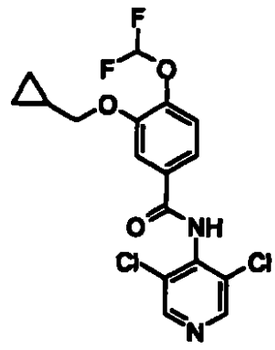


D-22888

(0 0 28)



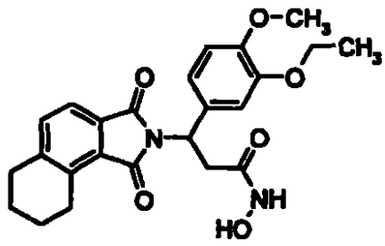
YM-58977
(0 0.29)

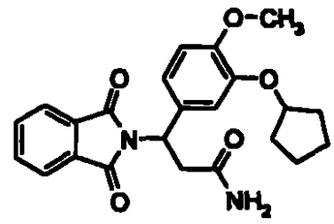


Roflumilast

(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





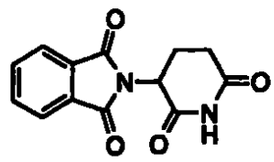
CDC-801

(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, Anrnheim, 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

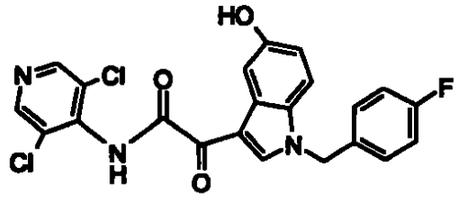
(0 0 33)

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

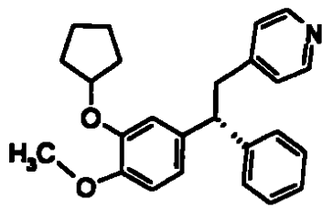
AWD-12,281, which is now designated as loteprednol, has been shown to be active in a rat model of allergic rhinitis, as described further below in a section which deals with allergic rhinitis and the use of PDE4 inhibitors to treat it AWD-12,281 may be represented by Formula (0 0 34)



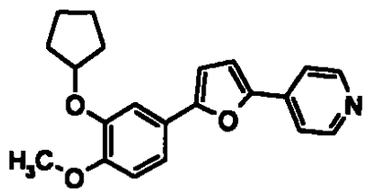
Loteprednol (AWD-12,281)

(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 Pérner *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)

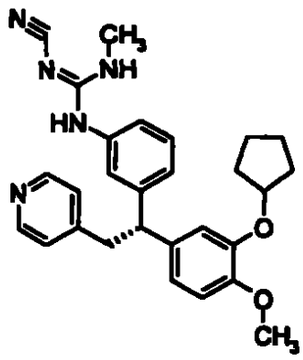


CDP840
(0 0 9)

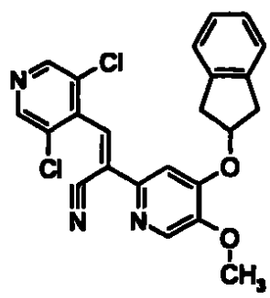


(0 0 35)

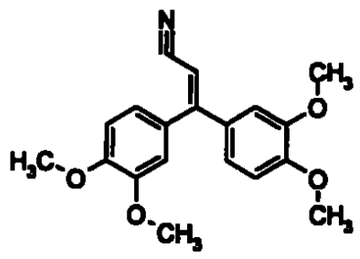
Other compounds which been found to be very potent PDE4 inhibitors are those represented by Formulas (0 0 36), (0 0 37), and (0 0 38)



(0 0 36)

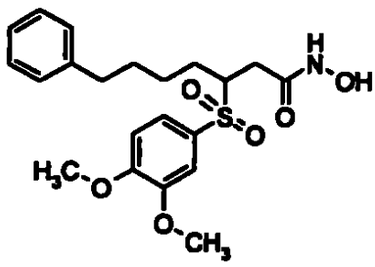


(0 0 37)

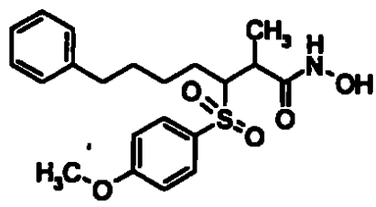


(0 0 38)

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)

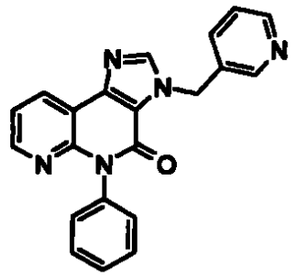


(0 0 40)

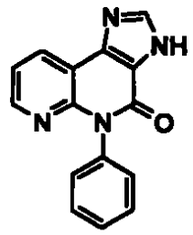
The respective $IC_{50}$ values for the compounds of Formulas (0 1 36) and (0 1 37) using a guinea-pig macrophage PDE4 assay were 1 nM and 30 nM

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 4866-4874, 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).

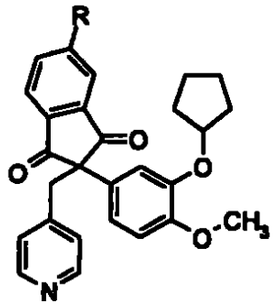


KF19514
(0 0 41)



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)

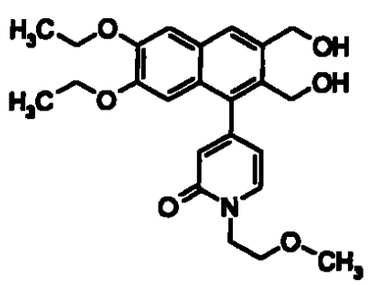


R = benzyloxy (0 0 43)

R = [1,4']-bipiperidinyl-1'-carbonyloxy (0 0 44)

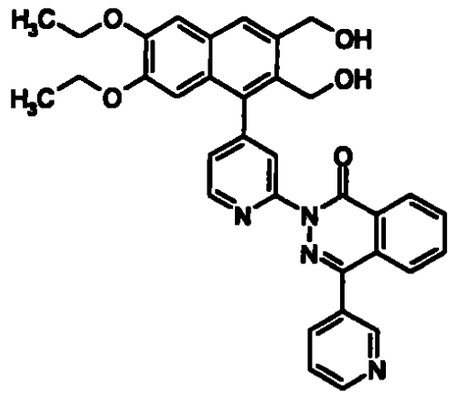
The PDE4 inhibitors that have been created heretofore fall into a significant number of different classes in terms of their chemical structures Such classes have been as diverse as phenanthridines and naphthyridines One class of PDE4 inhibitors are lignans such as T-440, which has been demonstrated to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

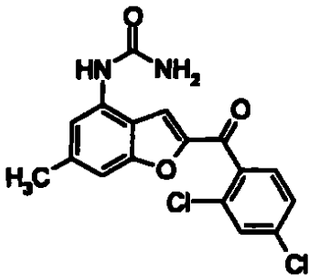
(0 0 45)



T-2585

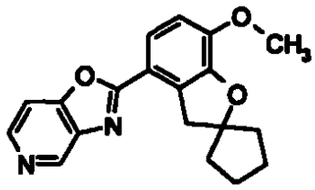
(0 0 46)

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)



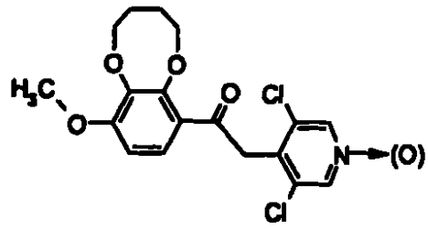
(0 0 47)

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)



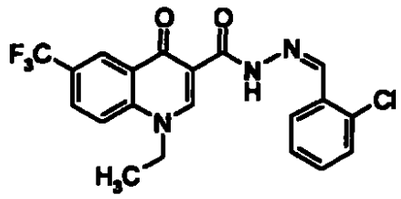
(0 0 48)

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

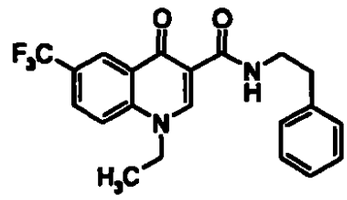


(0 0.49)

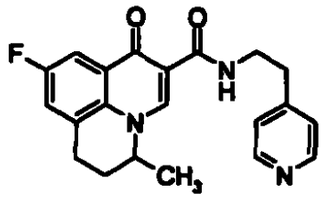
Quinolines and quinolones are a further class of PDE4 inhibitor structures, and they serve as surrogates for the catechol moiety of rolipram This compound and two compounds of similar structure may be represented by Formulas (0 0 50), (0 0 51), and (0 0 52)



(0 0 50)

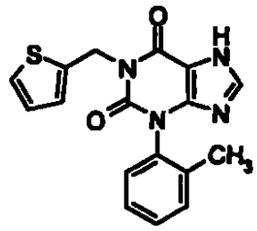


(0 0 51)



(0 0 52)

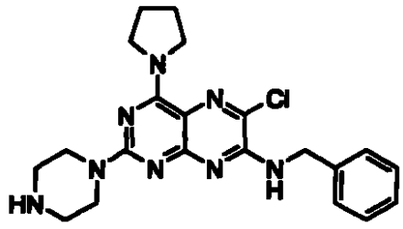
Purines, xanthines, and ptendines represent yet further classes of chemical compounds to which PDE4 inhibitors described heretofore in the art belong The compound V-11294A described further above and represented by Formula (0 0 22), is a purine A PDE4 inhibitor which is a xanthine compound, the class 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)

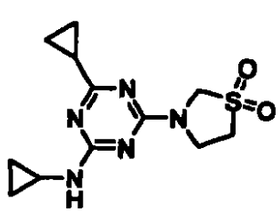
A potent PDE4 inhibitor belonging to the ptendine class of compounds has been demonstrated to have an $IC_{50}$ value of 16 nM against a PDE4 derived from tumor cells and to inhibit the growth of tumor cells at micromolar concentrations, Merz *et al*, "Synthesis of 7-

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)

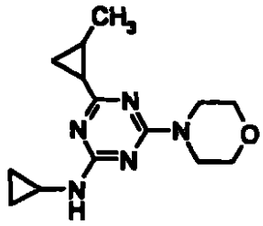


(0 0 55)

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)

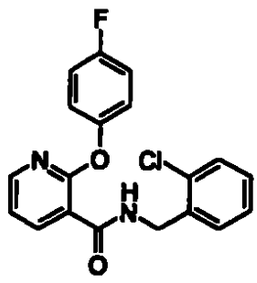


(0 0 57)

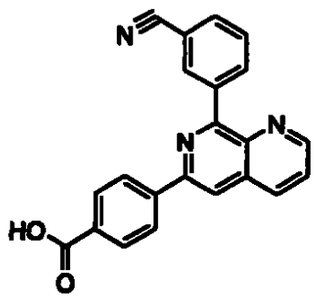
A triazine having a structure assumed to be closely related to that of the compounds of Formulas (0 0 56) and (0 0 57) is UCB-29936, which has been demonstrated to have activity in a murine model of septic shock, Danhaive *et al.*, "UCB29936, a selective phosphodiesterase Type IV inhibitor therapeutic 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

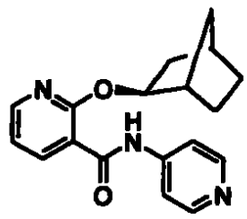


(0 0 58)

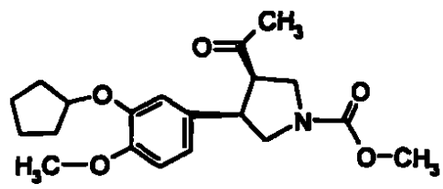


(0 0 59)

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)

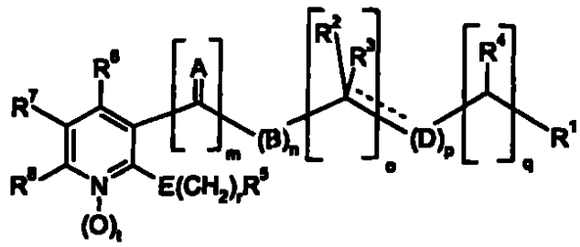


(0 0 61)

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 ).

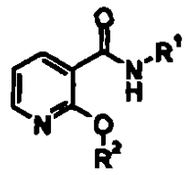
## 3.0 DESCRIPTION OF THE STATE OF THE ART

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)



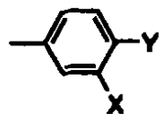
(0 1 1)

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)



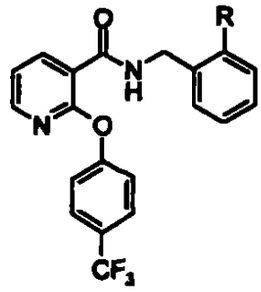
(0 1 2)

The nicotinamide nucleus of a typical compound disclosed in this patent is bonded directly to the $R^1$ group, which is defined as 1-pipendyl, 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)

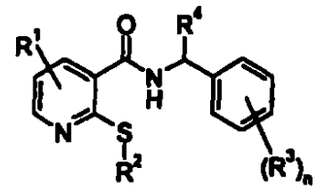


(0 1 3)

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)

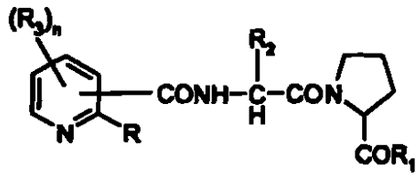
00831



(0 1 4)

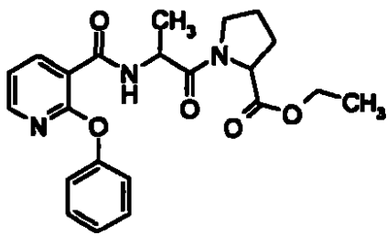
where n is 0-3, $R^1$ is selected from numerous groups, but is usually H, 6-$CH_3$, or 5-Cl, $R^2$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl, R1 and R2 is halo, CN, $NO_2$, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio, alkylsulfonyl, haloalkylsulfonyl, aryl, aryloxy, or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

*EP 500 989 (Mollner et al ) discloses ACE inhibitors of* Formula (0 1 5)



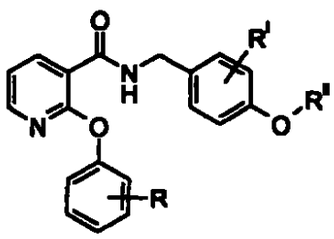
(0 1 5)

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)

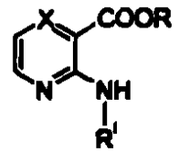
FR 2 140 772 (Anes) discloses compounds asserted to have utility as analgesics, tranquilizers, antipyretics, anti-inflammatories, and antirheumatics, of Formula (0 1 7)



(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).

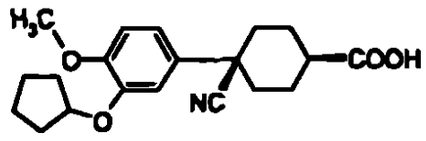


(0 1.8)

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

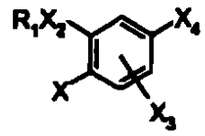
With regard to the disclosures of the above-identified patents and published patent applications, it will be appreciated that only the disclosure of WO 98/45268 (Marfat *et al*) concerns the inhibition of PDE4 isozymes The state of the art also contains information regarding compounds wholly dissimilar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



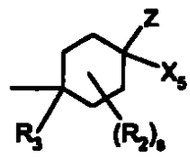
ARIFLO®
cis-[4-cyano-4-(3-cyclopentyl-oxy-4-methoxyphenyl)cyclo-hexane-1-carboxylic acid (0 1 9)

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)

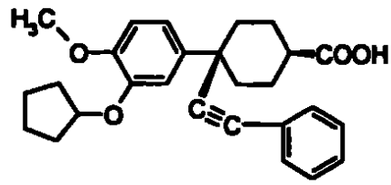
where $R_1$ = -$(CR_4R_5)_rR_6$ where r = 0 and $R_6$ = $C_{3-6}$ cycloalkyl, X = $YR_2$ where Y = O and $R_2$ = -$CH_3$, $X_2$ = O, $X_3$ = H, and $X_4$ = a moiety of partial Formula (0 1 10 1)



(0 1 10 1)

where $X_5$ = H, s = 0, $R_1$ and $R_2$ = CN, and E = 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.

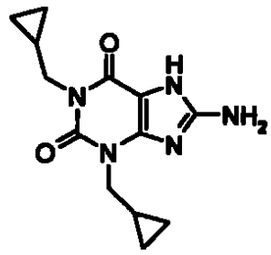
US 5,863,926 (Christensen *et al* ) discloses analogs of the ARIFLO® compound, *e g* , that of Formula (0 1 11)



(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

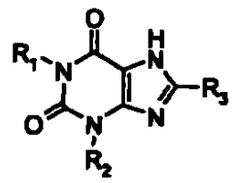
WO 99/20625 (Eggleston) discloses crystalline polymorphic forms of cipamfylline for treatment of $PDE_4$ and TNF mediated diseases, of Formula (0 1 12)



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)



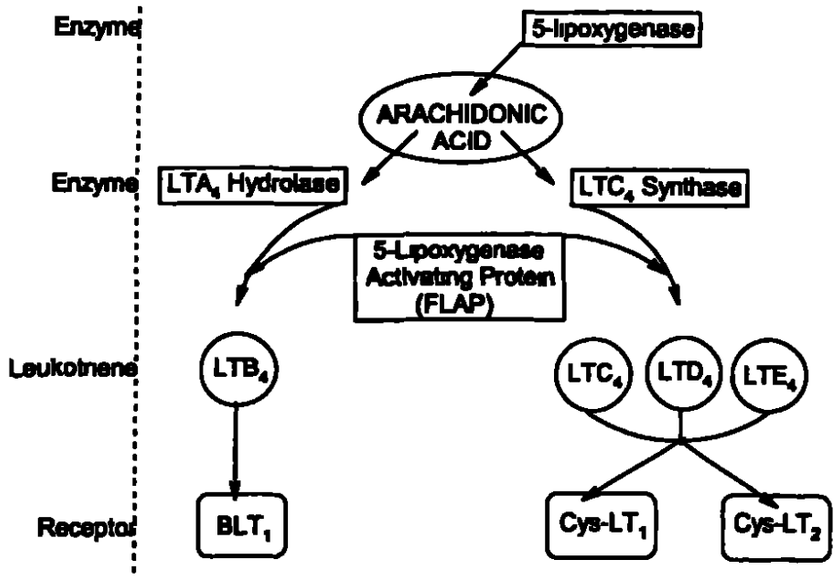
(0 1 13)

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

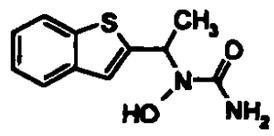
With regard to the disclosures of the above-identified patents and published patent applications, it will be appreciated that the compounds involved possess the same biological activity as the compounds of Formula (1 0 0) At the same time, however, the artisan will observe that the chemical structures 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)

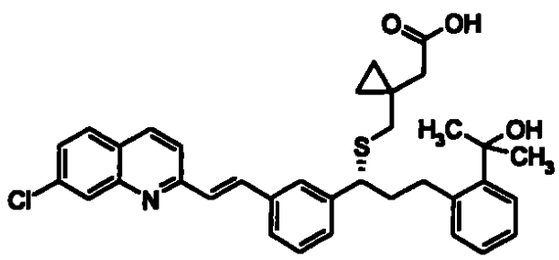
Another such agent is the $LTD_4$ receptor antagonist zafirlukast, a therapeutic agent identified as ACCOLATE® which may be represented by Formula (0 1 15)



ACCOLATE®

Zafirlukast (0 1 15)

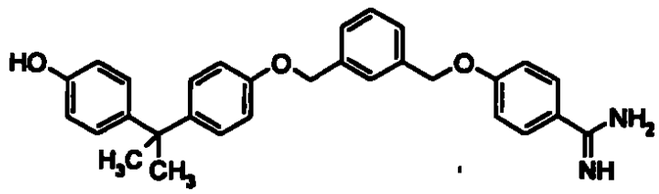
A further such $LTD_4$ receptor antagonist is montelukast, a therapeutic agent identified as SINGULAIR® which may be represented by Formula (0 1 16)



SINGULAIR®

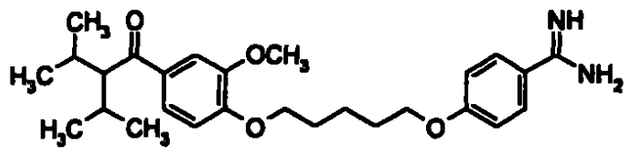
Montelukast (0 1 16)

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)



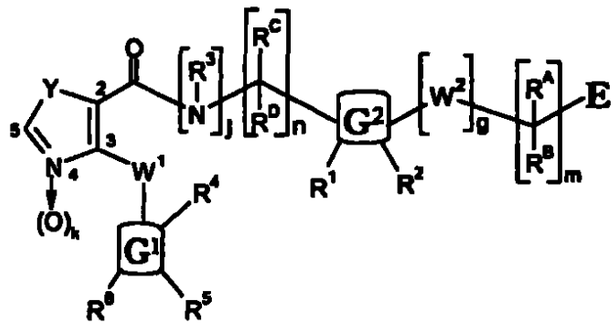
CGS-25019c (0 1 18)

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, 2, or 3,

-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 $-CR^{29}R^{30}-$,

— 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 $-S(=O)_t-$, where t is 0, 1, or 2, –O–, $-[N\Rightarrow(O)_k]-$ or $-N(R^3)-$, where k is 0 or 1 and $R^3$ has the same meaning as defined below; or $-CH(R^1{}_a)-$, where $R^1{}_a$ has the same meaning as defined below;

— 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 —

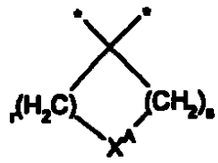
—$R^{11}$ is –F, –Cl, $-CF_3$, –CN, $-NO_2$, –OH, $-(C_1-C_3)$ alkoxy; $-(C_1-C_3)$ alkyl, or $-NR^{16}R^{17}$,

— 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 $G^2$ 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 $G^1$ as defined below; and $R^4$, $R^5$ and $R^6$ are each a member independently selected from the group consisting of

— the following —

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

— where —

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

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

— and —

*-(c)* an aryl or heterocyclyl moiety selected from the group consisting of phenyl, benzyl, furanyl, tetrahydrofuranyl, oxetanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolidinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, pyrazolyl, pyrazolidinyl, oxadiazolyl, thiadiazolyl, imidazolyl, imidazolidinyl,

pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pipendinyl, 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, $-C(=O)R^{16}$, $-OR^{16}$, $-(C_1-C_4)$ 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 —

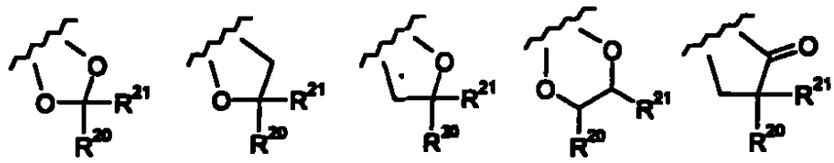
$-R^{12}$ is a member independently selected from the group consisting of –F, –Cl, $-CO_2R^{16}$, $-OR^{16}$, –CN, $-C(=O)NR^{16}R^{19}$, $-NR^{16}R^{19}$, $-NR^{16}C(=O)R^{19}$, $-NR^{16}C(=O)OR^{19}$, $-NR^{16}S(=O)_pR^{19}$, $-S(=O)_pNR^{16}R^{19}$, where p is 1 or 2, $-(C_1-C_4)$ alkyl, and $-(C_1-C_4)$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

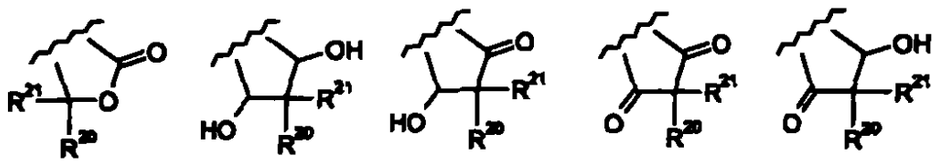
$-R^{18}$ and $R^{19}$ are independently selected from the group consisting of –H, $-(C_1-C_4)$ alkyl, and phenyl, where said alkyl or phenyl is substituted by 0-3 of –F, or –Cl,

— or in the case where $G^1$ is phenyl —

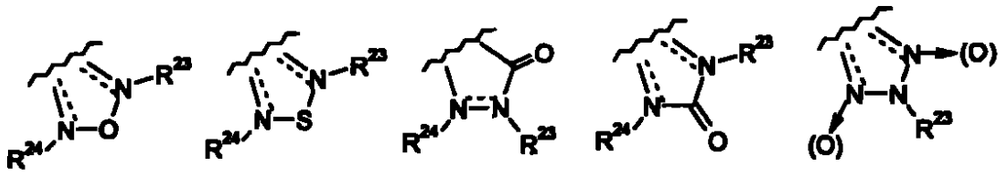
-(d) $R^5$ and $R^6$ are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1 3 1) through (1 3 15)



(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,

-$G^1$ 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 $G^1$ is not a discontinuous or restricted biaryl moiety as defined under $G^2$ 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 $G^1$ is substituted on any ring or rings thereof by $R^4$, $R^5$ and $R^6$, which have the same meaning as defined above,

$-G^2$ is 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, or that is a 7- to 18-membered discontinuous or restricted biaryl moiety, wherein for each of the carbon ring systems recited, 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,

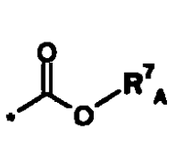
— wherein —

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

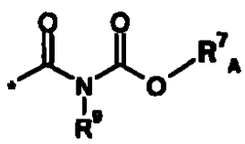
$-E$ is a member independently selected from the group consisting of

— the following —

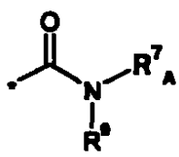
*-(a)* *the group consisting of partial Formulas (1 1 1) through (1 1 15)*



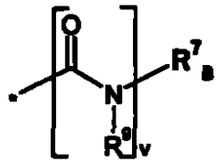
(1 1 1)



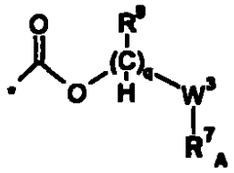
(1 1.2)



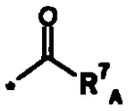
(1 1.3)



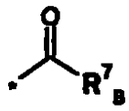
(1 1 4)



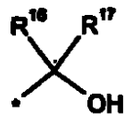
(1 1 5)



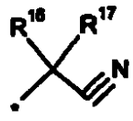
(1 1 6)



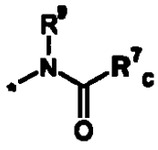
(1 1 7)



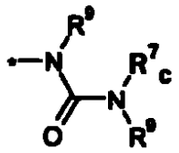
(1 1 8)



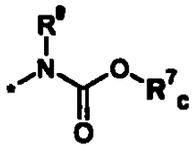
(1 1 9)



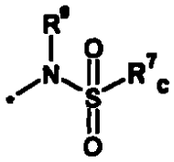
(1 1 10)



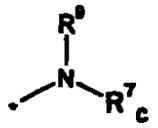
(1 1 11)



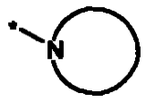
(1 1 12)



(1 1 13)



(1 1 14)



(1 1 15)

— wherein —

where $R^{16}$ and $R^{17}$ have the same meanings as defined above, and $R^8$ 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, $R^8$ has the meaning of –H in at least one instance, or two instances, respectively;

–v 0 or 1,

–$W^3$ is —O—, —$N(R^8)$—, where $R^8$ 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, benzyl, or pyridyl, where said phenyl, benzyl, or pyridyl 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,

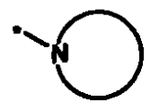
— where —

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 $\mathbb{E}$ is further selected from —

*-(b)* a moiety comprising a member selected from the group consisting of -O-P(=O)(OH)$_2$ (phosphono), –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 (sulfuno), –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$$R^{25}$, -C(=O)NHS(=O)$_2$$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^{28}$,

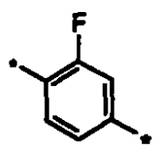
— where —

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

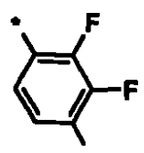
— or —

a pharmaceutically acceptable salt thereof

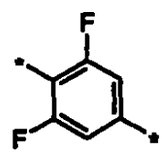
The present invention is concerned in particular with a compound of Formula (1 0 0) as above-recited wherein the group $G^2$ and the substituents $R^1$ and $R^2$ attached thereto are selected in such a way that the resulting portion of a compound of Formula (1 0 0) is represented by partial Formulas (2 5 1) through (2 5 50)



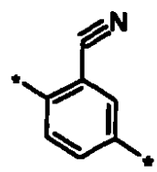

(2 5 1)



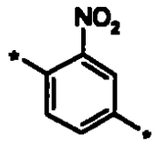

(2 5 2)



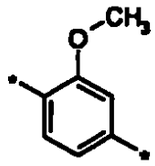

(2 5 3)



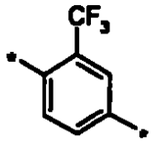

(2 5.4)



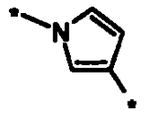

(2 5 5)



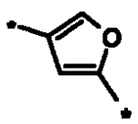

(2 5 6)



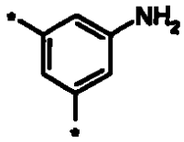

(2 5 7)



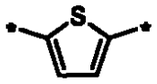

(2 5 8)



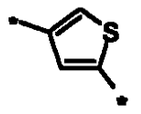

(2 5 9)



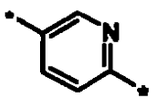

(2 5 10)



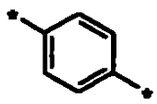

(2 5 11)



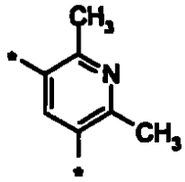

(2 5 12)



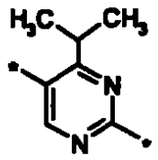

(2 5 13)



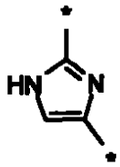
(2 5 14)



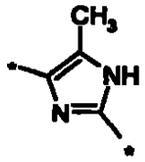

(2 5 15)



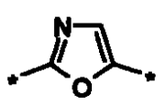

(2 5 16)



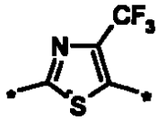

(2 5 17)




(2 5 18)




(2 5 19)



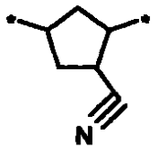

(2 5 20)



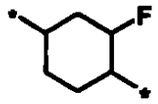
(2 5.21)



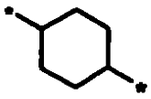
(2 5 22)



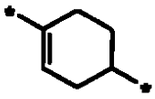

(2 5.23)



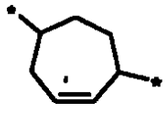

(2 5 24)



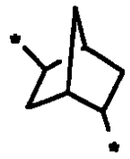
(2 5.25)



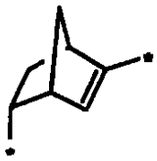
(2 5 26)



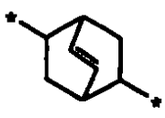
(2 5 27)



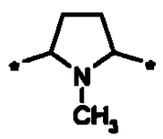
(2 5 28)



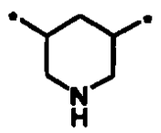
(2 5.29)



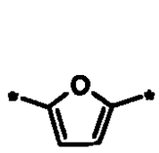
(2 5 30)



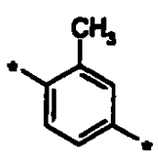

(2 5 31)



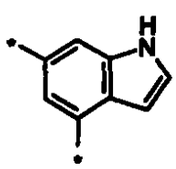

(2 5 32)



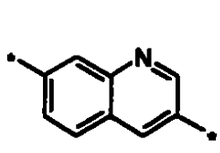
(2 5 33)



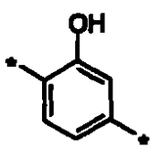
(2 5 34)



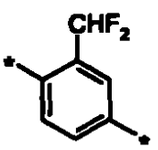
(2 5 35)



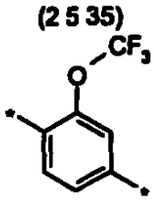
(2 5 36)



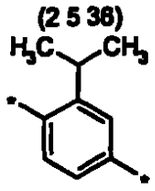
(2 5 37)



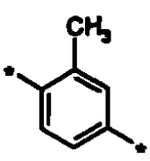
(2 5 38)



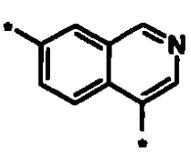
(2 5 39)



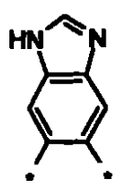
(2 5.40)



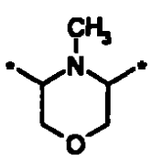
(2 5 41)



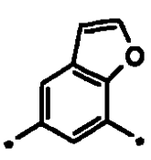
(2 5 42)



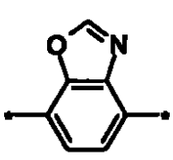
(2 5 43)



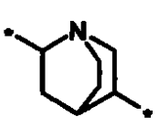
(2 5 44)



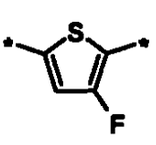
(2 5 45)



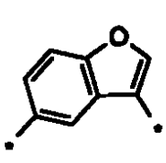
(2 5 46)



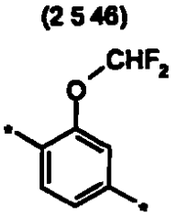
(2 5 47)



(2 5 48)



(2 5.49)

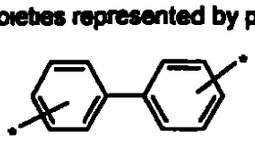


(2 5 50)

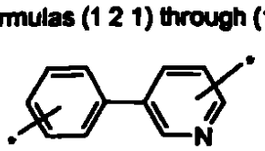
The present invention is also concerned with a compound of Formula (1 0 0) as above-recited wherein the group $G^2$ is a 7- to 18-membered discontinuous or restricted biaryl moiety comprising a member selected from the group consisting of

– the following –

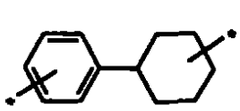
-moieties represented by partial Formulas (1 2 1) through (1 2 32)



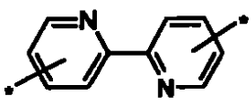
(1 2 1)



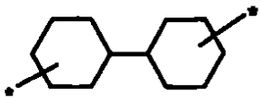
(1 2.2)



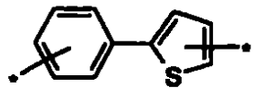
(1.2 3)



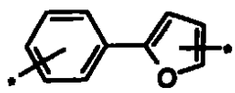
(1 2 4)



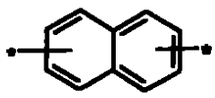
(1 2 5)



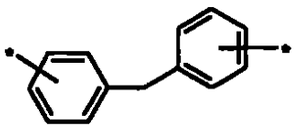
(1.2 6)



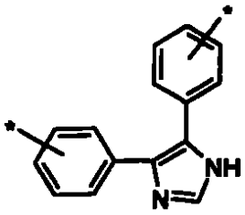
(1 2 7)



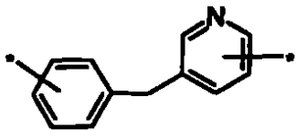
(1.2 8)



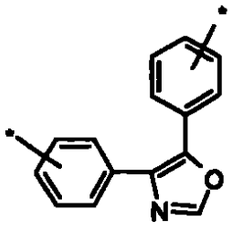
(1.2 9)



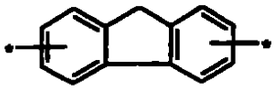
(1 2 10)



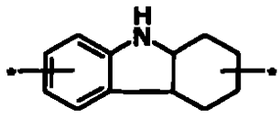
(1 2 11)



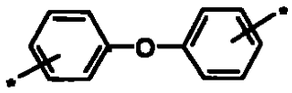
(1 2 12)



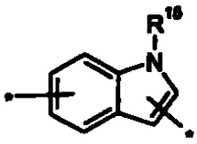
(1 2 13)



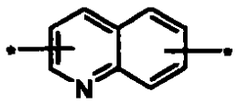
(1.2 14)



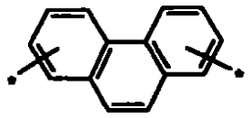
(1.2 15)



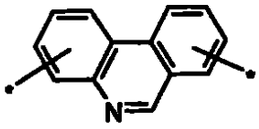
(1 2 16)



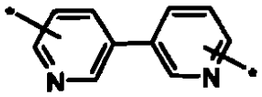
(1 2 17)



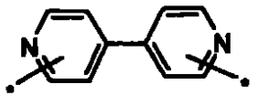
(1 2 18)



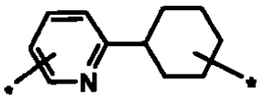
(1 2 19)



(1 2 20)



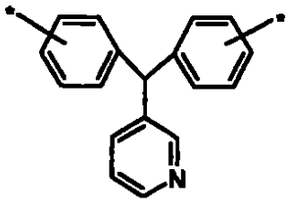
(1.2 21)



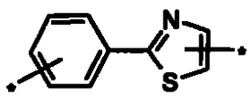
(1 2 22)



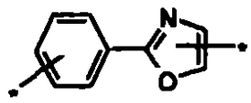
(1.2 23)



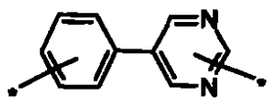
(1 2 24)



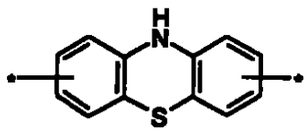
(1 2 25)



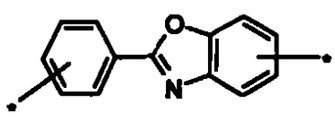
(1 2 26)



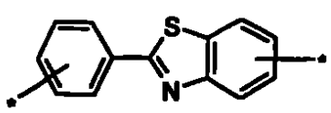
(1 2.27)



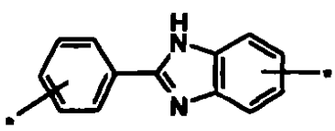
(1.2.28)



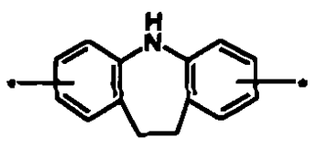
(1 2 29)



(1 2 30)



(1 2 31)

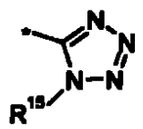


(1.2 32)

wherein " * " is a symbol indicating the two points of attachment of said group $G^2$ to the remaining components of Formula (1 0 0)

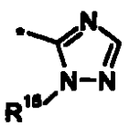
The present invention is concerned in particular with a compound of Formula (1 0 0) as above-recited wherein the terminal group E comprises a member selected from the group consisting of partial Formulas (1 1 1) through (1 1 3), (1 1 5), (1 1 6), and (1 1 10) through (1 1 14), in which a preferred meaning of $R^7_A$ or $R^7_C$ is the meaning hydrogen, methyl, trifluoromethtyl, iso-propyl, phenyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl

The present invention is also concerned with a compound of Formula (1 0 0) in which E 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 32) illustrated below



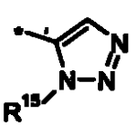
tetrazol-5-yl

(1 4 1)



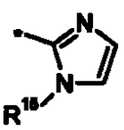
1,2,4-triazol-3-yl

(1 4 2)



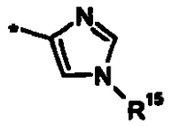
1,2,3-triazol-5-yl

(1 4 3)



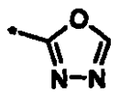
imidazol-2-yl

(1 4 4)



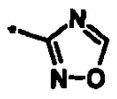
imidazol-4-yl

(1 4 5)



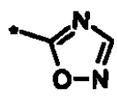
1,3,4-oxadiazolyl

(1 4 6)



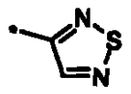
1,2,4-oxadiazol-3-yl

(1.4 7)



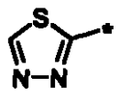
1,2,4-oxadiazol-5-yl

(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)



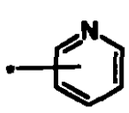
pyrrolyl

(1.4 15)



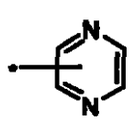
pyrazolyl

(1 4 16)



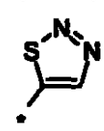
pyridyl

(1 4 17)



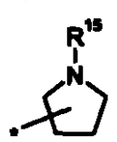
pyrazinyl

(1 4 18)



1,2,3-thiadiazol-5-yl

(1 4 19)



pyrrolidinyl

(1.4 20)



furanyl

(1 4.21)



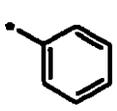
tetrahydrofuranyl

(1.4.22)



thienyl

(1.4.23)



phenyl

(1.4.24)



cyclopropyl

(1 4.25)



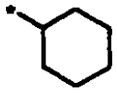
cyclobutyl

(1 4.26)



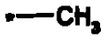
cyclopentyl

(1 4 27)



cyclohexyl

(1 4.28)



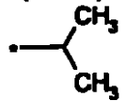
methyl

(1 4.29)



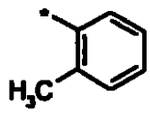
trifluoromethyl

(1 4 30)



*iso*-propyl

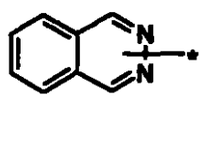
(1 4 31)



*o*-tolyl

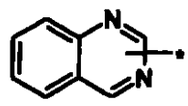
(1 4 32)

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 $R^{15}$



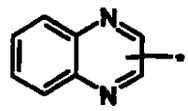
phthalazinyl

(1 5.21)



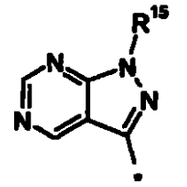
quinazolinyl

(1 5 22)



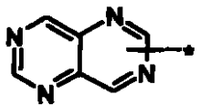
quinoxalinyl

(1 5.23)



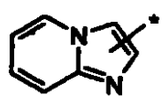
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(1 5 24)



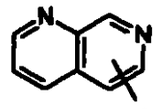
pyrimido[5,4-*d*]-pyrimidinyl

(1 5 25)



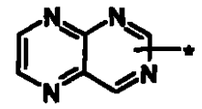
imidazo-[1,2-*a*]-pyridinyl

(1 5.26)



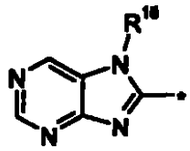
1,7-naphthyridinyl

(1 5 27)



pteridinyl

(1 5.28)

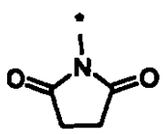


1*H*-purinyl

(1 5.29)

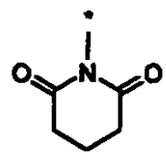
where "*" indicates the point of attachment to the remaining portion of Formula (1 0 0), and where each carbon atom is optionally substituted by a substituent $R^{14}$, and where $R^{14}$ and $R^{15}$ have the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms, thereof

The present invention is also concerned with a compound of Formula (1 0 0) wherein the terminal group E 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 E comprises a member selected from the group consisting of partial Formulas (1 7 1) through (1 7 46)



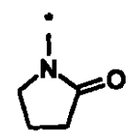
succinimid-1-yl

(1 7 1)



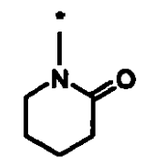
glutarimid-1-yl

(1 7.2)



pyrrolidin-2-on-1-yl

(1 7 3)

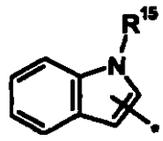


piperid-2-on-1-yl

(1 7.4)

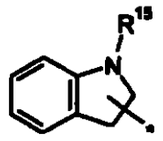
have the same meaning as defined above, and all tautomer forms, and optionally N-oxide forms, thereof

The present invention is further concerned in particular with a compound of Formula (1 0.0) as above-recited wherein the terminal group E comprises partial Formulas (1 1 4) and (1 1 10) through (1 1 14), and wherein preferred meanings of $R^7a$ and $R^7c$ 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)



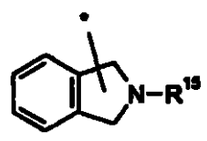
indolyl

(1 5 1)



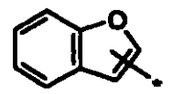
indolinyl

(1 5 2)



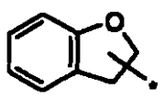
isoindolinyl

(1 5 3)



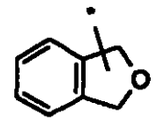
benzo[*b*]furanyl

(1 5.4)



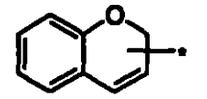
2,3-dihydrobenzo-furanyl

(1 5 5)



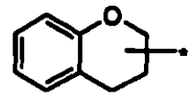
1,3-dihydroisobenzo-furanyl, phthalanyl

(1 5 6)



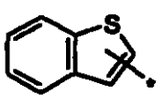
2*H*-1-benzopyranyl

(1 5 7)



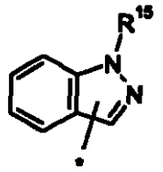
chromanyl

(1 5 8)



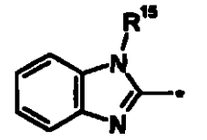
benzothienyl

(1 5 9)



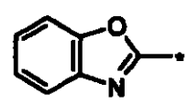
1*H*-indazolyl

(1 5 10)



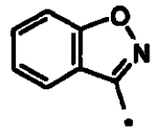
benzimidazolyl

(1 5 11)



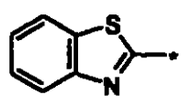
benzoxazolyl

(1 5 12)



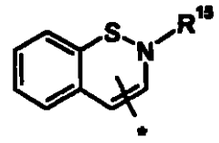
benzisoxazolyl

(1 5 13)



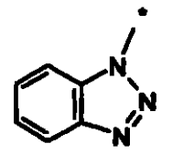
benzothiazolyl

(1 5 14)



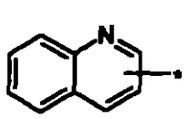
2H-1,2-benzothiazinyl

(1 5 15)



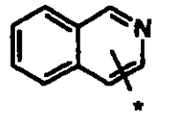
benzotriazolyl

(1 5 16)



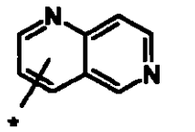
quinolinyl

(1 5 17)



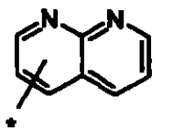
isoquinolinyl

(1 5 18)



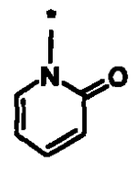
1,6-naphthyridinyl

(1 5 19)



1,8-naphthyridinyl

(1 5 20)



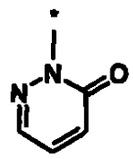
pyrid-2-on-1-yl

(1 7 5)



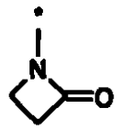
pyrid-4-on-1-yl

(1 7 6)



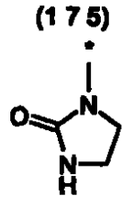
pyridazin-3-on-2-yl

(1 7 7)



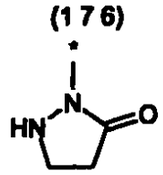
azetidin-2-on-1-yl

(1 7.8)



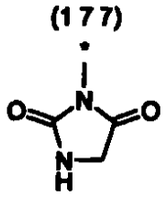
imidazolidin-2-on-1-yl

(1 7 9)



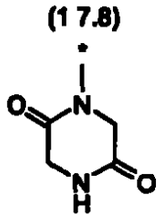
pyrazol-5-on-1-yl

(1 7 10)



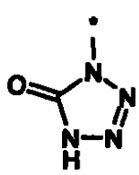
imidazolidin-2,4-dion-1-yl

(1 7 11)



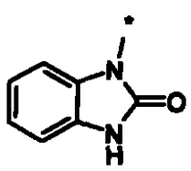
piperazin-2,5-dion-1-yl

(1 7 12)



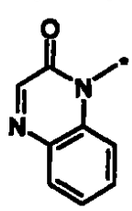
4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl

(1 7 13)



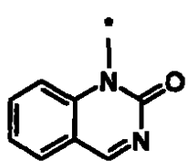
benzimidazolin-2-on-1-yl

(1 7 14)



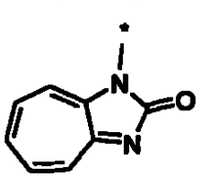
1*H*-quinoxalin-2-on-1-yl

(1 7 15)



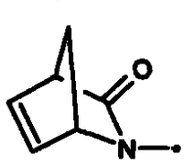
1*H*-quinazolin-2-on-1-yl

(1 7 16)



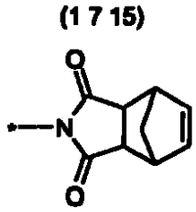
1H-cycloheptimidazol-2-on-1-yl

(1 7 17)



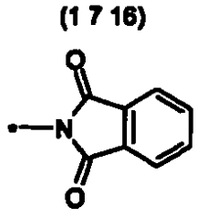
2-azabicyclo[2.2 1]-hept-5-en-3-on-1-yl

(1 7 18)



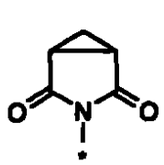
norborn-5-en-2,3-dicarboximid-1-yl

(1 7 19)



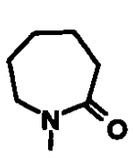
phthalimid-1-yl, 1*H*-isoindole-1,3(2*H*)-dion-1-yl

(1 7.20)



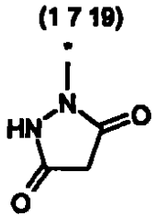
3-azabicyclo[3 1 0]-hexane-2,4-dion-3-yl

(1 7 21)



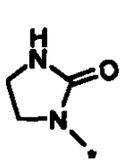
2*H*-azepin-2-on-1-yl

(1 7.22)



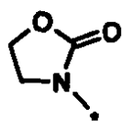
pyrazolidin-3,5-dion-1-yl

(1 7 23)



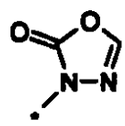
imidazolidin-2-on-1-yl

(1 7 24)



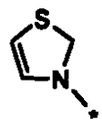
oxazolidin-2-on-1-yl

(1 7 25)



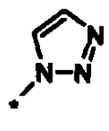
1,3,4-oxadiazol-2(3*H*)-on-3-yl

(1 7.26)



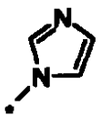
thiazol-3-yl

(1 7.27)



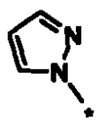
1*H*-1,2,3-triazol-1-yl

(1 7.28)



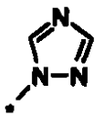
imidazol-1-yl

(1 7 29)



pyrazol-1-yl

(1 7 30)



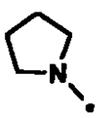
1*H*-1,2,4-triazol-1-yl

(1 7 31)



azetidin-1-yl

(1 7 32)



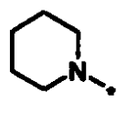
pyrrolidin-1-yl

(1 7.33)



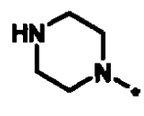
tetrazol-1-yl

(1 7 34)



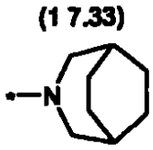
piperidin-1-yl

(1 7 35)



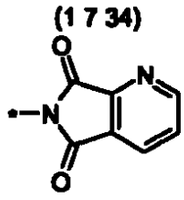
piperazin-1-yl

(1 7 36)



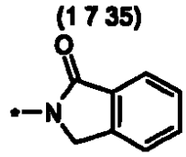
3-azabicyclo[3.2.2]-non-3-yl

(1 7 37)



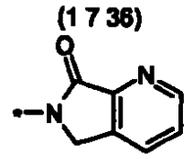
pyrrolo[3,4-*b*]pyridin-5,7-dion-6-yl

(1 7 38)



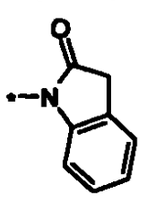
2,3-dihydro-*iso*-indol-1-on-2-yl

(1 7 39)



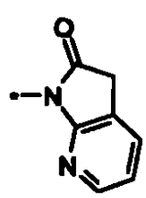
pyrrolo[3,4-*b*]pyridin-7-on-6-yl

(1 7 40)



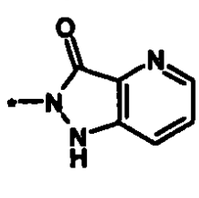
1,3-dihydro-indol-2-on-1-yl

(1 7 41)



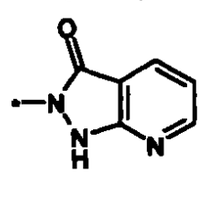
pyrrolo[4,5-*b*]pyridin-3-on-2-yl

(1 7 42)



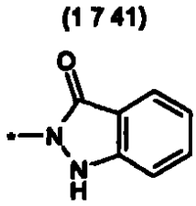
1*H*-pyrazolo[4,5-*e*]pyridin-7-on-2-yl

(1 7 43)



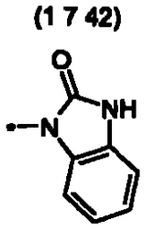
1*H*-pyrazolo[4,5-*b*]pyridin-4-on-2-yl

(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 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, urticarogenic 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 chororetinitis,

– 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, sarcordosis, 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*, Polymyxin 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

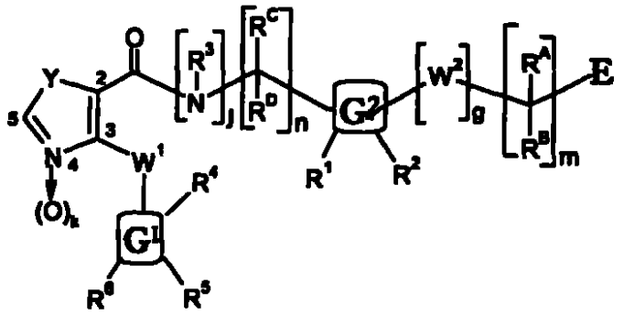
In particular, the compounds of Formula (1 0 0) are useful int the treatment of (1) inflammatory diseases and conditions comprising joint inflammation, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, inflammatory bowel disease, ulcerative colitis, chronic glomerulonephritis, dermatitis, 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

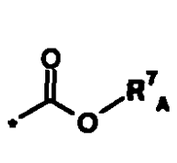
The present invention is concerned with novel compounds which may be represented by Formula (1 0 0) as follows



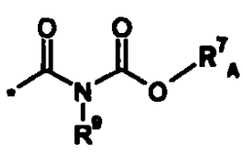
(1 0 0)

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

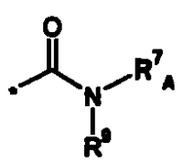
The meaning of the terminal moiety E set forth in detail above is that of a member independently selected from the group consisting of partial Formulas (1 1 1) through (1 1 15)



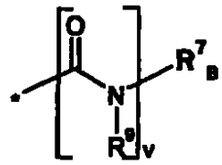
(1 1 1)



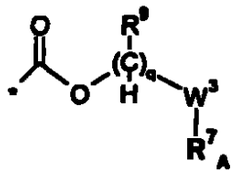
(1 1 2)



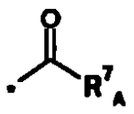
(1 1 3)



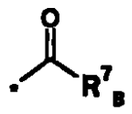
(1 1.4)



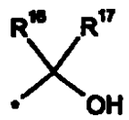
(1 1 5)



(1 1 6)



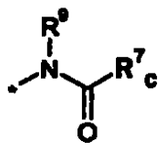
(1 1 7)



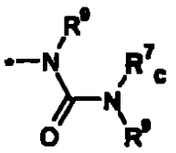
(1 1 8)



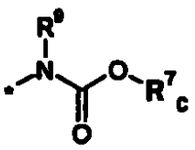
(1 1 9)



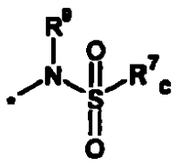
(1 1 10)



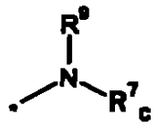
(1 1 11)



(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 "-($C_1$-$C_8$) 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

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

Both $G^1$ and $G^2$ 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 $G^1$ is not permitted to be such a discontinuous carbon ring system The moiety $G^2$ on the other hand, is required to be discontinuous in this situation It is further provided herein that the moiety $G^2$ may have the meaning of a carbon ring system that is discontinuous, or it may have the meaning of a "restricted biaryl" carbon ring system These two aspects 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

Further, however, it should be noted that the moiety $G^2$ may have the meaning of a carbon ring system as defined above that is neither discontinuous nor a restricted biaryl Thus, $G^2$ may be a saturated or unsaturated mono- or polycyclic optionally containing heteroatoms as described above Accordingly, the moiety $G^2$ has the meaning, *e g*, of phenyl, cyclohexyl, or pyridyl The moiety $G^1$ also has this meaning.

The types of restricted biaryl and discontinuous ring systems that may comprise a meaning of $G^2$, but that may not comprise a meaning of $G^1$ 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*-benzoimidazole (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 $G^2$ but may not be a meaning of $G^1$

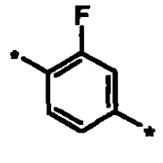
As used herein, the expression "saturated or unsaturated carbon ring system that is 7- to 12-membered, fused or discontinuous, polycyclic" is intended to include such saturated fused bi- and tricyclic carbon ring systems as norbornane, bicyclo[2 2 2]octanyl, bicyclo[3 2 1]octanyl, bicyclo[3 3 0]octanyl, 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 disontinuous bicyclic carbon ring systems as biphenylene

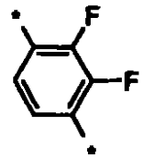
The carbon ring systems included within the scope of the above-quoted expression and described above also include moieties wherein optionally one carbon atom thereof may be replaced by a heteroatom selected from N, O, or S, and where N is selected, optionally a second carbon atom thereof may be replaced by a heteroatom selected from N, O, and S The resulting moieties include pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyridyl, pyrimidinyl, pipendinyl, piperazinyl, imidazolyl, imidazolidinyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, morpholinyl, quinuclidinyl, and azabicyclo[3 3 0]octanyl Both the moiety $G^1$ and the moiety $G^2$ may have these meanings

Preferred compounds of Formula (1 0 0) include those wherein $G^2$ comprises especially a member selected from the group consisting of phenyl, pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl, imidazolyl, imidazolidinyl, oxazolyl, isoxazolyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, morpholinyl, quinuclidinyl, and azabicyclo[3 3 0]octanyl, a monocyclic -($C_5$-$C_7$) cycloalkyl moiety; a monocyclic -($C_5$-$C_7$) cycloalkenyl moiety that is a member selected from the group consisting of cyclopentanyl, cyclohexanyl, and cycloheptenyl, and a bicyclic -($C_7$-$C_{10}$) cycloalkyl or -($C_7$-$C_{10}$) cycloalkenyl moiety that is a member selected from the group consisting of norbornanyl, norbornenyl, bicyclo[2.2 2]octanyl, bicyclo[3.2 1]octanyl, bicyclo[3 3 0]octanyl, bicyclo[2.2 2]oct-5-enyl, bicyclo[2.2 2]oct-7-enyl, bicyclo[3 3 1]nonanyl, cyclodecanyl, and adamantanyl

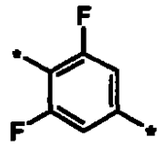
Further preferred embodiments of the compounds of Formula (1 0 0) include those wherein particularly $G^2$ and the substituents $R^1$ and $R^2$ are selected in such a way that this portion of the right-hand terminus of said compound of Formula (1 0 0) is represented by the following partial Formulas (2 5 1) through (2 5 50) set out below



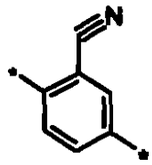
(2 5 1)



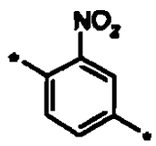
(2 5 2)



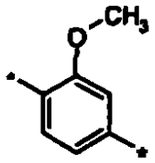
(2 5 3)



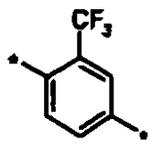
(2 5 4)



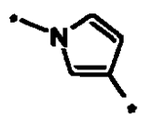

(2 5 5)



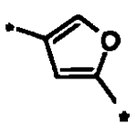

(2 5 6)



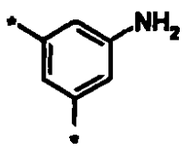

(2 5 7)



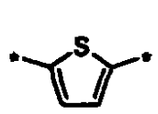

(2 5 8)



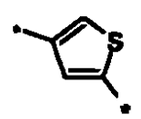

(2 5 9)



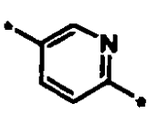

(2 5 10)



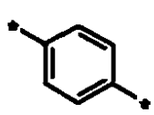

(2 5 11)



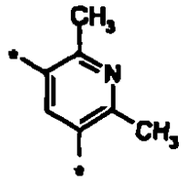

(2 5 12)



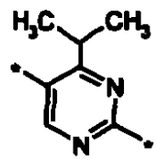

(2 5 13)



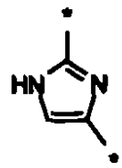
(2 5 14)



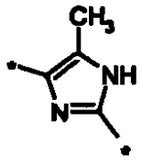

(2 5 15)



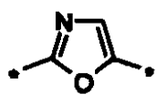

(2 5 16)



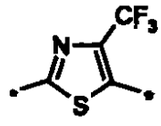

(2 5 17)



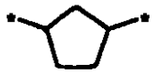

(2 5 18)



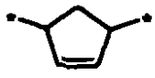

(2 5 19)



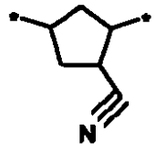

(2 5 20)



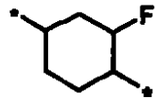
(2 5 21)



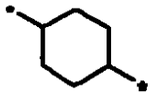
(2 5 22)



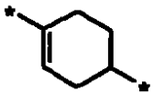

(2 5 23)



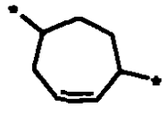

(2 5 24)



(2 5 25)



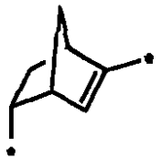
(2 5 26)



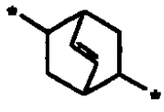
(2 5.27)



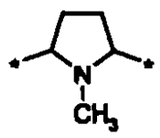
(2 5 28)



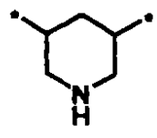
(2 5 29)



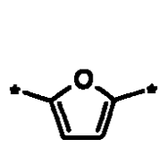
(2 5 30)



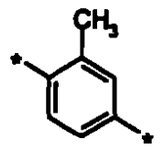

(2 5 31)



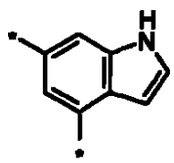

(2 5 32)



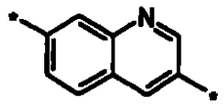
(2 5 33)



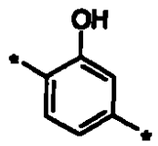
(2 5.34)



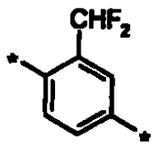
(2 5 35)



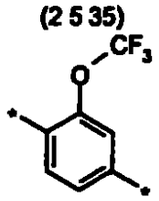
(2 5 36)



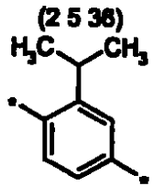
(2 5 37)



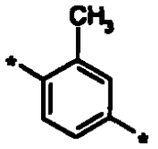
(2 5.38)



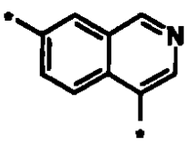
(2 5.39)



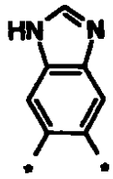
(2 5 40)



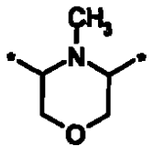
(2 5 41)



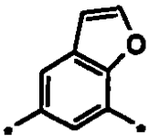
(2 5 42)



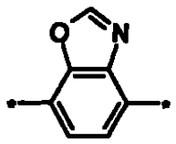
(2.5.43)



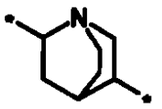
(2 5 44)



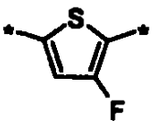
(2 5 45)



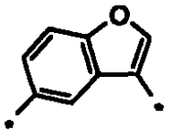
(2 5 46)



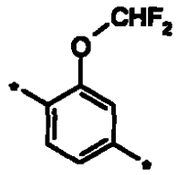
(2 5 47)



(2.5 48)



(2 5 49)



(2 5 50)

Other preferred embodiments of the compouds of Formula (1 0 0) are illustrated in the paragraphs that follow, which recite preferred meanings of various substituents and components of Formula (1 0 0)

(i) Embodiments of the present invention include those that are a compound of Formula (1 0 0) wherein Y is –S–, –O–, –NH–, or $–CH_2–$, ◇◇ $G^1$ is phenyl or pyridyl, ◇◇ $G^2$ is phenyl, cyclopentyl, cyclohexyl, pyridyl, oxadiazolyl, thiadiazolyl, biphenyl, 3-phenyl-pyridine, cyclohexyl-benzene, [2,2']bipyridinyl, or bicyclohexyl, ◇◇ j is 1, ◇◇ m is 0 or 1, ◇◇ n is 1, ◇◇ E 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, (b) $–CH_3$ substituted by 0-3 $R^{10}$ where $R^{10}$ is –F, (c) $-CH_3$ 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 $R^{10}$ is $-NR^{16}R^{17}$ or $-NR^{16}C(=O)R^{17}$ where $R^{16}$ and $R^{17}$ are –H or $-CH_3$, (d) cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, or (e) phenyl, benzyl, or pyridyl 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 $-CH_2CH_3$, ◇◇ $R^B$ 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; ◇◇ $R^A$ 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, –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 Y is –S– or $-CH_2-$, E is a moiety of partial Formulas (1 1 1), (1 1.3), (1 1 6) or (1 1 10), $R^9$ is –H, g is 0 and $W^2$ is absent; $R^A$ 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) where $R^{20}$ and $R^{21}$ are –H or $-CH_3$, or a moiety of partial Formula (1 3 11), (1 3 12), or (1 3 15) where $R^{23}$ and $R^{24}$ are absent or are -H, or $-CH_3$

(iii) Further embodiments of the present invention comprise a compound of Formula (1 0 0) wherein Y is –S–, –O–, –NH–, or $-CH_2-$, ◇◇ $G^1$ is phenyl or pyridyl, ◇◇ $G^2$ is phenyl, cyclopentyl, cyclohexyl, pyridyl, oxadiazolyl, thiadiazolyl, biphenyl, 3-phenyl-pyridine, cyclohexyl-benzene, [2,2']bipyridinyl, or bicyclohexyl, ◇◇ j is 1; ◇◇ m is 0 or 1, ◇◇ n is 1, ◇◇ E is a moiety selected from partial Formula (1 1 4) where $R^7$ 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 $-CH_3$, ◇◇ $R^B$ 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, ◇◇ $R^A$ 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, –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)

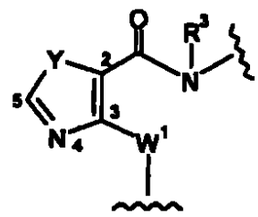
(iv) Preferred embodiments of the type described in the paragraph immediately above are those wherein Y is –S– or –$CH_2$–, $R^9$ is –H, g is 0 and $W^2$ is absent; $R^A$ and $R^B$ are both –H, $R^C$ and $R^D$ are both -H, $R^3$ is –H, $R^4$ is –H, $R^5$ is –H, –F, –Cl, –CN, –$OCH_3$, -C(=O)$CH_3$, or –$NO_2$, $R^6$ 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) where $R^{20}$ and $R^{21}$ are –H or –$CH_3$, or a moiety of partial Formula (1 3 11), (1 3 12), or (1 3 15) where $R^{23}$ and $R^{24}$ are absent or are -H, or -$CH_3$

(v) Further embodiments of the present invention include a compound of Formula (1 0 0) wherein Y is –S–, –O–, –NH–, or –$CH_2$–, ◇◇ $G^1$ is phenyl or pyridyl, ◇◇ $G^2$ is phenyl, cyclopentyl, cyclohexyl, pyridyl, oxadiazolyl, thiadiazolyl, biphenyl, 3-phenyl-pyridine, cyclohexyl-benzene, [2,2']bipyridinyl, or bicyclohexyl, ◇◇ j is 1, ◇◇ m is 0 or 1, ◇◇ n is 1, ◇◇ E 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, ◇◇ $R^A$ 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 - and the other is –H or -$CH_3$, ◇◇ $R^1$ and $R^2$ are –H, –F, or -$OCH_3$, ◇◇ $R^3$ is –H or -$CH_3$, ◇◇ $R^4$, $R^5$ and $R^6$ are -H, –F, –Cl, –$OCH_3$, –CN, -$NO_2$, or -C(=O)$R^3$ or -C(=O)$OR^3$ where R 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 Y is –S– or –$CH_2$–, $R^9$ is –H, g is 0 and $W^2$ is absent; $R^A$ 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 thiazolyl-, oxazolyl-, pyrrolyl-, or imidazolyl-amide of Formula (1 0 1)



(1 0 1)

This portion of the core nucleus is elaborated by defining the Y moiety as being –S(=O)$_t$–, where t is 0, 1, or 2, –O–, -[N⇨(O)$_k$]–, or –N($R^3$)–, where k is 0 or 1 and $R^3$ has the same meaning as defined herein, or –CH($R^1{}_a$)–, where $R^1{}_a$ has the same meaning as defined herein, and further where the symbol ⇨(O) indicates a nitrogen heteroatom in the form of its N-oxide when k is 1 Accordingly, said portion of the core nucleus becomes, respectively, a thiazolyl, oxazolyl, pyrrolyl, or imidazolyl moiety

It has already been pointed out above that in the case of 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 –S(=O)$_t$–, where t is 0, 1, or 2, the compounds of the present invention are thiazolyl-amides that may be present in the form of their sulfinyl or sulfonyl derivatives However, it is preferred that t is 0, and the thiazolyl-amide derivatives are the preferred meaning of Y in the compounds of Formula (1 0 0)

Where Y has the meaning of –O–, the compounds of the present invention are oxazolyl-amides, which are the next most preferred compounds of Formula (1 0 0) after the thiazolyl-amides

Where Y has the meaning of –CH($R^1{}_a$)–, the compounds of the present invention are pyrrolyl-amides, which after the thiazolyl-amides and oxazolyl-amides, are the most preferred compounds of Formula (1 0 0) The substituent $R^1{}_a$ is selected independently from the other substituents that form the compounds of Formula (1 0 0), but it is preferably –H, –F, –$CH_3$, or –$OCH_3$

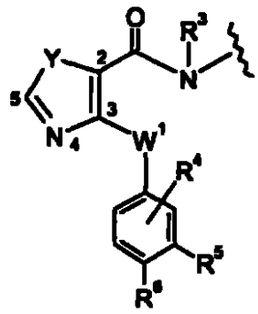
Finally, where Y has the meaning of —[N⇒(O)$_k$]— the compounds of the present invention are imidazolyl-amides It is preferred that k is 0 The imidazolyl-amides are not as preferred as the thiazolyl-amides, oxazolyl-amides, and pyrrolyl-amides of Formuoa (1 0 0) described above

In addition to –H, $R^1_a$ of the –CH($R^1_a$)– moiety is defined as a member selected from the group consisting of –F, –Cl, –CN, –$NO_2$, –($C_1$-$C_4$) alkyl, –($C_2$-$C_4$) alkynyl, fluorinated-($C_1$ -$C_3$) alkyl, fluorinated-($C_1$ -$C_3$) alkoxy; -$OR^{16}$; 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 –CH($R^1_a$)– 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 $G^1$

The thiazolyl- and analogous amide nuclei of the compounds of Formula (1 0 0) where Y is –S–, *etc.*, are characterized by the formation at the 3-position carbon atom of the thiazolyl or analogous ring, of a linkage to a ring system comprising the moiety $G^1$ In preferred embodiments, the moiety $G^1$ 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 Accordingly, where the moiety $G^1$ has the meaning of a phenyl ring, the *para*- ($R^5$), *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 $G^1$ 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, 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

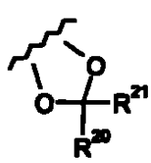
Preferred embodiments of the present invention further include those wherein both $R^5$ and $R^6$ are both –F, wherein $R^5$ is –H and $R^6$ is –F, and wherein $R^6$ is –H and $R^5$ is –F, $-OR^{16}$,

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

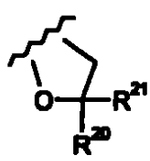
$R^5$ and $R^6$ may also be selected from substituents comprising $-(C_1-C_4)$ alkyl and $-(C_1-C_4)$ alkoxy wherein said alkyl and alkoxy are substituted with 0 to 3 substituents -F or -Cl, or 0 or 1 substituent $(C_1-C_2)$ alkoxycarbonyl–, $(C_1-C_2)$ alkylcarbonyl–, or $(C_1-C_2)$ alkylcarbonyloxy–

**5 2 0 $G^1$ is Phenyl and $R^5$ and $R^6$ Are Taken Together**

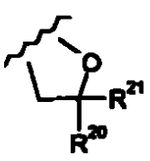
Where the moiety $G^1$ has the preferred meaning of a phenyl ring, $R^5$ and $R^6$ may also be taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1 3 1) through (1 3 15)



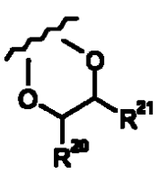
(1 3 1)



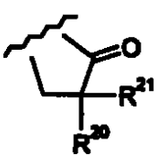
(1 3.2)



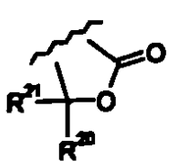
(1 3 3)



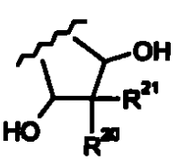
(1 3.4)



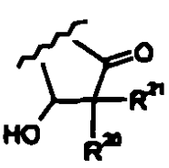
(1 3 5)



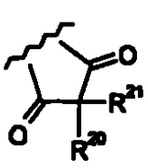
(1 3 6)



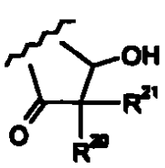
(1 3.7)



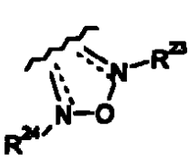
(1 3 8)



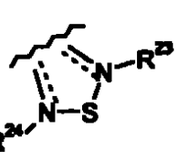
(1 3 9)



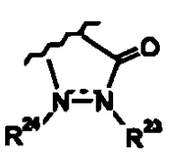
(1 3 10)



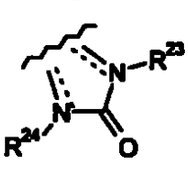
(1 3 11)



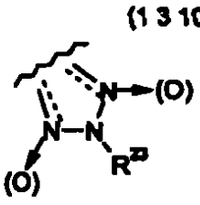
(1 3 12)



(1.3 13)



(1 3 14)

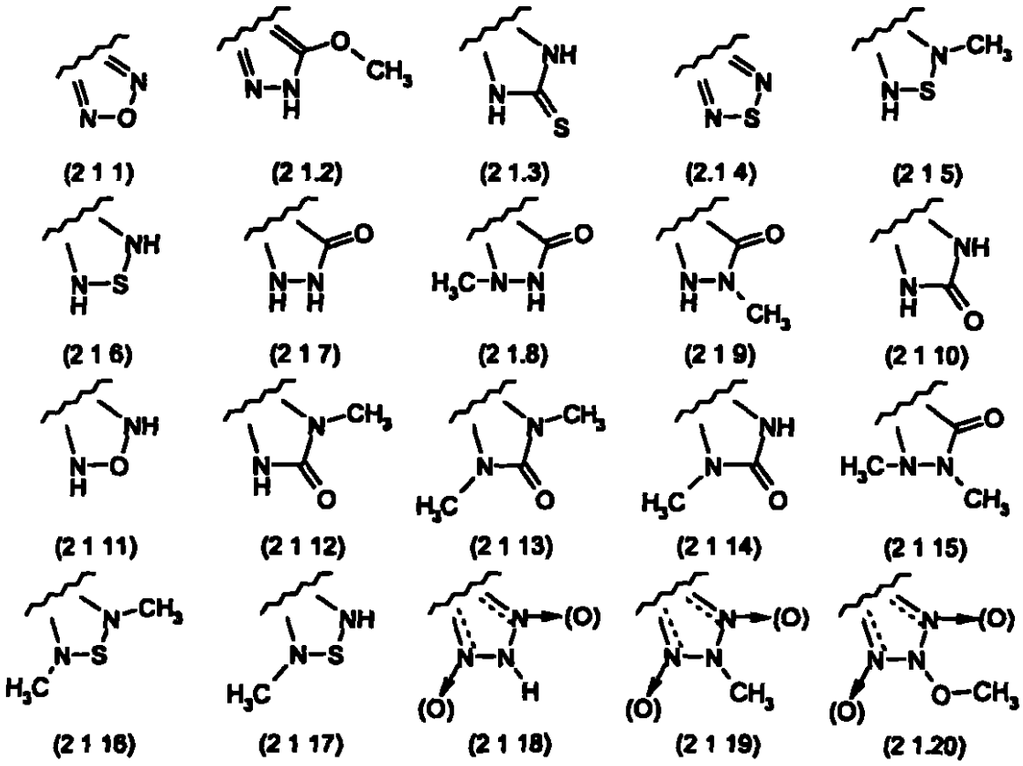


(1 3 15)

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 $-[N(\Rightarrow O)]-$ 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 $G^1$ 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 $G^1$ 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)

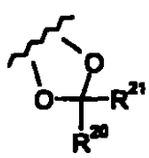
(2 1 16) (2 1 17) (2 1 18) (2 1 19) (2 1.20)

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

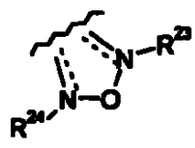
The artisan of ordinary skill in the preparation of organic molecules will appreciate that the compounds of Formula (1 0 0) wherein $R^5$ and $R^6$ are taken together to form moieties of the above-illustrated partial Formulas (2 1 2), (2 1 3), (2 1 7), (2 1 8), (2 1 10), (2 1 12), and (2 1 14) exist 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

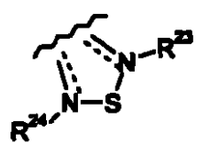
Preferred embodiments of the present invention result directly from the definition of $R^5$ and $R^6$ as taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3 1), (1 3 11), (1 3 12), and (1 3 15)



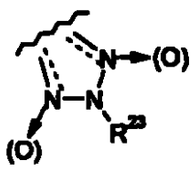
(1 3 1)



(1 3 11)

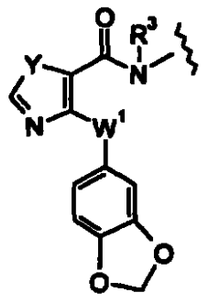


(1 3 12)

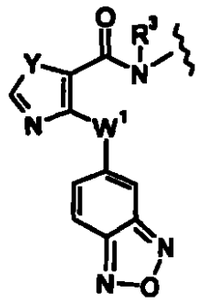


(1.3 15)

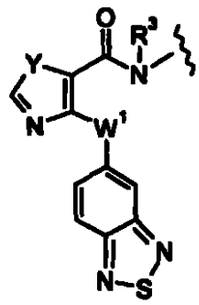
Accordingly, there further results moieties of partial Formulas (1 0 15) through (1.0 18)



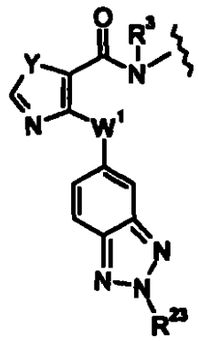
(1 0 15)



(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), $W^1$ has the meaning of –O– whereby an ether linkage is created to attach the benzo-fused, bicyclic heterocycle to the core nucleus described above

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

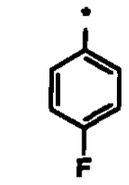
In other embodiments of the compounds of Formula (1 0 0) the substituents $R^{20}$ and $R^{21}$ on the benzo-fused, bicyclic heterocycles represented by partial Formula (1 3 1) are –H, -F, –Cl, $–CH_3$, $–CH_2F$, $–CHF_2$, or $–CF_3$ Preferably, $R^{20}$ and $R^{21}$ are both –H or –F, in which case 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

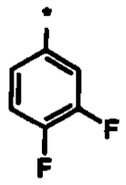
5.2.1 $G^1$ Is Other Than Phenyl

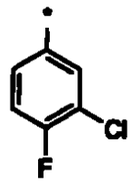
In addition to those embodiments of the present invention where $G^1$ has the preferred meaning of phenyl, the present invention has also been defined above as being concerned with a compound of Formula (1 0 0) wherein $G^1$ has the meaning defined above as a moiety comprising a saturated or unsaturated 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 $G^1$ comprises especially a member selected from the group consisting of pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyridyl, pyrimidinyl, pipendinyl, piperazinyl, imidazolyl, imidazolidinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, quinuclidinyl, and azabicyclo[3 3 0]octanyl, a monocyclic -($C_3$-$C_7$) cycloalkyl moiety; a monocyclic -($C_5$-$C_7$) cycloalkenyl moiety that is a member selected from the group consisting of cyclopentenyl, cyclohexenyl, and cycloheptenyl, and a bicyclic -($C_7$-$C_{10}$) cycloalkyl or -($C_7$-$C_{10}$) cycloalkenyl moiety that is a member selected from the group consisting of norbornanyl, norbornenyl, bicyclo[2 2 2]octanyl, bicyclo[3.2 1]octanyl, bicyclo[3 3 0]octanyl, bicyclo[2 2 2]oct-5-enyl, bicyclo[2 2 2]oct-7-enyl, bicyclo[3 3 1]nonanyl, cyclodecanyl, and adamantanyl

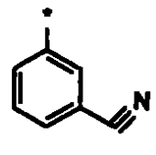
5 2 2 Representative Subgeneric $G^1$ Moieties

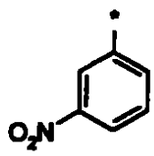
The present invention is still further concerned especially with a compound of Formula (1 0 0) wherein particularly $G^1$ and the substituents $R^4$, $R^5$, and $R^6$ are selected in such a way that the left-hand terminus of said compound of Formula (1 0 0) is represented by the following partial Formulas (2 0 1) through (2 0 72)

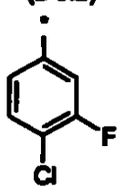

(2 0 1)

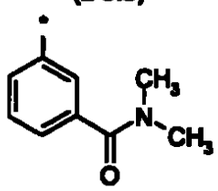

(2 0.2)

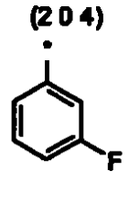

(2 0.3)

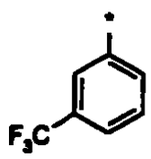

(2 0 4)

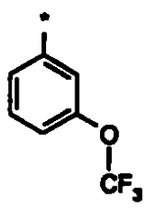

(2 0 5)

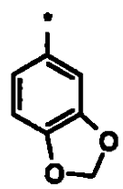

(2 0 6)

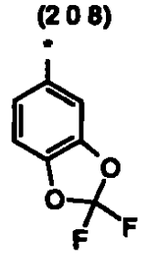

(2 0 7)

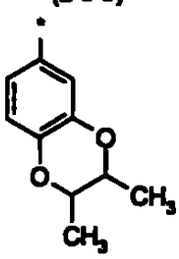

(2 0 8)

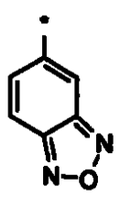

(2 0 9)

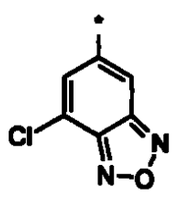

(2 0 10)

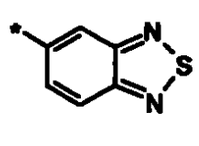

(2 0 11)

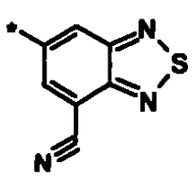

(2 0 12)

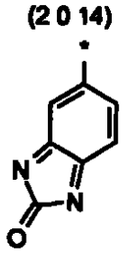

(2 0 13)

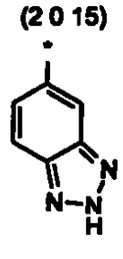

(2 0 14)

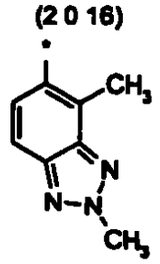

(2 0 15)

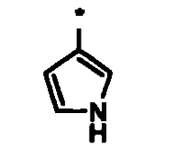

(2 0 16)


(2 0 17)

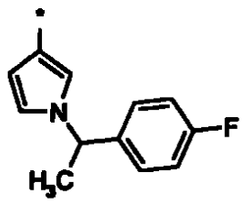

(2 0 18)


(2 0 19)

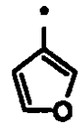

(2 0 20)



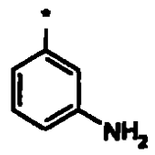
(2 0 21)



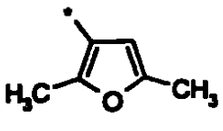
(2 0 22)



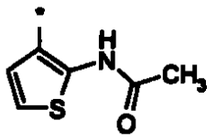
(2 0 23)



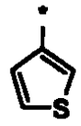
(2 0.24)



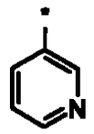
(2 0 25)



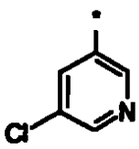
(2 0.26)



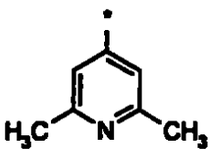
(2 0.27)



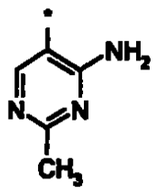
(2 0 28)



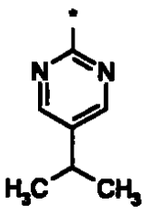
(2 0.29)



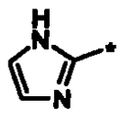
(2 0 30)



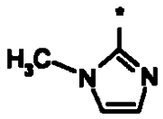
(2 0 31)



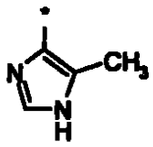
(2 0 32)



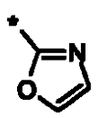
(2 0 33)



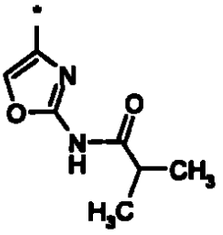
(2 0 34)



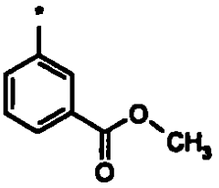
(2 0 35)



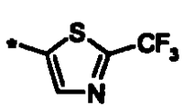
(2 0 36)



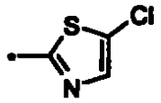
(2 0.37)



(2 0 38)



(2 0 39)



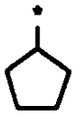
(2 0 40)



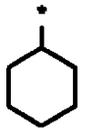
(2 0 41)



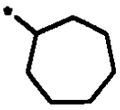
(2 0 42)



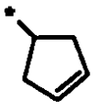
(2 0.43)



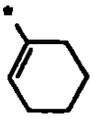
(2 0 44)



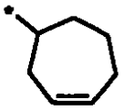
(2 0 45)



(2 0 46)



(2 0 47)



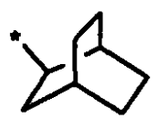
(2 0 48)



(2 0 49)



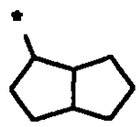
(2 0 50)



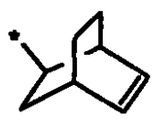
(2 0 51)



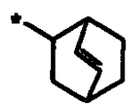
(2 0 52)



(2 0 53)



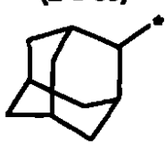
(2 0 54)



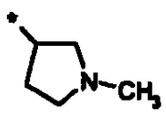
(2 0 55)



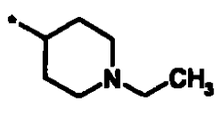
(2 0 56)



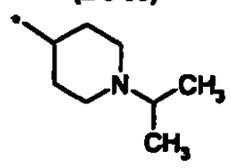
(2 0 57)



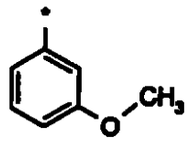
(2 0 58)



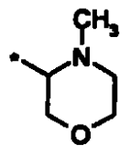
(2 0 59)



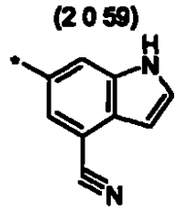
(2 0 60)



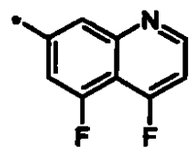
(2 0 61)



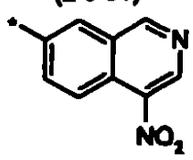
(2 0 62)



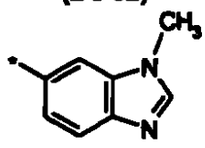
(2 0 63)



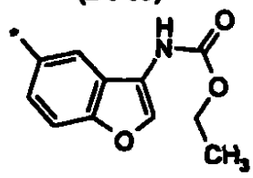
(2 0 64)



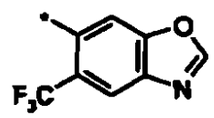
(2 0 65)



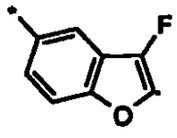
(2 0 66)



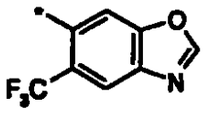
(2 0 67)



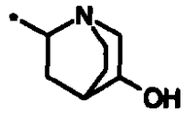
(2 0 68)



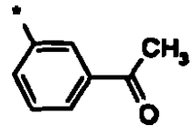
(2 0 69)



(2 0 70)



(2 0 71)

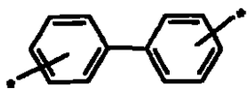


(2 0 72)

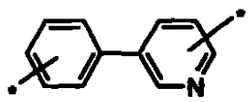
## 5.3 0 The $G^2$ Moiety

The moiety $G^2$ is one of the key features of the compounds of Formula (1 0 0) and is preferably phenyl, but may also be 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 $G^2$ thus comprise 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-

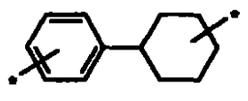
diphenyl-1H-imidazole (1.2 10), 3-benzyl-pyridine (1 2 11), 4,5-diphenyl-oxazole (1.2 12), fluorene (1 2 13), 9*H*-carbazole (1 2 14), phenyl ether (1 2 15), 1*H*-indole (1 2 16), quinoline (1.2 17), phenanthrene (1 2 18), phenanthridine (1 2 19), [3,3']bipyridinyl (1 2 20); [4,4']bipyridinyl (1.2.21), 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), where the numbers in parentheses refer to the corresponding partial Formulas 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



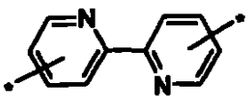
(1.2 1)



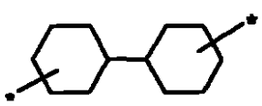
(1.2.2)



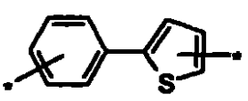
(1 2 3)



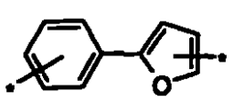
(1 2.4)



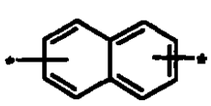
(1 2 5)



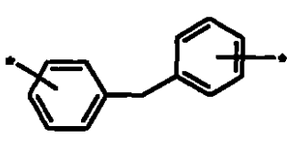
(1.2 6)



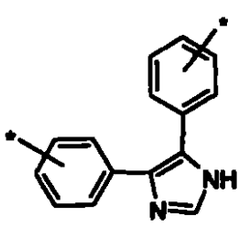
(1 2 7)



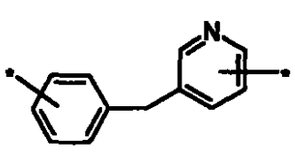
(1 2 8)



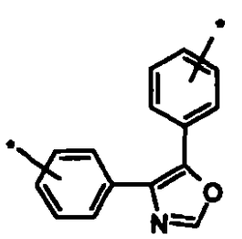
(1 2 9)



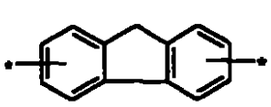
(1 2 10)



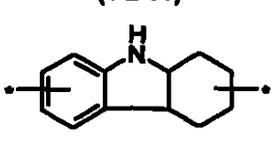
(1 2 11)



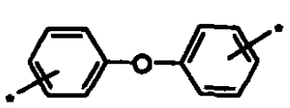
(1.2 12)



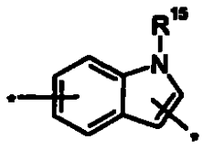
(1.2 13)



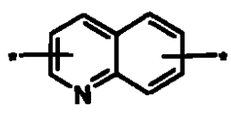
(1 2 14)



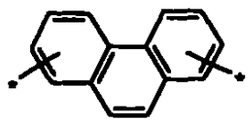
(1.2 15)



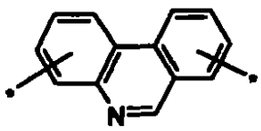
(1.2 16)



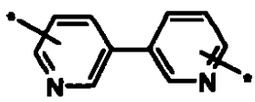
(1 2 17)



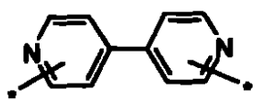
(1 2 18)



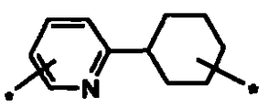
(1.2 19)



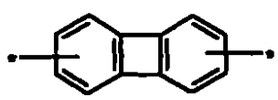
(1.2 20)



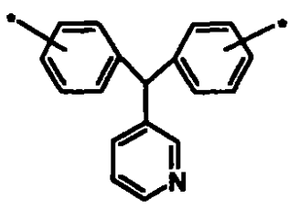
(1.2.21)



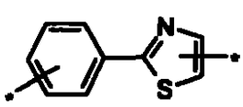
(1.2 22)



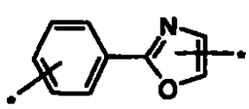
(1.2 23)



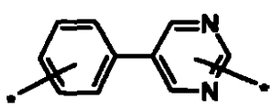
(1.2.24)



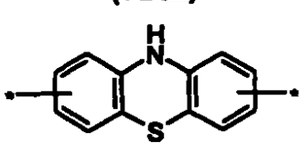
(1 2 25)



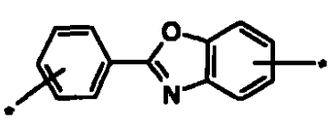
(1 2.26)



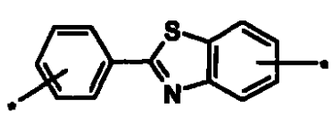
(1.2 27)



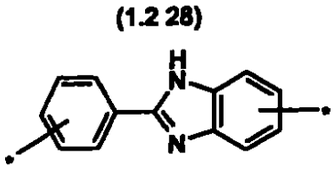
(1.2 28)



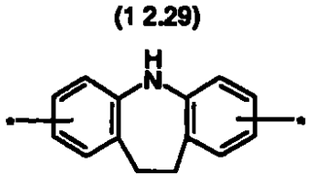
(1 2.29)



(1 2.30)



(1 2 31)



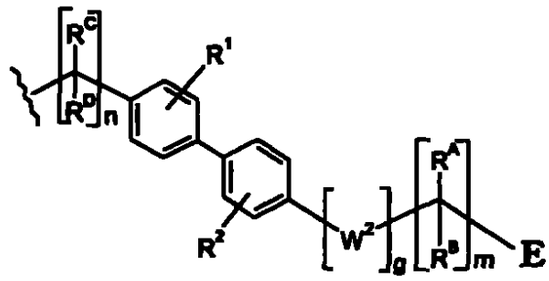
(1.2.32)

The above-illustrated groups of partial Formulas (1 2 1) through (1.2 39) which define the moiety $G^2$ 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 39) which define $G^2$ $R^1$ 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, –$NO_2$, –$C(=O)NR^{12}R^{13}$, –$OC(=O)NR^{15}R^{12}$, –$NR^{14}C(=)NR^{15}R^{12}$; –$NR^{14}C(=NR^{14})NR^{15}R^{12}$, –$NR^{14}C(=NCN)NR^{15}R^{12}$, –$NR^{14}C(=N\text{-}NO_2)NR^{15}R^{12}$, –$C(=NR^{14})NR^{15}R^{12}$, –$OC(=NR^{14})NR^{15}R^{12}$; –$OC(=N\text{–}NO_2)NR^{15}R^{12}$,

$-NR^{15}R^{12}$, $-CH_2NR^{15}R^{12}$, $-NR^{14}C(=O)R^{12}$, $-NR^{14}C(=O)OR^{12}$, $=NOR^{12}$, $-NR^{14}S(=O)_pR^{13}$, 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 $G^2$ Is Biphenyl Substituted by $R^1$ and $R^2$

The left-hand-side of a compound of Formula (1 0 0) has thiazolyl- and analogous amide nuclei 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 embodiments where $G^2$ has the 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, and the biphenyl group is substituted in the 4-position by the moiety containing the substituents $R^A$, $R^B$, and E. This preferred right-hand-side of the compound of Formula (1 0 0) may be represented by Formula (1 0 4)

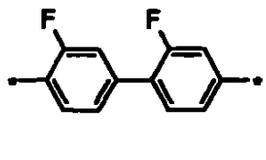


(1 0 4)

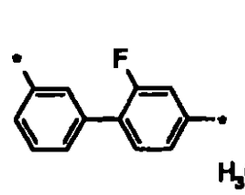
Where $R^1$ and/or $R^2$ is –H, there will be no substituent at any position attached to the remainder of the left-hand side of the molecule of Formula (1 0 0) Such embodiments are not as preferred as those compounds of the present invention which have a substituent, especially a substituent at the 2-position 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

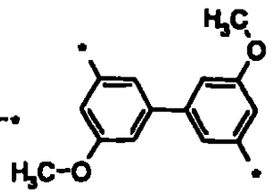
Accordingly, embodiments of the present invention in which the moiety $G^2$ is biphenyl substituted by $R^1$ and optionally $R^2$ include those represented by partial Formulas (2 6 1) through (2 6 12)



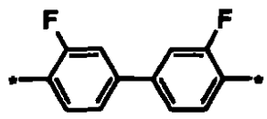
(2 6 1)



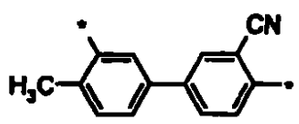
(2 6.2)



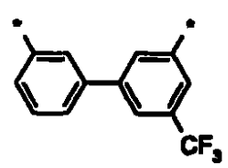
(2 6.3)



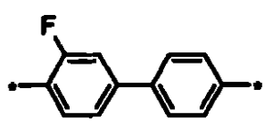
(2 6 4)



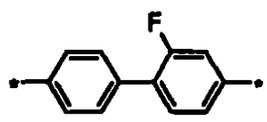
(2 6 5)



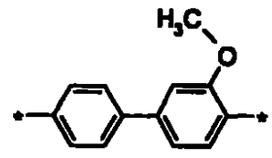
(2 6 6)



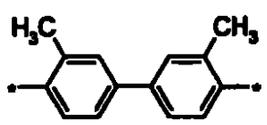
(2 6 7)



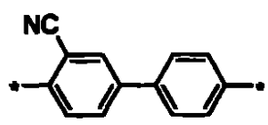
(2 6.8)



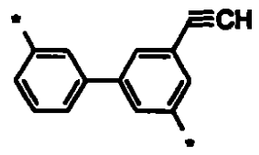
(2 6 9)



(2 6 10)



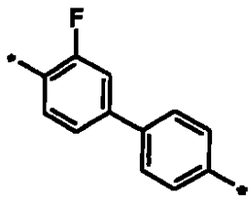
(2 6 11)



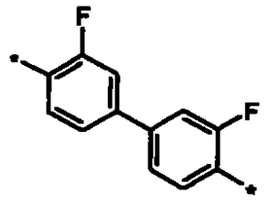
(2 6 12)

## 5 3 2 $G^2$ In Specific Embodiments

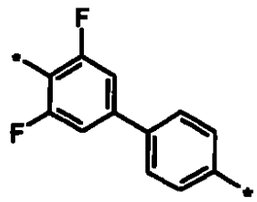
Embodiments of the present invention may be further illustrated with regard to the moiety $G^2$ and the substituents $R^1$ and $R^2$, where $G^2$ has the preferred meanings of phenyl, cyclohexyl, and pyridyl, as well as other meanings such as biphenyl, by the right-hand terminus of a compound of Formula (1 0 0) represented by the following partial Formulas (3 0 1) through (3 0 74)



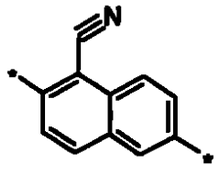
(3 0 1)



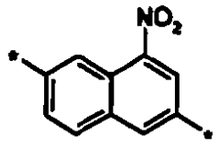
(3 0.2)



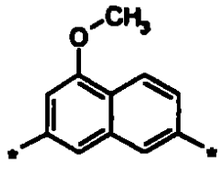
(3 0 3)



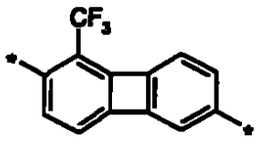
(3 0 4)



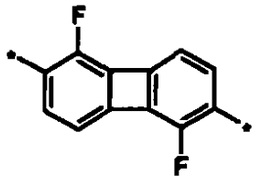
(3 0 5)



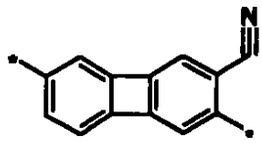
(3 0 6)



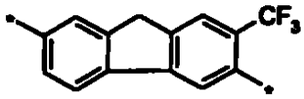
(3 0 7)



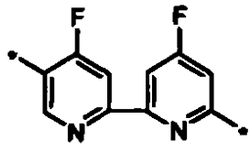
(3 0 8)



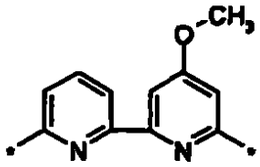
(3 0 9)



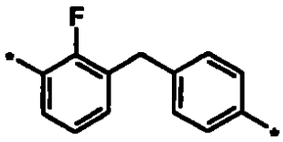
(3 0 10)



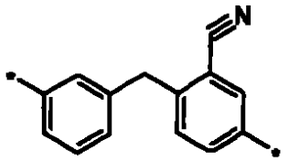
(3 0 11)



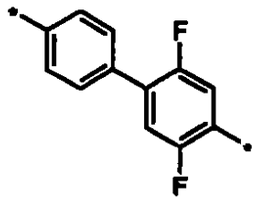
(3 0 12)



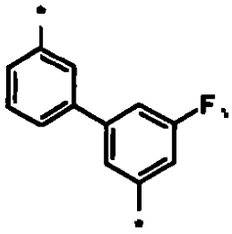
(3 0 13)



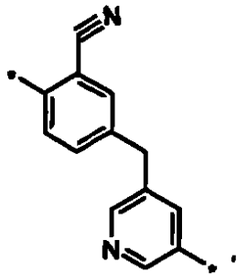
(3 0 14)



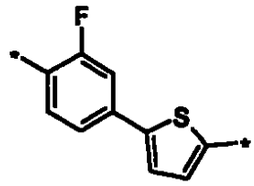
(3 0 15)



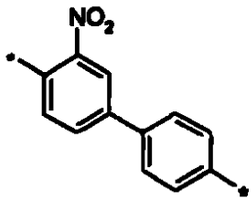
(3 0 16)



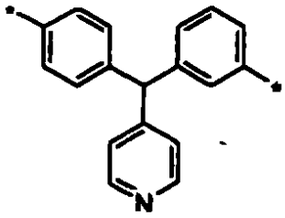
(3 0 17)



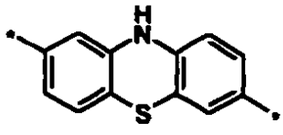
(3 0 18)



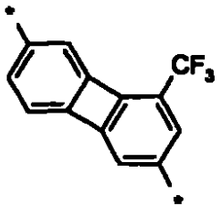
(3 0 19)



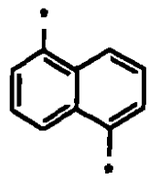
(3 0 20)



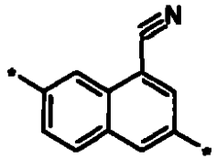
(3 0 21)



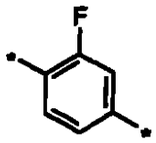

(3 0 22)



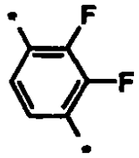
(3 0 23)



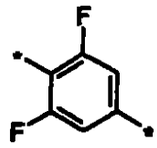

(3 0 24)



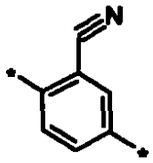

(3 0 25)



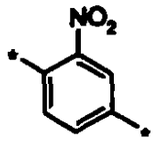

(3 0 26)



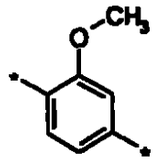

(3 0 27)



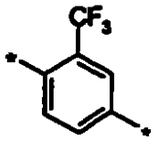

(3 0 28)



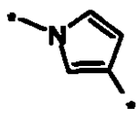

(3 0 29)



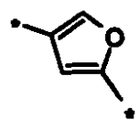

(3 0 30)



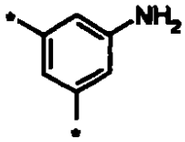

(3 0 31)



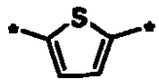

(3 0 32)



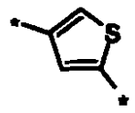

(3 0 33)



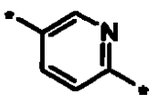

(3 0 34)



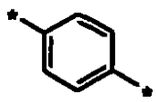

(3 0 35)



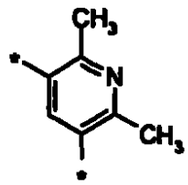

(3 0 36)



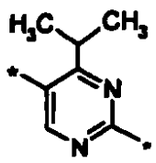

(3 0 37)



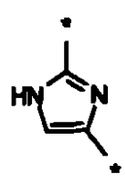
(3 0 38)



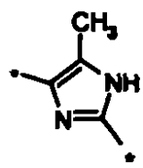

(3 0 39)



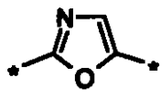

(3 0 40)



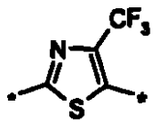

(3 0 41)



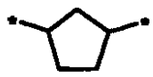

(3 0 42)



(3 0 43)



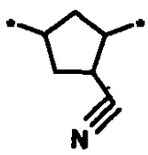
(3 0 44)



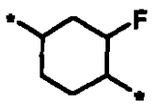
(3 0.45)



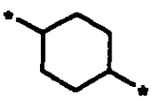
(3 0 46)



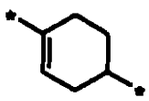
(3 0.47)



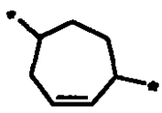
(3 0.48)



(3 0 49)



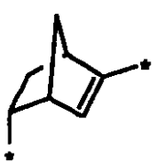
(3 0 50)



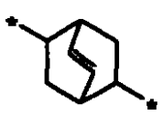
(3 0 51)



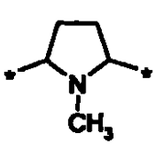
(3 0 52)



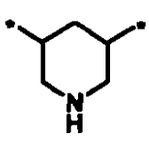
(3 0 53)



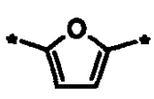
(3 0 54)



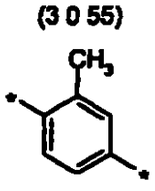
(3 0 55)



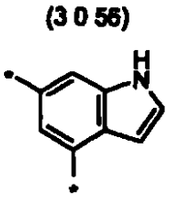
(3 0 56)



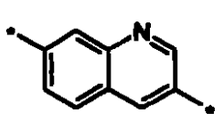
(3 0 57)



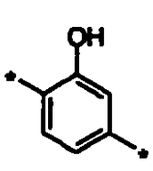
(3 0 58)



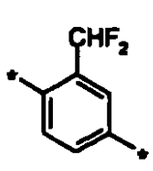
(3 0 59)



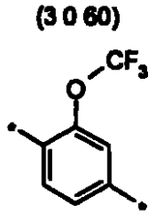
(3 0 60)



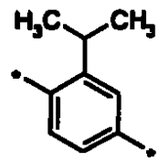
(3 0 61)



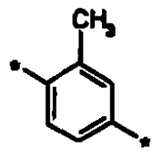
(3 0 62)



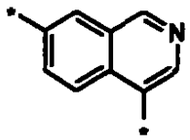
(3 0 63)



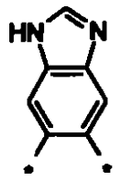
(3 0 64)



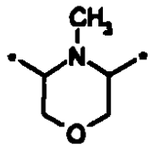
(3 0 65)



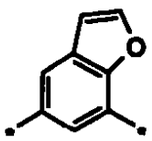
(3 0 66)



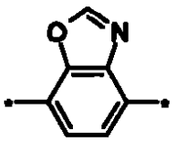
(3 0 67)



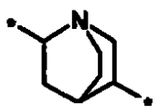
(3 0 68)



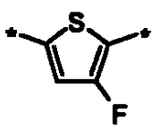
(3 0 69)



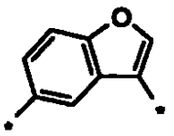
(3 0 70)



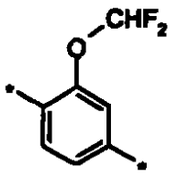
(3 0 71)



(3 0 72)



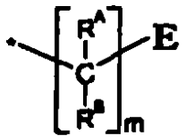
(3.0 73)



(3 0 74)

## 5.4.0 The $R^A$ and $R^B$ Substituents

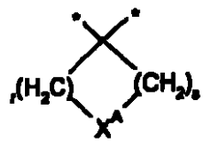
The group of partial Formula (1 0 4) above is substituted in the 4-position by a moiety containing the substituents E, $R^A$, and $R^B$, which may be represented by partial Formula (1 1 15).



(1 1 15)

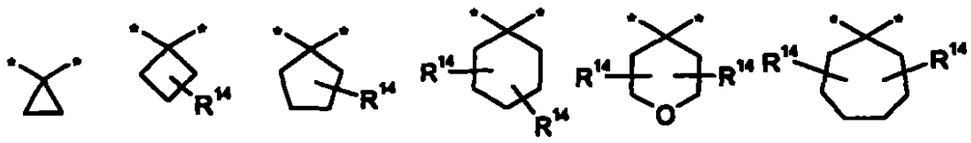
where m is 0, 1, 2, or 3 In the more preferred embodiments of the compounds of the present invention, m has the meaning of 0 or 1 When m is 1 the moiety $-[R^A-C-R^B]-$ is present, and $R^A$ and $R^B$ are preferably each a member independently selected from the group consisting of -H, and ($C_1$-$C_4$) 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)

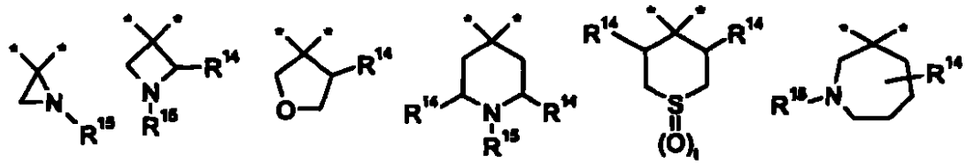


(1 2 0)

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, $-NR^{13}-$ where $R^{13}$ 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)



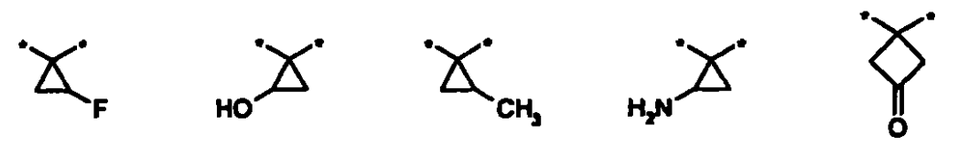
(1 5 1) (1 5 2) (1 5 3) (1 5 4) (1 5 5) (1 5 6)



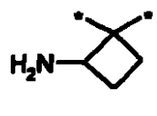
(1 5 7) (1 5 8) (1 5 9) (1 5 10) (1 5 11) (1 5 12)

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)



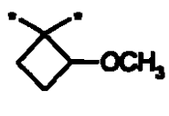
(3 1 1) (3 1 2) (3 1 3) (3 1 4) (3 1 5)



(3 1 6)



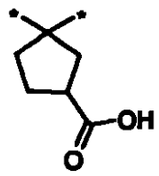
(3 1 7)



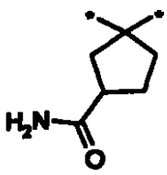
(3 1 8)



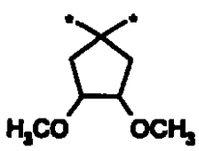
(3 1 9)



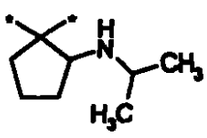
(3 1 10)



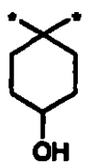
(3 1 11)



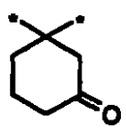
(3 1 12)



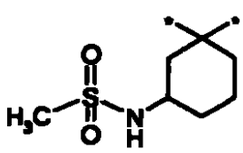
(3 1 13)



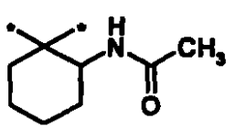
(3 1 14)



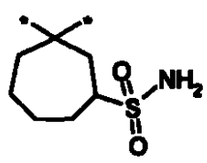
(3 1 15)



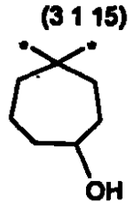
(3 1.16)



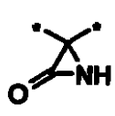
(3.1 17)



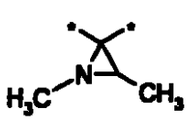
(3 1 18)



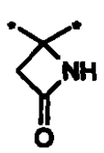
(3 1 19)



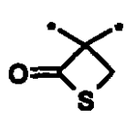
(3 1.20)



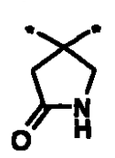
(3 1.21)



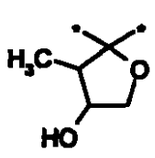
(3 1.22)



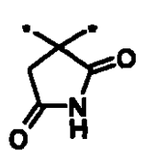
(3 1.23)



(3 1 24)



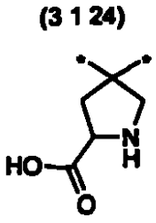
(3 1.25)



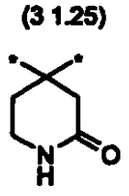
(3 1 26)



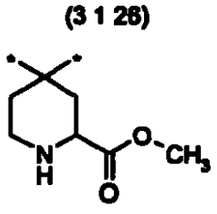
(3 1.27)



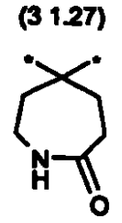
(3 1.28)



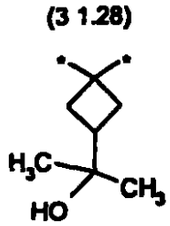
(3 1.29)



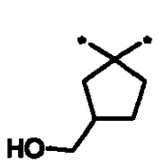
(3 1 30)



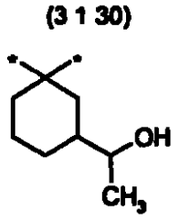
(3 1 31)



(3 1 32)



(3 1.33)



(3 1 34)

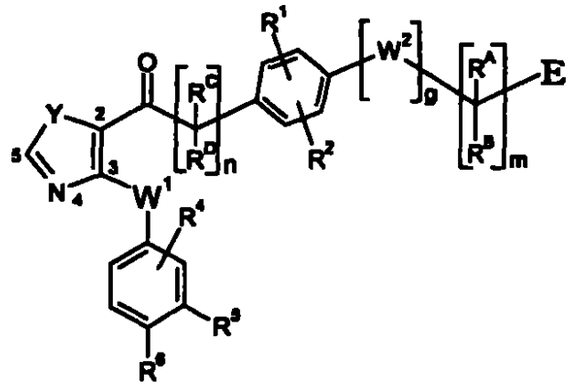
5.4.1 The $R^C$ and $R^D$ Substituents

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 thiazolyl- and analogous amides 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 $G^1$ has the preferred meaning of phenyl, $G^2$ has the preferred meaning of phenyl, cyclopentyl, cyclohexyl, pyridyl, oxadiazolyl, thiadiazolyl, biphenyl, 3-phenyl-pyridine, cyclohexyl-benzene, [2,2']bipyridinyl, or bicyclohexyl, especially phenyl, cyclohexyl, or 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.*, E, $W^1$, $W^2$, 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 thiazolyl- and analogous amides in structure.

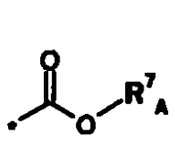
5 6 0 E is a Moiety of Partial Formulas (1.1 1) – (1.1 15)

E 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 E 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 E 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 E 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 bioisosteric in that they permit the compounds of Formula (1 0 0) containing them to achieve PDE4 inhibition essentially equivalent to that achieved by other moieties, especially acid, amide, alcohol, and inverse amide moieties

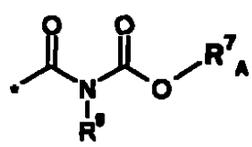
Accordingly, E is a member selected from the group of moieties defined by partial Formulas (1 1 1) through (1 1 15), and said moieties include substituents $R^{7A}$, $R^{7B}$, and $R^{7C}$, as well as $R^{7B}$, $R^{9}$, $R^{16}$, and $R^{17}$, and in the case of partial Formula (1 1 15) the moiety consists 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 E is a Moiety of Partial Formulas (1.1 1), (1 1.2), or (1 1.3)

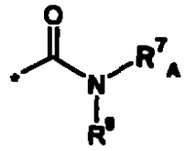
Embodiments of the present invention wherein the definition of the E group is illustrated by partial Formulas (1 1 1), (1 1.2), and (1 1 3), are as follows



(1 1 1)



(1 1 2)



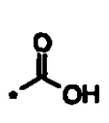
(1 1 3)

One of a number of preferred moieties for defining the E group is that of partial Formula (1 1 1) where $R^{7A}$ has the meaning of –H, which is a preferred meaning of this substituent Where $R^{7A}$ 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

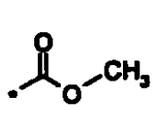
$R^{10}$ is an optional substituent of the moieties that define $R^7_A$, and there may be up to three such substituents when present The meaning of the $R^{10}$ substituent includes phenyl or pyridyl where said phenyl or pyridyl is in turn optionally substituted by up to 3 substituents $R^{11}$ where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

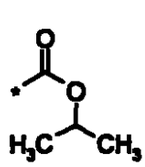
These and other preferred embodiments of the compounds of Formula (1 0 0) comprising the moieties of partial Formula (1 1 1) based on the preferred meanings of $R^7_A$ and $R^8$ as described above, include, *inter alia*, the following groups illustrated by partial Formulas (3 5 1) through (3 5 15)



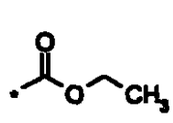
(3 5 1)



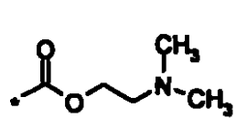
(3 5.2)



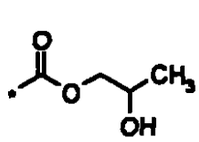
(3 5.3)



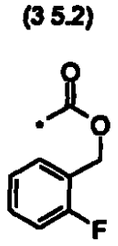
(3 5.4)



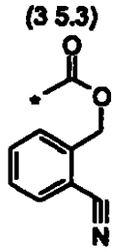
(3 5 5)



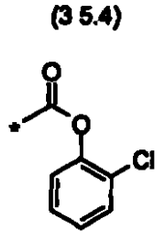
(3 5 6)



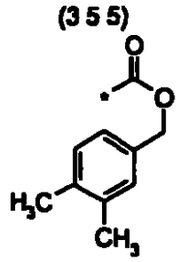
(3 5 7)



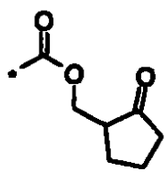
(3 5 8)



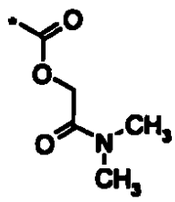
(3 5 9)



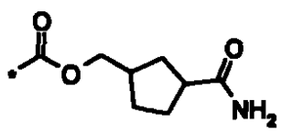
(3 5 10)



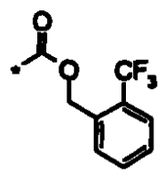
(3 5 11)



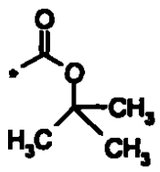
(3 5 12)



(3 5 13)



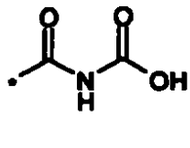
(3 5 14)



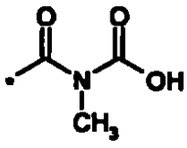
(3 5 15)

The E 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 –$CH_3$.

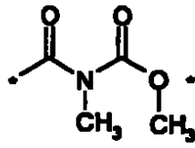
Accordingly, embodiments of the present invention where the E group is represented by partial Formula (1 1 2) may be illustrated as follows by partial Formulas (4 1 1) through (4 1 5)



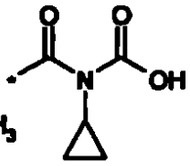
(4 1 1)



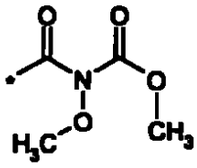
(4 1.2)



(4 1 3)

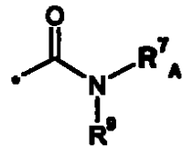


(4 1 4)



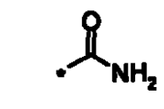
(4 1 5)

Those embodiments wherein the definition of E is that of an amide group, are illustrated by partial Formula (1 1 3)

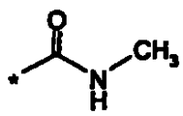


(1 1 3)

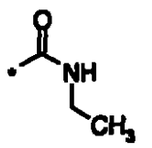
These and other preferred embodiments of the compounds of Formula (1 0 0) comprising moieties of partial Formula (1 1 3), based on the meanings of $R^7{}_A$ and $R^9$ described above, include, *inter alia*, the following groups illustrated by partial Formulas (4 5 1) through (4 5 20)



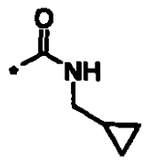
(4 5 1)



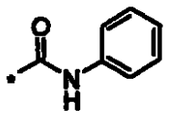
(4 5.2)



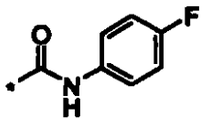
(4 5 3)



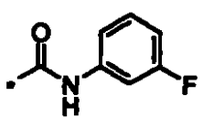
(4 5.4)



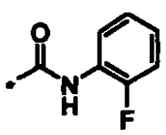
(4 5 5)



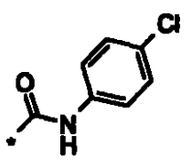
(4 5 6)



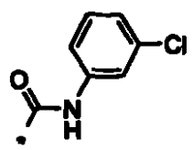
(4 5 7)



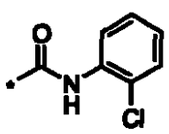
(4 5 8)



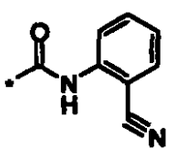
(4 5 9)



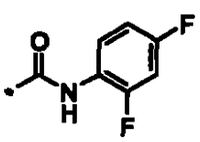
(4 5 10)



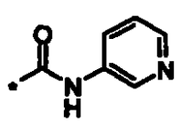
(4 5 11)



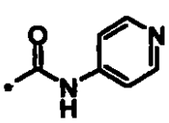
(4 5 12)



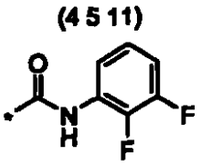
(4 5 13)



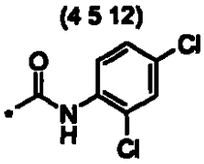
(4 5 14)



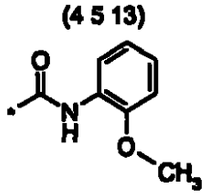
(4 5 15)



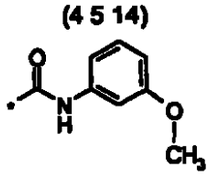
(4 5 16)



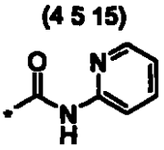
(4 5 17)



(4 5 18)



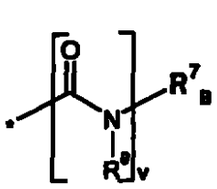
(4 5 19)



(4 5 20)

**5 6.2 E Is a Moiety of Partial Formula (1 1.4)**

Preferred embodiments of the present invention also comprise those compounds of Formula (1 0 0) wherein terminal moiety **E** falls within the scope of partial Formula (1 1 4), *i.e* , embodiments of this type are encompassed within the scope of the **E** moiety when it has the meaning of partial Formula (1 1 4)

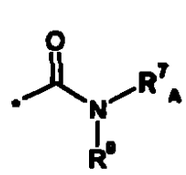


(1 1 4)

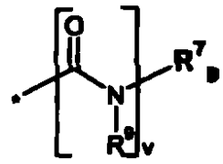
wherein $R^7_B$ is a monocyclic or bicyclic heterocyclyl which is a member selected from the group consisting of tetrazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-3-on-5-yl, 1,2,3-triazol-5-yl, imidazol-2-yl, imidazol-4-yl, imidazolidin-2-on-4-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-on-3-yl, 1,2,4-oxadiazol-5-yl, 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, parathiazinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, indolinyl, isoindolinyl, benzo[*b*]furanyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, 2*H*-1-benzopyranyl, 2-*H*-chromenyl, chromanyl, benzothienyl, 1*H*-indazolyl; benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl, benzotriazinyl, phthalazinyl, 1,8-naphthyridinyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyrazolo[3,4-*d*]pyrimidinyl, pyrimido[4,5-*d*]pyrimidinyl, imidazo[1,2-*a*]pyridinyl, pyridopyridinyl, pteridinyl, and 1*H*-purinyl

Partial Formulas (1 1.3) and (1 1.4) are similar and the distinction between them should be noted Partial Formulas (1 1 3) and (1 1 4) are as follows



(1 1 3)



(1 1.4)

Where v is 0, $R^7_B$ 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)N$R^9$— 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)N$R^9$— 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

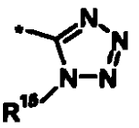
The optional nitrogen heterocyclyl substituent $R^{13}$ comprises –H, -C(=O)$R^{16}$, –$OR^{16}$, preferably –$OCH_3$, –($C_1$-$C_4$) alkyl–$OR^{16}$, -C(=O)$OR^{16}$, -($C_1$-$C_2$) alkyl-C(=O)$OR^{16}$; -C(=O)$NR^{16}R^{17}$, –($C_1$-$C_4$) alkyl, preferably –$CH_3$, –($C_2$-$C_4$) alkenyl, -$(CH_2)_u$–($C_3$-$C_7$) 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, -$CO_2R^{15}$, –$OR^{16}$, –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, 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 $R^{15}$ 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 $R^{16}$ 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 4 1) through (1 4 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 –$CH_3$.

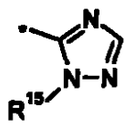
There is also pointed out the distinction between the substituents $R^9$ and $R^{15}$, both of which are attached only to nitrogen atoms in any of the meanings of the moiety E The substituent $R^{15}$ is attached only to a nitrogen atom that is an integral, component part of any heterocyclic moiety that 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 (1.4 1) through (1 4.20), 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 E 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)



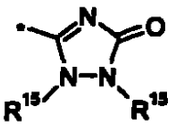
tetrazol-5-yl

(1.4 1)



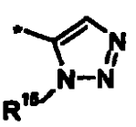
1,2,4-triazol-3-yl

(1 4.2)



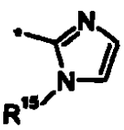
1,2,4-triazol-3-on-5-yl

(1.4 3)



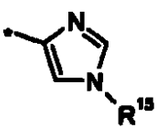
1,2,3-triazol-5-yl

(1 4.4)



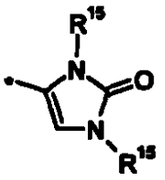
imidazol-2-yl

(1 4 5)



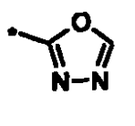
imidazol-4-yl

(1.4 6)



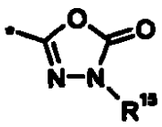
imidazolidin-2-on-4-yl

(1.4 7)



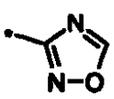
1,3,4-oxadiazolyl

(1.4.8)



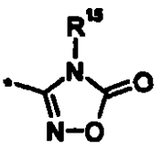
1,3,4-oxadiazol-2-on-5-yl

(1 4 9)



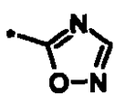
1,2,4-oxadiazol-3-yl

(1 4 10)



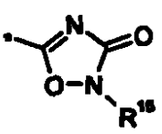
1,2,4-oxadiazol-5-on-3-yl

(1 4 11)



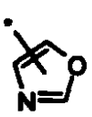
1,2,4-oxadiazol-5-yl

(1.4 12)



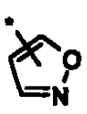
1,2,4-oxadiazol-3-on-5-yl

(1 4 13)



oxazolyl

(1 4 14)



isoxazolyl

(1 4 15)



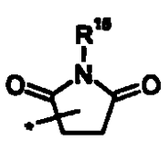
pyrrolyl

(1.4 16)



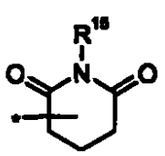
pyrazolyl

(1.4 17)



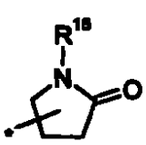
succinimidyl

(1.4 18)



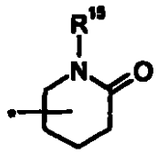
glutarimidyl

(1 4 19)

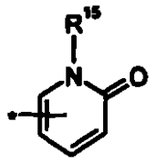


pyrrolidonyl

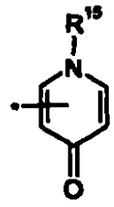
(1 4 20)



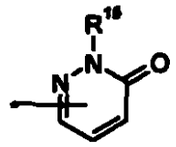
2-piperidonyl
(1.4.21)



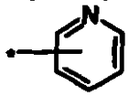
2-pyridonyl
(1.4.22)



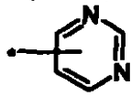
4-pyridonyl
(1.4.23)



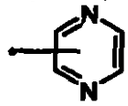
pyridazin-3-onyl
(1.4.24)



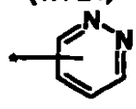
pyridyl
(1.4.25)



pyrimidinyl
(1.4.26)

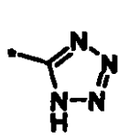


pyrazinyl
(1.4.27)

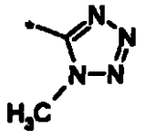


pyridazinyl
(1.4.28)

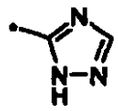
In order to provide another demonstration of preferred embodiments of the compounds of Formula (1.0.0) with reference to the E group where it is a moiety of partial Formula (1.1.4) and v is 0 or 1, and $R^7_B$ is a monocyclic heterocyclic group, there is set out below the groups consisting of partial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



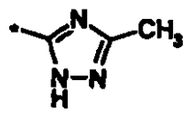
(4.8.1)



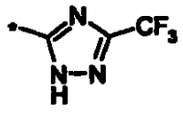
(4.8.2)



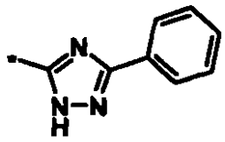
(4.8.3)



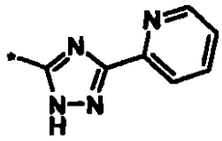
(4.8.4)



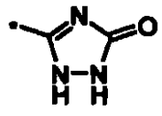
(4.8.5)



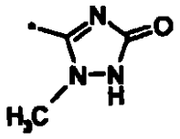
(4.8.6)



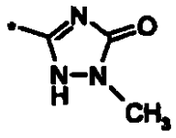
(4.8.7)



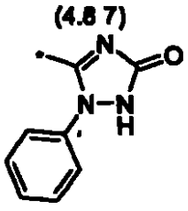
(4.8.8)



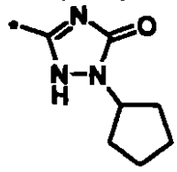
(4.8.9)



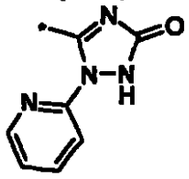
(4.8.10)



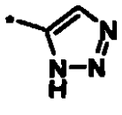
(4.8.11)



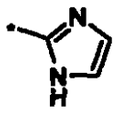
(4.8.12)



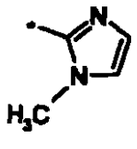
(4.8.13)



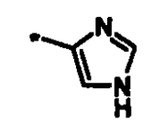
(4.8.14)



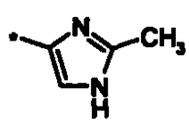
(4.8.15)



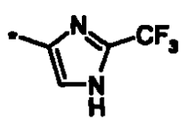
(4.8.16)



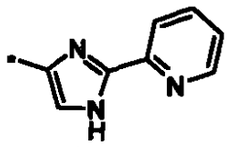
(4 8 17)



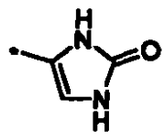
(4 8 18)



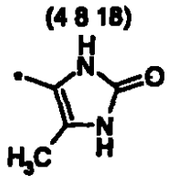
(4 8 19)



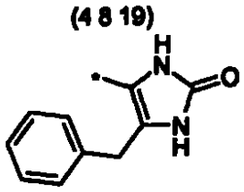
(4 8.20)



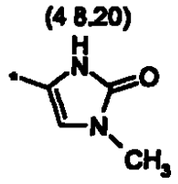
(4 8 21)



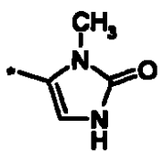
(4 8 22)



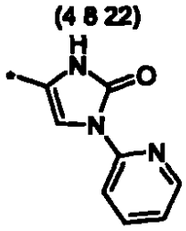
(4 8.23)



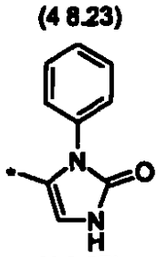
(4 8.24)



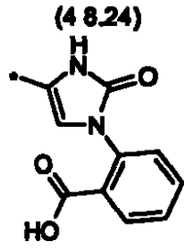
(4 8.25)



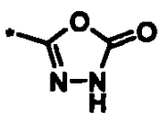
(4 8 26)



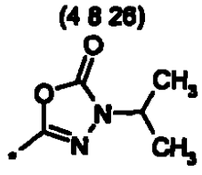
(4 8 27)



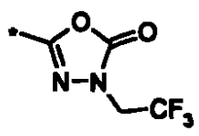
(4 8.28)



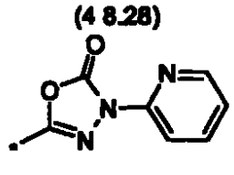
(4.8 29)



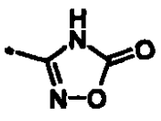
(4 8 30)



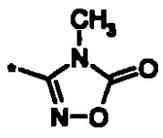
(4 8 31)



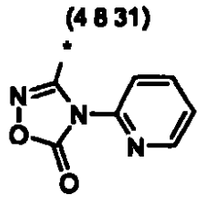
(4 8 32)



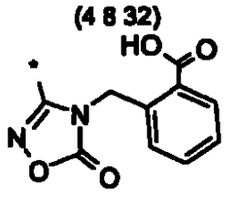
(4 8 33)



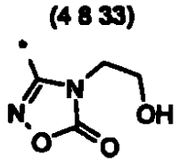
(4 8 34)



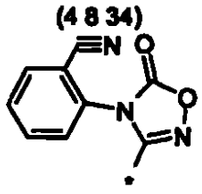
(4 8 35)



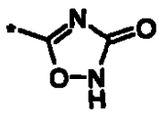
(4 8 36)



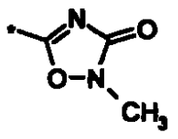
(4 8 37)



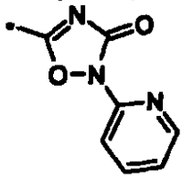
(4 8 38)



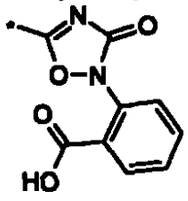
(4.8 39)



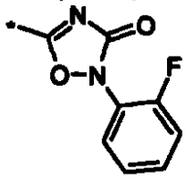
(4 8 40)



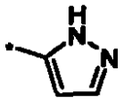
(4 8 41)



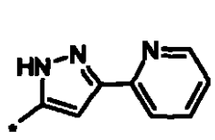
(4 8 42)



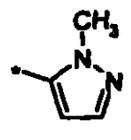
(4.8 43)



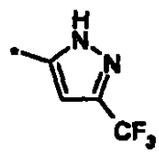
(4 8 44)



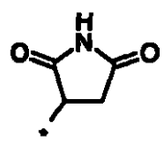
(4 8 45)



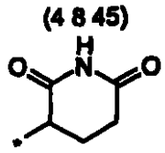
(4 8 46)



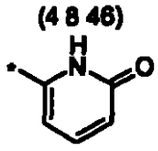
(4 8 47)



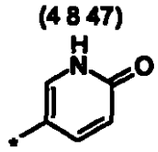
(4 8.48)



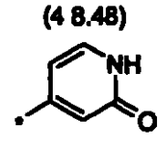
(4 8.49)



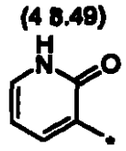
(4.8 50)



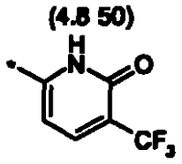
(4 8 51)



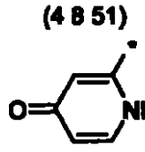
(4 8 52)



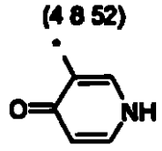
(4 8 53)



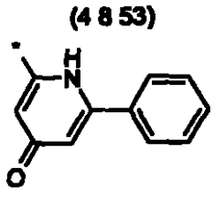
(4.8 54)



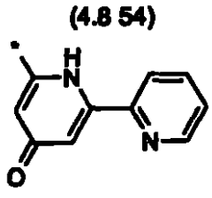
(4 8 55)



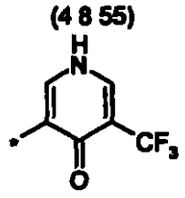
(4.8 56)



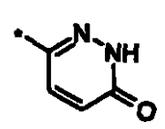
(4 8 57)



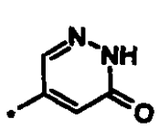
(4 8 58)



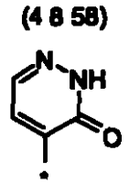
(4.8 59)



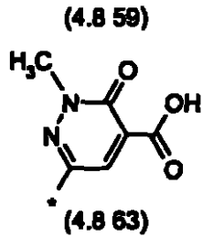
(4 8 60)



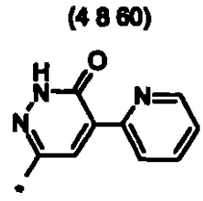
(4 8 61)



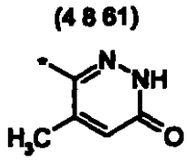
(4.8 62)



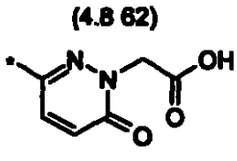
(4.8 63)



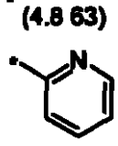
(4 8 64)



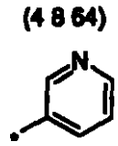
(4 8 65)



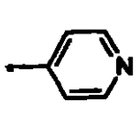
(4 8 66)



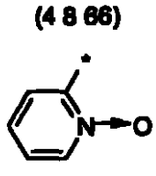
(4.8 67)



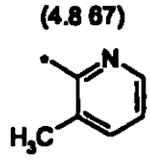
(4.8 68)



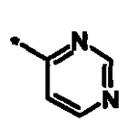
(4 8 69)



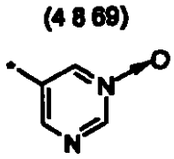
(4 8 70)



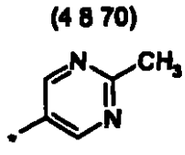
(4.8 71)



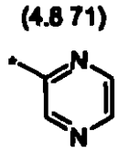
(4 8 72)



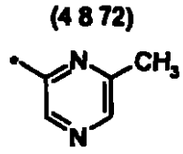
(4 8 73)



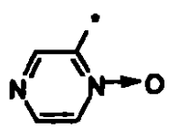
(4 8 74)



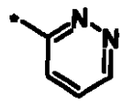
(4 8 75)



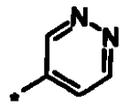
(4 8 76)



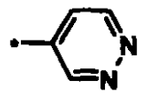
(4 8 77)



(4 8 78)



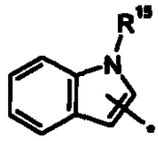
(4 8 79)



(4 8 80)

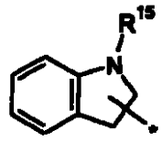
Preferred embodiments of the present invention where the group E is a moiety of partial Formula (1 1 4) and v is 0 or 1, also include those wherein the moiety $R^7$B is a bicyclic heterocyclic group selected from the group consisting of indolyl, indolinyl, isoindolinyl, benzo[*b*]furanyl, 2,3-dihydrobenzofuranyl, 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 E group where it is a moiety of partial Formula (1 1 4), v is 0 or 1, and 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 E moiety is selected in such preferred embodiments



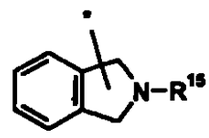
indolyl

(5 0 1)



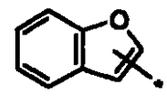
indolinyl

(5 0 2)



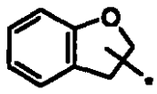
isoindolinyl

(5 0 3)



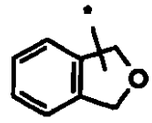
benzo[*b*]furanyl

(5 0 4)



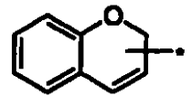
2,3-dihydrobenzo-furanyl

(5 0 5)



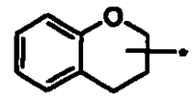
1,3-dihydroisobenzo-furanyl, phthalanyl

(5 0 6)



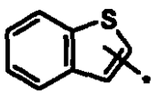
2*H*-1-benzopyranyl

(5 0 7)



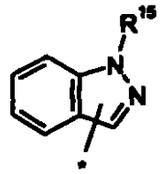
chromanyl

(5 0 8)



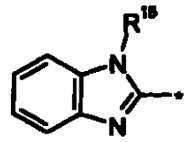
benzothienyl

(5 0 9)



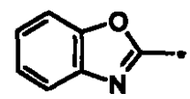
1*H*-indazolyl

(5 0 10)



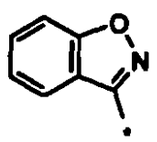
benzimidazolyl

(5 0 11)

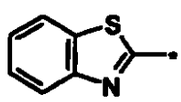


benzoxazolyl

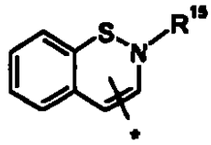
(5 0 12)



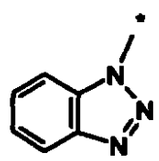
benzisoxazolyl
(5 0 13)



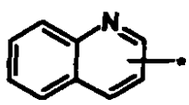
benzothiazolyl
(5 0 14)



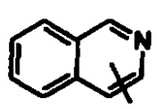
2H-1,2-benzothiazinyl
(5.0 15)



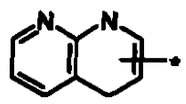
benzotriazolyl
(5 0 16)



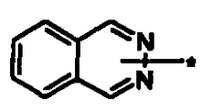
quinolinyl
(5 0 17)



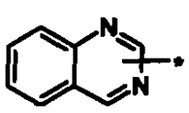
isoquinolinyl
(5 0 18)



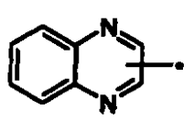
1,8-naphthyridinyl
(5 0 19)



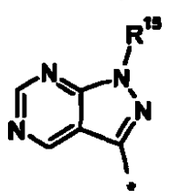
phthalazinyl
(5 0.20)



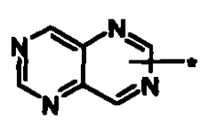
quinazolinyl
(5 0.21)



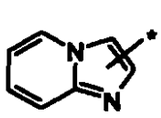
quinoxalinyl
(5 0.22)



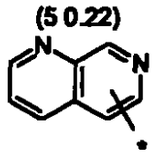
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl
(5 0.23)



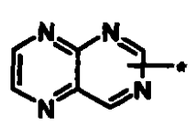
pyrimido[5,4-*d*]-pyrimidinyl
(5 0.24)



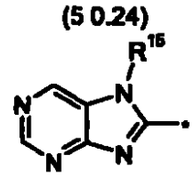
imidazo-[1,2-*a*]-pyridinyl
(5 0.25)



pyridopyridinyl
(5 0 26)



pteridinyl
(5 0.27)

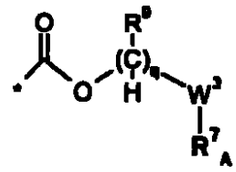


1*H*-purinyl
(5 0.28)

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

5 **5 6.3 E Is a Moiety of Partial Formula (1.1.5)**

There are further embodiments of the compounds of Formula (1 0 0) in which the E moiety comprises a group falling within the scope of partial Formula (1 1 5)

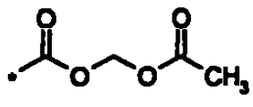


(1 1 5)

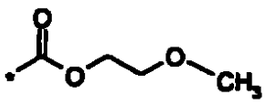
wherein q is 1, 2, or 3, provided that where q is 2 or 3, $R^9$ has the meaning of –H in at least one instance, or two instances, respectively; $W^3$ is –O–, –N($R^9$)–, or –OC(=O)– where $R^9$ has the same meaning as defined above, and $R^7$ has the same meaning as defined above

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

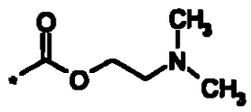
Representative embodiments of the compounds of Formula (1 0 0) in which the **E** moiety falls within the scope of partial Formula (1 1 5) are those illustrated by partial Formulas (6 0 1) through (6 0 6)



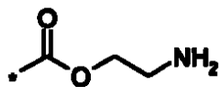
(6 0 1)



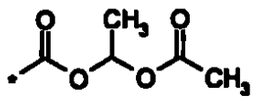
(6 0.2)



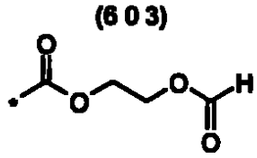
(6 0 3)



(6 0.4)



(6 0 5)

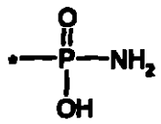


(6 0 6)

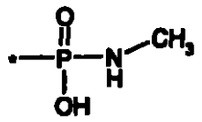
5 6.4 **E** Is Other Than a Carboxylic Acid

Embodiments of the compounds of Formula (1 0 0) include those wherein the **E** 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 **E** moiety may be selected, and they include the following -O-P(=O)(OH)$_2$ (phosphono), -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$, -S(=O)$_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

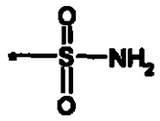
Preferred embodiments of the compounds of Formula (1 0 0) wherein E is a phosphorus or sulfur acid or a derivative thereof, are those wherein E is -P(=O)(OH)NHR$^{25}$ (substituted phosphoramido), -S(=O)$_2$NHR$^{25}$ or -NHS(=O)$_2$R$^{25}$ (sulfonamido), or -C(=O)NHS(=O)$_2$R$^{25}$ (acylsulfonamido), 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)



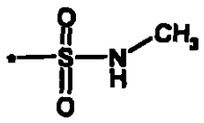
(6 5 1)



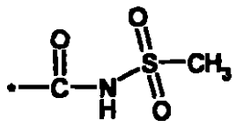
(6 5.2)



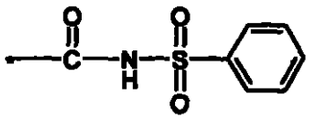
(6 5.3)



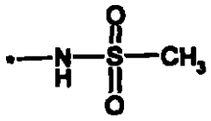
(6 5 4)



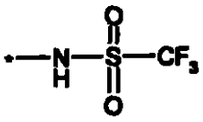
(6 5 5)



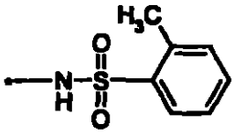
(6 5 6)



(6 5 7)



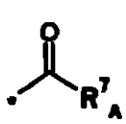
(6 5 8)



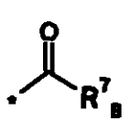
(6 5 9)

5 6.5 E is a Moiety of Partial Formulas (1 1 6) through (1 1 9)

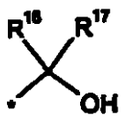
There are further embodiments of the compounds of Formula (1 0 0) in which the E moiety comprises a group falling within the scope of partial Formulas (1 1 6) through (1 1 9)



(1 1 6)



(1 1 7)



(1 1 8)



(1 1 9)

where R$^{7A}$, R$^{7B}$, R$^{16}$, and R$^{17}$ have the same meaning as defined above For example, R$^{16}$ and R$^{17}$ are each independently selected from –H, –(C$_1$-C$_4$) alkyl, –(C$_2$-C$_4$) alkenyl, -(C$_3$-C$_8$) cycloalkyl, phenyl, benzyl, and pyridyl, wherein said alkyl, alkenyl, cycloalkyl, phenyl, benzyl, or pyridyl is substituted by 0 to 3 substituents selected from the group consisting of -F, –Cl, –CF$_3$, –CN, and –(C$_1$-C$_3$) alkyl

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



(1 1 6) (1 1 7)

$R^7_A$ in the moiety of partial Formula (1 1 6) has the same meaning as defined further above, but in preferred embodiments of the compounds of Formula (1.0 0) $R^7_A$ has especially the meaning of –H, –($C_1$-$C_8$) alkyl, preferably methyl, ethyl, *iso*-propyl, or *tert*-butyl, -($C_2$-$C_8$) alkenyl, preferably 2-propenyl, -($C_2$-$C_8$) alkynyl, preferably ethynyl Each of these meanings of $R^7$ is optionally substituted by up to 3 substituents $R^{10}$ The meaning of $R^{10}$ is the same as defined above, but is preferably phenyl or pyridyl optionally substituted by up to 3 $R^{11}$ where $R^{11}$ is preferably –F, $-CF_3$, –CN, $-CH_3$, or $-OCH_3$ $R^{10}$ also preferably has the meaning of –F, $-CF_3$, $-OR^{16}$, –CN, $-C(=O)OR^{16}$, $-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, or $-NR^{16}S(=O)_2R^{17}$, where $R^{16}$ and $R^{17}$ are preferably –H, methyl, ethyl, cyclopropyl, phenyl, benzyl, or pyridyl optionally substituted by up to 3 of –F, or 1 of $-CF_3$, -CN, or $-CH_3$.

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

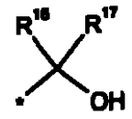
$R^7_A$ also has the meaning of phenyl, benzyl, or pyridyl, where said phenyl, benzyl, or pyridyl is optionally substituted by up to 3 substituents $R^{10}$ where $R^{10}$ has the same preferred meanings as defined in the paragraph immediately above

$R^7_B$ in the moiety of partial Formula (1 1 7) has the same meaning as defined further above, but in preferred embodiments of the compounds of Formula (1 0 0) $R^7_B$ has especially the meaning of tetrazol-5-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-5-yl, imidazol-2-yl; imidazol-4-yl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, morpholinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, pyridyl, indolyl, benzo[*b*]furanyl, 2,3-dihydrobenzofuranyl, 1*H*-indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl

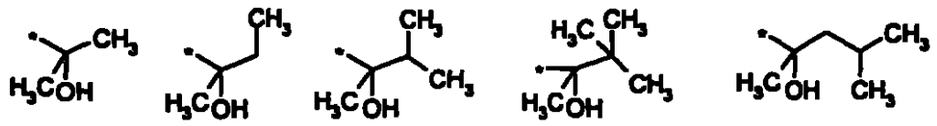
Any of the above-recited especially preferred meanings of $R^7_B$ is optionally substituted on a carbon atom by $R^{14}$ where $R^{14}$ has the same meaning as defined above, and on a nitrogen atom by $R^{15}$ where $R^{15}$ has the same meaning as defined above Especially included in the case of such nitrogen atom substituents, are all tautomer forms of the moieties

of partial Formula (1 1 9) Sulfur atoms of said moieties are optionally substituted by 1 or 2 oxygen atoms

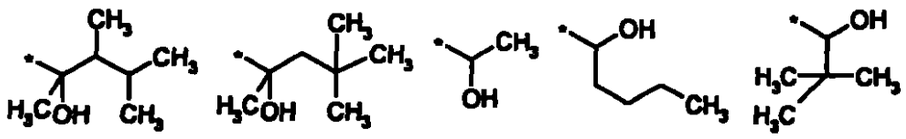
In order to illustrate further meanings of E that fall within the scope of partial Formulas (1 1 6), (1 1 7), (1 1 8), and (1 1 9), there are depicted below moieties of partial Formulas (3 3 1) through (3.3 15) that represent different meanings that fall within the scope partial Formula (1 1 8)



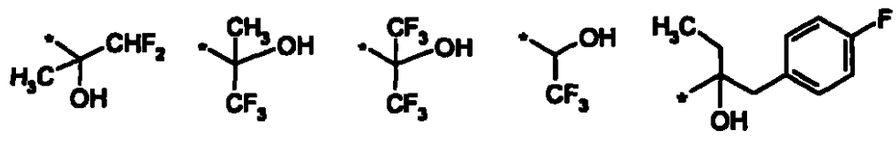
(1 1 8)



(3 3 1) (3 3.2) (3 3 3) (3 3 4) (3.3 5)

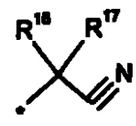


(3 3 6) (3 3 7) (3 3.8) (3 3 9) (3 3 10)

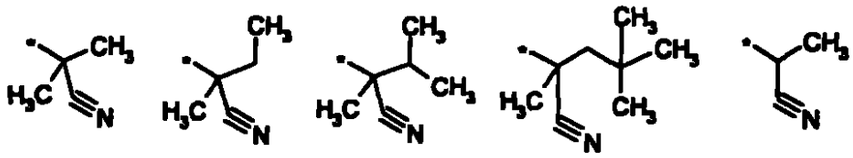


(3 3 11) (3 3 12) (3 3 13) (3 3 14) (3 3 15)

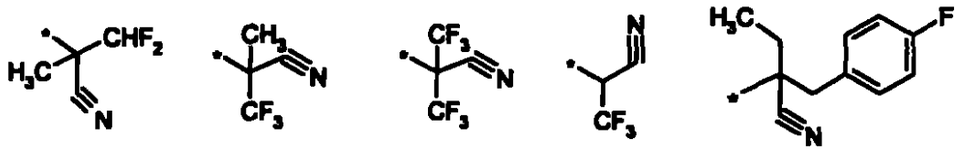
Further meanings of E are those that fall within the scope of partial Formula (1 1 9), in which a nitrile group, –C≡N, replaces the hydroxyl group of partial Formula (1 1.8) Accordingly, there are depicted below moieties of partial Formulas (3 8 1) through (3 8 10) that represent different meanings that fall within the scope partial Formula (1 1 9)



(1 1 9)

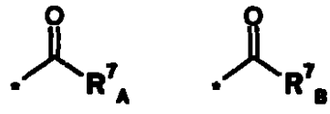


(3.8 1) (3 8.2) (3 8 3) (3 8 4) (3.8 5)

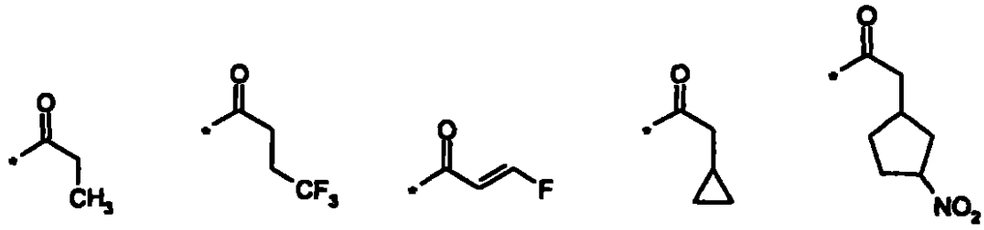


(3 8 6) (3 8 7) (3 8 8) (3 8 9) (3 8 10)

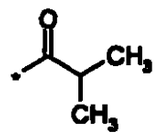
In order to illustrate additional meanings of E that fall within the scope of partial Formulas (1 1 6), (1 1 7), (1 1 8), and (1 1 9), there are depicted below moieties of partial Formulas (3 9 1) through (3 9 9) that represent different meanings that fall within the scope partial Formulas (1 1 6) and (1 1 7).



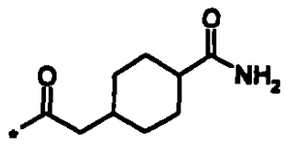
(1 1 6) (1 1 7)



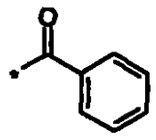
(3 9 1) (3 9.2) (3 9 3) (3 9 4) (3 9 5)



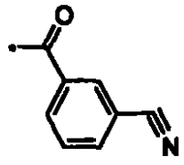
(3 9 6)



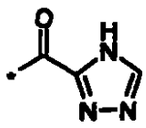
(3 9 7)



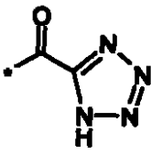
(3 9 8)



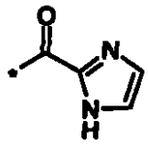
(3 9 9)



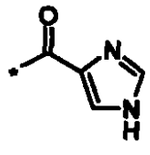
(3 9 10)



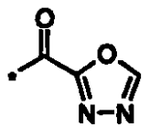
(3 9 11)



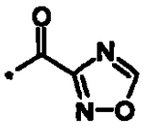
(3 9 12)



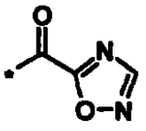
(3 9 13)



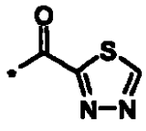
(3 9 14)



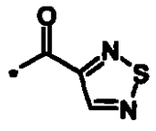
(3 9 15)



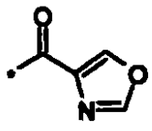
(3 9 16)



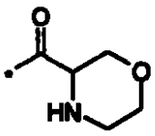
(3 9 17)



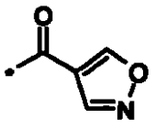
(3 9 18)



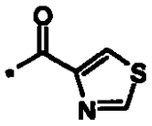
(3 9 19)



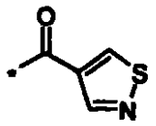
(3 9 20)



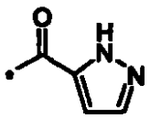
(3 9.21)



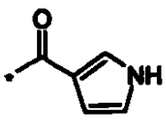
(3 9.22)



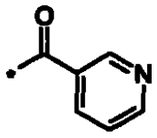
(3 9 23)



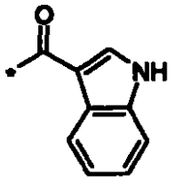
(3 9.24)



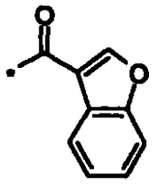
(3 9 25)



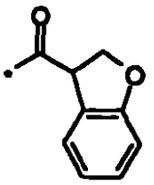
(3 9 26)



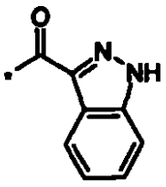
(3 9.27)



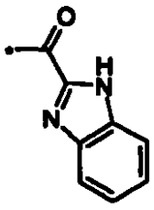
(3 9.28)



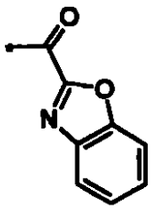
(3 9.29)



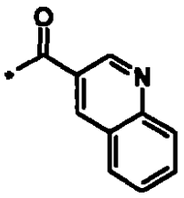
(3 9 30)



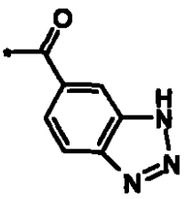
(3 9 31)



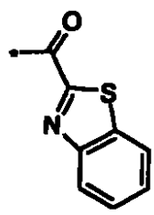
(3 9 32)



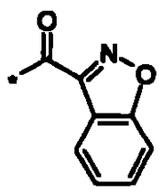
(3 9 33)



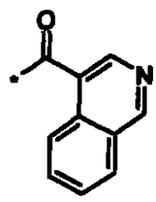
(3 9 34)



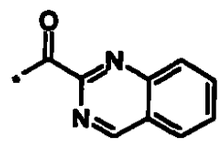
(3 9 35)



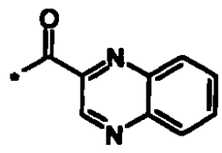
(3.9.36)



(3 9 37)



(3 9 38)



(3 9 39)

5 6.6 **E is a Moiety of Partial Formulas (1 1.10) through (1 1 15)**

**E** 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 **E** 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 **E** 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)-$R^7_C$.

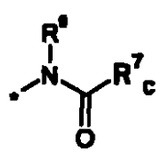
**E** may also be selected as the moiety defined by partial Formula (1.1 11). Where both occurrences of the substituent $R^9$ have the meaning of –H as is preferred, then the resulting embodiments of the compounds of Formula (1 0 0) will have the following right-hand terminus —NHC(=O)NH—$R^7_C$ Similarly, where **E** is selected as the moiety defined by partial Formula (1 1 11) 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—$R^7_C$.

E 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 $R^8$ 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 E defined by partial Formulas (1 1 12) and (1 1 13) are not, however, as preferred as the meanings of E defined by partial Formulas (1 1 10) and (1 1 11), and sometimes (1 1 12)

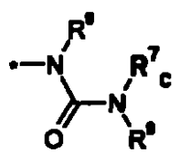
Finally, E may be selected as the moiety defined by partial Formula (1 1 6) in which a nitrogen atom of a heterocycle is attached by a direct bond to the remaining portion of a compound of Formula (1 0 0) In some preferred embodiments, a carbon atom in said nitrogen-containing heterocycle that is α to said nitrogen atom may be carbonyl, *i e* , oxo (=O) substituted The most preferred meanings of E in the compounds of Formula (1 0 0) are those defined by partial Formulas (1 1 1), (1 1 10), and (1 1 15)

5 6.7 E is a Moiety of Partial Formulas (1.1.10) through (1.1 14)

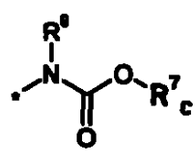
Embodiments of the present invention wherein the definition of the E group is illustrated by partial Formulas (1 1 10), (1 1 11), (1 1 12), (1 1 13), and (1 1 14), are as follows



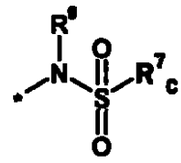
(1 1 10)



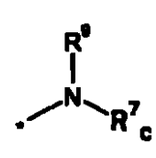
(1 1 11)



(1 1 12)



(1 1 13)



(1 1 14)

One of a number of preferred moieties for defining the E 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($C_3$-$C_8$) 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

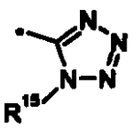
$R^8$ is a substituent appearing in each of the E moieties represented by partial Formulas (1 1 10), (1 1 11), (1 1 12), (1 1 13), and (1 1 14) $R^8$ has the meaning of –H, -($C_1$-$C_4$) alkyl, preferably methyl, -($C_3$-$C_7$) cycloalkyl, preferably cyclopropyl or cyclopentyl,

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), $-OR^{18}$, $-NO_2$, $-CN$, $-C(=O)OR^{18}$, $-O-C(=O)R^{18}$, $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$, 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 $-NHS(=O)_2CH_3$

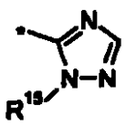
The sub-substituents $R^{16}$ and $R^{17}$ comprise $-H$, $-(C_1-C_4)$ alkyl, preferably $-CH_3$, $-(C_2-C_4)$ alkenyl, $-(C_3-C_6)$ cycloalkyl, preferably cyclopropyl, phenyl, benzyl, or pyridyl Said alkyl, alkenyl, cycloalkyl, phenyl, benzyl, or pyridyl groups are in turn optionally substituted by up to 3 substituents $-F$, $-Cl$, or $-CN$

As an illustration of preferred subgeneric embodiments of the present invention wherein the E 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, and monocyclic heterocyclic groups which define $R^7c$, of partial Formulas (7 0 1) through (7 0 41)



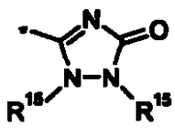
tetrazol-5-yl

(7 0 1)



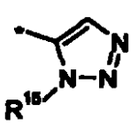
1,2,4-triazol-3-yl

(7 0 2)



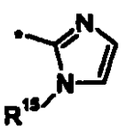
1,2,4-triazol-3-on-5-yl

(7 0 3)



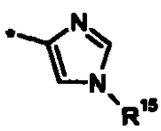
1,2,3-triazol-5-yl

(7 0 4)



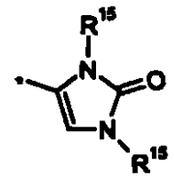
imidazol-2-yl

(7 0 5)



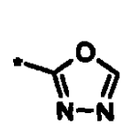
imidazol-4-yl

(7 0 6)



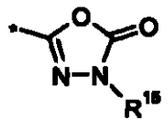
imidazolidin-2-on-4-yl

(7 0 7)



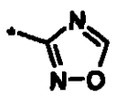
1,3,4-oxadiazolyl

(7 0 8)



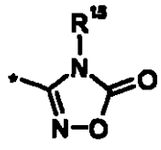
1,3,4-oxadiazol-2-on-5-yl

(7 0 9)



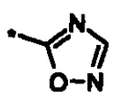
1,2,4-oxadiazol-3-yl

(7 0 10)



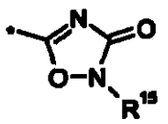
1,2,4-oxadiazol-5-on-3-yl

(7 0 11)



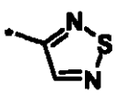
1,2,4-oxadiazol-5-yl

(7 0 12)



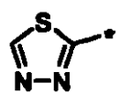
1,2,4-oxadiazol-3-on-5-yl

(7 0 13)



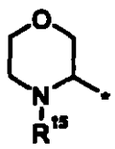
1,2,5-thiadiazol-2-yl

(7 0 14)



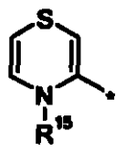
1,3,4-thiadiazolyl

(7 0 15)



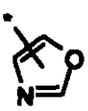
morpholin-3-yl

(7 0 16)



parathiazin-3-yl

(7 0 17)



oxazolyl

(7 0 18)



isoxazolyl

(7 0 19)



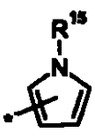
thiazolyl

(7 0 20)



isothiazolyl

(7 0 21)



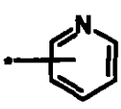
pyrrolyl

(7 0 22)



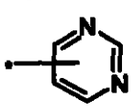
pyrazolyl

(7 0 23)



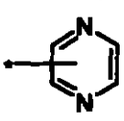
pyridyl

(7 0.24)



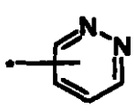
pyrimidinyl

(7 0 25)



pyrazinyl

(7 0 26)



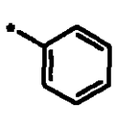
pyridazinyl

(7 0 27)



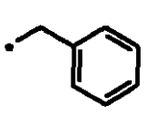
1,2,3-thiadiazol-5-yl

(7 0 28)



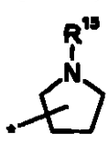
phenyl

(7.0.29)



benzyl

(7 0 30)



pyrrolidinyl

(7.0 31)

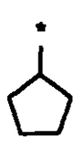


cyclopropyl

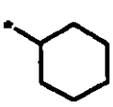
(7 0 32)



cyclobutyl



cyclopentyl



cyclohexyl



furanyl

(7 0 33)



tetrahydrofuranyl

(7 0 34)



thienyl

(7 0 35)



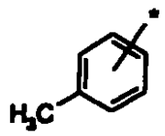
methyl

(7 0 36)



trifluoromethyl

(7 0 37)



toluyl

(7 0 38)

(7 0.39)

(7 0 40)

(7 0.41)

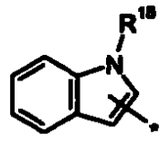
where "*" indicates the point of attachment of each partial Formula (7 0 1) through (7 0 41) to the remaining portion of Formula (1 0 0), and where each carbon atom of partial Formulas (7 0 1) through (7 038) is optionally substituted by a substituent $R^{14}$, and where $R^{14}$ and $R^{15}$ have the 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 41) 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 E 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 9) through (1 1 13) 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

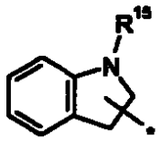
Preferred embodiments of the present invention where the group E is a moiety of partial Formulas (1 1 10) through (1 1 14) also include those wherein the moiety $R^7c$ is a bicyclic heterocyclic group selected from the group consisting of indolyl, indolinyl, isoindolinyl, benzo[*b*]furanyl, 2,3-dihydrobenzofuranyl, 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 E 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 E moiety is selected in such preferred embodiments



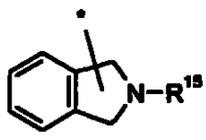
indolyl

(7 5 1)



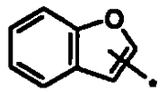
indolinyl

(7 5.2)



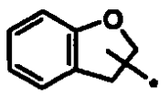
isoindolinyl

(7 5 3)



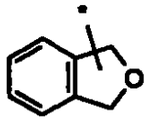
benzo[*b*]furanyl

(7 5.4)



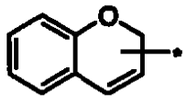
2,3-dihydrobenzo-furanyl

(7 5 5)



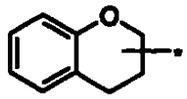
1,3-dihydroisobenzo-furanyl, phthalanyl

(7 5 6)



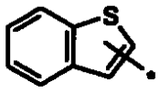
2*H*-1-benzopyranyl

(7 5 7)



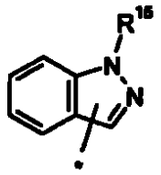
chromanyl

(7 5 8)



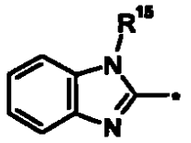
benzothienyl

(7 5 9)



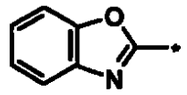
1*H*-indazolyl

(7 5 10)



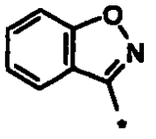
benzimidazolyl

(7 5 11)



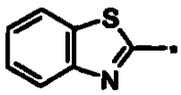
benzoxazolyl

(7 5 12)



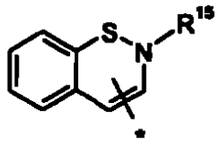
benzisoxazolyl

(7 5 13)



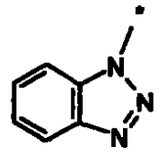
benzothiazolyl

(7 5 14)



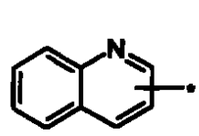
2*H*-1,2-benzothiazinyl

(7 5 15)



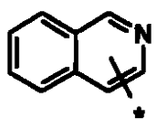
benzotriazolyl

(7 5 16)



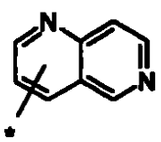
quinolinyl

(7 5 17)



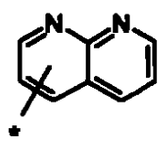
isoquinolinyl

(7 5 18)



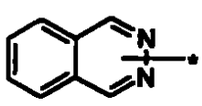
1,6-naphthyridinyl

(7 5 19)



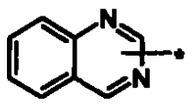
1,8-naphthyridinyl

(7 5 20)



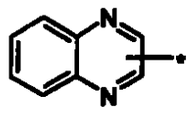
phthalazinyl

(7 5 21)



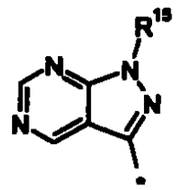
quinazolinyl

(7 5.22)



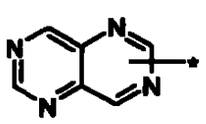
quinoxalinyl

(7 5.23)



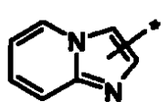
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(7 5.24)



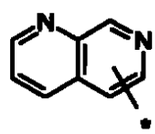
pyrimido[5,4-*d*]-pyrimidinyl

(7 5 25)



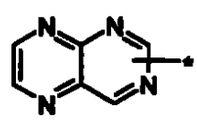
imidazo-[1,2-*a*]-pyridinyl

(7 5.26)



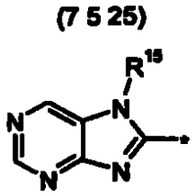
1,7-naphthyridinyl

(7 5.27)



pteridinyl

(7 5 28)



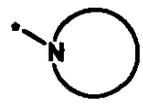
1*H*-purinyl

(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 **5 6.8 E 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 E falls within the scope of partial Formula (1 1 15), *i e*, embodiments of this type are encompassed within the scope of the E moiety when it has the meaning of partial Formula (1 1 15)



(1 1 15)

It will be understood that where the terminal moiety E 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 15) 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 –$NO_2$.

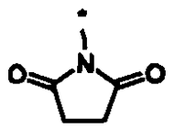
Any one or more of the nitrogen atoms included in said nitrogen-containing heterocyclic groups included within the scope of partial Formula (1 1 15), provided that they are not a point of attachment of said heterocyclic group, are optionally substituted by up to 3 substituents $R^{15}$ Any sulfur atom 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, -$CO_2R^{16}$, –$OR^{16}$; –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, preferably 2, –($C_1$-$C_4$) alkyl, preferably –$CH_3$, and -($C_1$-$C_4$) alkoxy, where $R^{11}$ has the meaning of –$OR^{15}$ above and $R^{19}$ 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 $R^{19}$ and

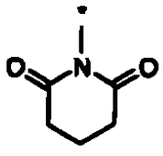
$R^{19}$ substituents comprise –H, or –($C_1$-$C_2$) alkyl, preferably –$CH_3$, optionally substituted with up to 3 –F, or –Cl

The present invention is also concerned with a compound of Formula (1 0 0) wherein the terminal group E 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 E comprises a member selected from the group consisting of partial Formulas (1 7 1) through (1 7 46)



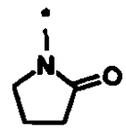
succinimid-1-yl

(1 7 1)



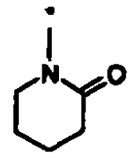
glutarimid-1-yl

(1 7.2)



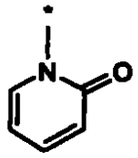
pyrrolidin-2-on-1-yl

(1 7.3)



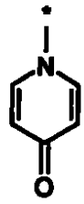
piperid-2-on-1-yl

(1 7 4)



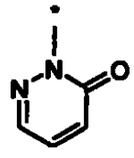
pyrid-2-on-1-yl

(1 7 5)



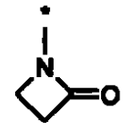
pyrid-4-on-1-yl

(1 7 6)



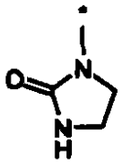
pyridazin-3-on-2-yl

(1 7 7)



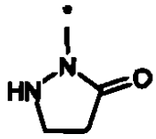
azetidin-2-on-1-yl

(1 7.8)



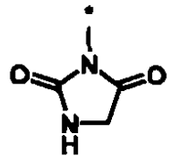
imidazolidin-2-on-1-yl

(1 7 9)



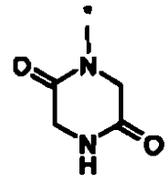
pyrazol-5-on-1-yl

(1 7 10)



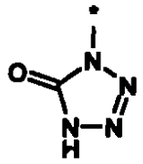
imidazolidin-2,4-dion-1-yl

(1 7 11)



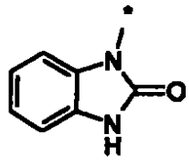
piperazin-2,5-dion-1-yl

(1 7 12)



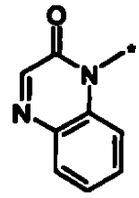
4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl

(1 7 13)



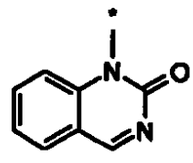
benzimidazolin-2-on-1-yl

(1 7 14)



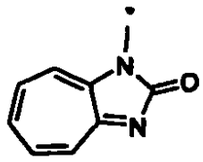
1*H*-quinoxalin-2-on-1-yl

(1 7 15)



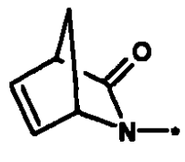
1*H*-quinazolin-2-on-1-yl

(1 7 16)



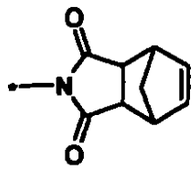
1H-cycloheptimidazol-2-on-1-yl

(1 7 17)



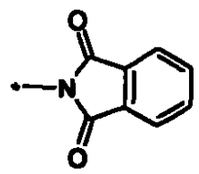
2-azabicyclo[2 2 1]-hept-5-en-3-on-1-yl

(1 7 18)



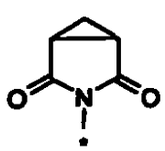
norborn-5-en-2,3-dicarboximid-1-yl

(1 7 19)



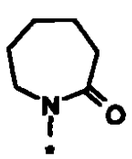
phthalimid-1-yl, 1*H*-isoindole-1,3(2*H*)-dion-1-yl

(1 7.20)



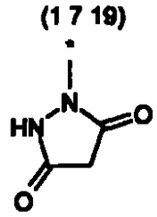
3-azabicyclo[3 1 0]-hexane-2,4-dion-3-yl

(1 7 21)



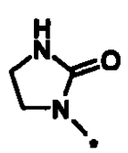
2*H*-azepin-2-on-1-yl

(1 7 22)



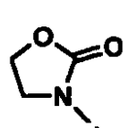
pyrazolidin-3,5-dion-1-yl

(1 7 23)



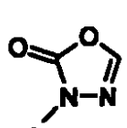
imidazolidin-2-on-1-yl

(1 7.24)



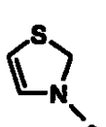
oxazolidin-2-on-1-yl

(1 7 25)



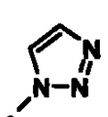
1,3,4-oxadiazol-2(3*H*)-on-3-yl

(1 7.26)



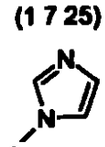
thiazol-3-yl

(1 7.27)



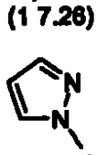
1*H*-1,2,3-triazol-1-yl

(1 7.28)



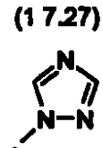
imidazol-1-yl

(1 7 29)



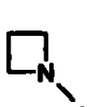
pyrazol-1-yl

(1 7 30)



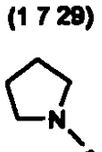
1*H*-1,2,4-triazol-1-yl

(1 7 31)



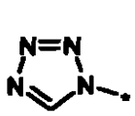
azetidin-1-yl

(1 7 32)



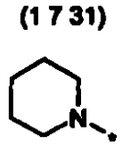
pyrrolidin-1-yl

(1 7 33)



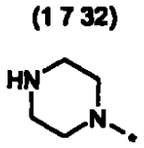
tetrazol-1-yl

(1 7 34)



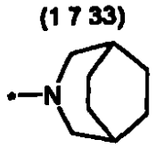
pipendin-1-yl

(1 7 35)



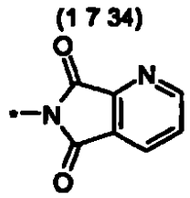
piperazin-1-yl

(1 7.36)



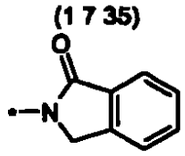
3-azabicyclo[3 2 2]-non-3-yl

(1 7 37)



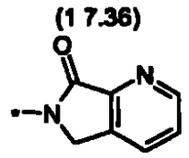
pyrrolo[3,4-*b*]pyridin-5,7-dion-6-yl

(1 7 38)



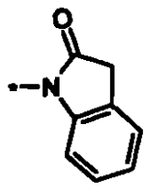
2,3-dihydro-*iso*-indol-1-on-2-yl

(1 7 39)



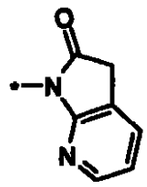
pyrrolo[3,4-*b*]pyridin-7-on-6-yl

(1 7 40)



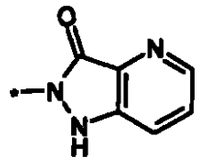
1,3-dihydro-indol-2-on-1-yl

(1 7.41)



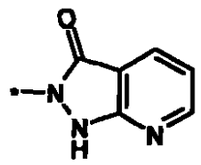
pyrrolo[4,5-*b*]pyridin-3-on-2-yl

(1 7 42)



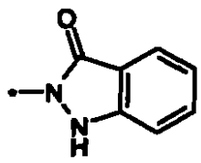
1*H*-pyrazolo[4,5-*e*]pyridin-7-on-2-yl

(1 7.43)



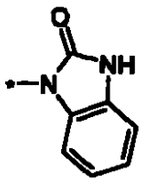
1*H*-pyrazolo[4,5-*b*]pyridin-4-on-2-yl

(1 7 44)



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

(1 7 45)

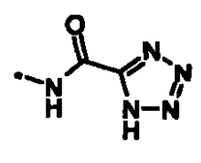


1*H*-benzimidazol-2-on-3-yl

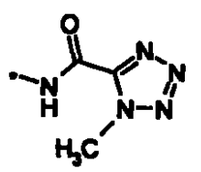
(1 7 46)

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

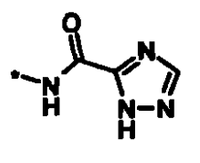
The present invention is further illustrated regarding preferred subgeneric groups comprising compounds of Formula (1 0 0) wherein $R^7c$ and $R^9$ of partial Formulas (1 1 10) through (1 1 15) are all selected in such a way that E comprises a member selected from the group consisting of the following partial Formulas (8 0 1) through (8 0 139)



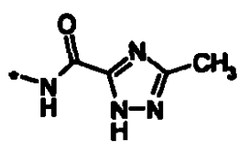
(8 0 1)



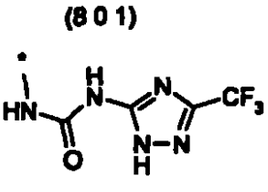
(8 0 2)



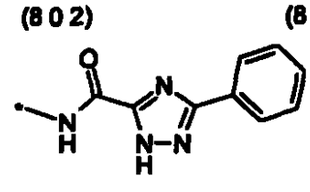
(8 0 3)



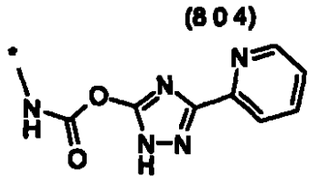
(8 0 4)



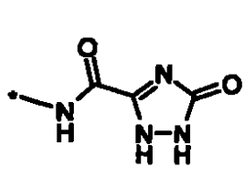
(8 0 5)



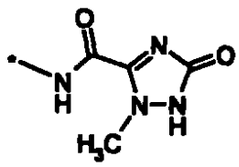
(8 0 6)



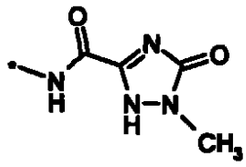
(8 0 7)



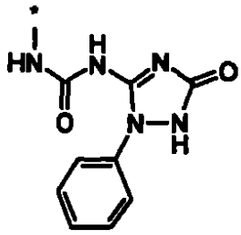
(8 0 8)



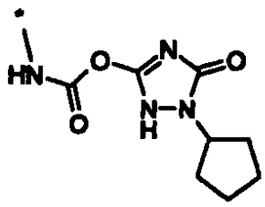
(8 0 9)



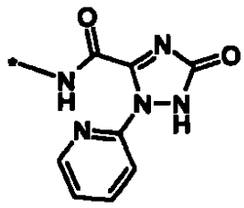
(8 0 10)



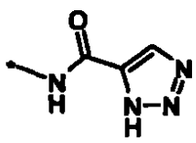
(8 0 11)



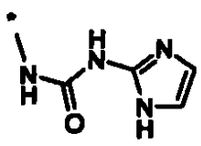
(8 0 12)



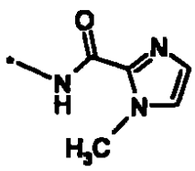
(8 0 13)



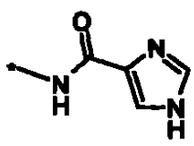
(8 0 14)



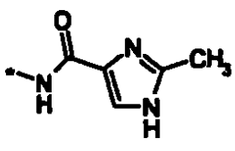
(8 0 15)



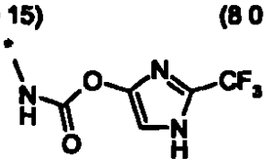
(8 0 16)



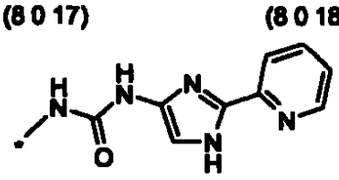
(8 0 17)



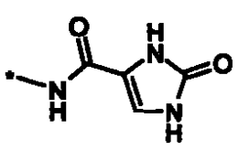
(8 0 18)



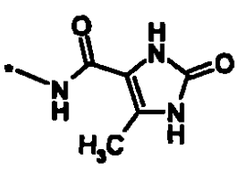
(8 0 19)



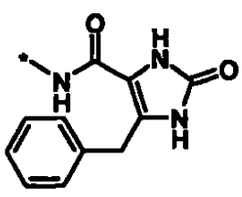
(8 0.20)



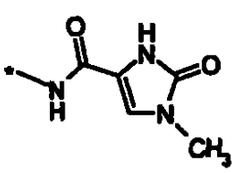
(8 0.21)



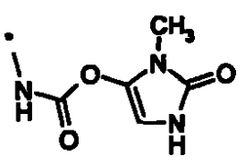
(8 0 22)



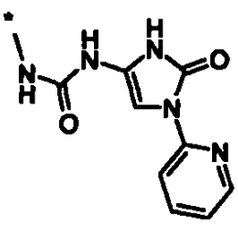
(8 0 23)



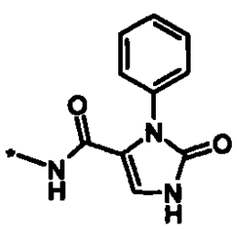
(8 0.24)



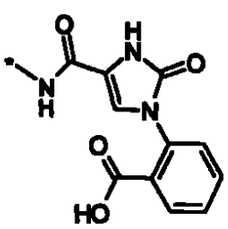
(8 0 25)



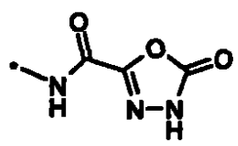
(8 0 26)



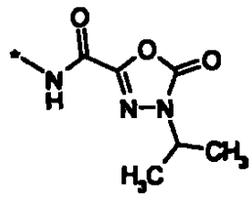
(8 0 27)



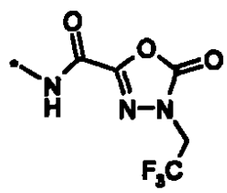
(8 0 28)



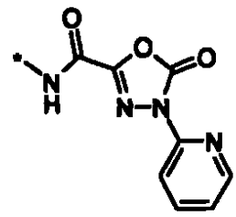
(8 0 29)



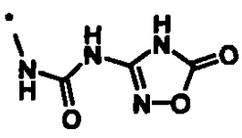
(8 0 30)



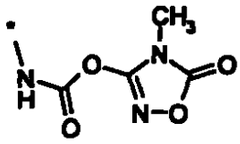
(8 0 31)



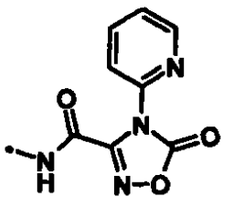
(8 0.32)



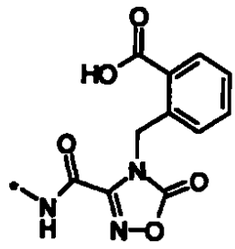
(8 0 33)



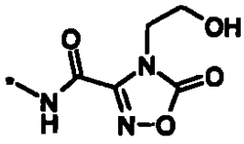
(8 0 34)



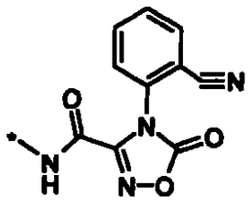
(8 0 35)



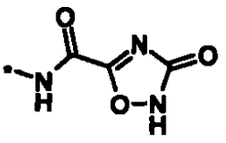
(8 0 36)



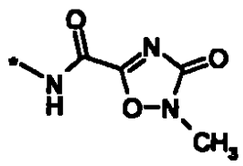
(8 0 37)



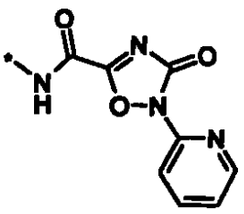
(8 0 38)



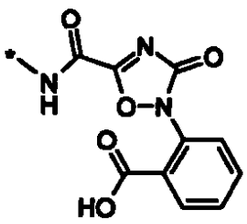
(8 0 39)



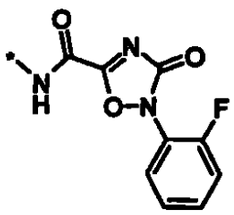
(8 0 40)



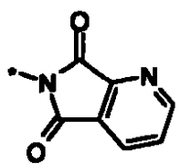
(8 0 41)



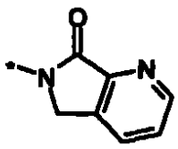
(8 0 42)



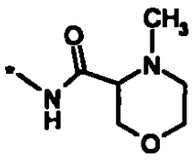
(8 0.43)



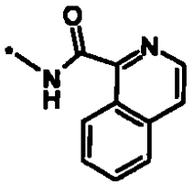
(8 0 44)



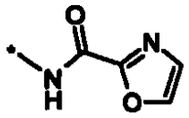
(8 0 45)



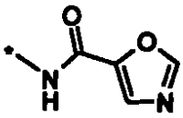
(8 0 46)



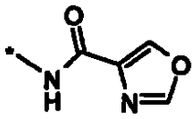
(8 0 47)



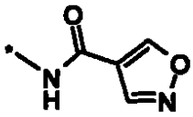
(8 0 48)



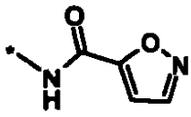
(8 0 49)



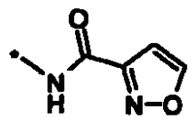
(8 0 50)



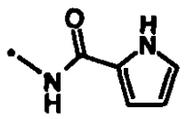
(8 0 51)



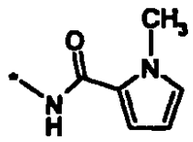
(8 0 52)



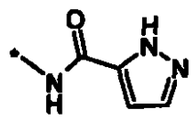
(8 0 53)



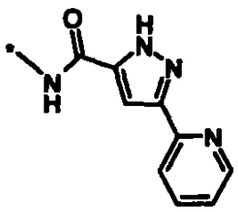
(8 0 54)



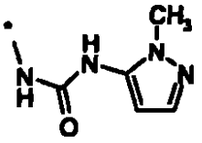
(8 0 55)



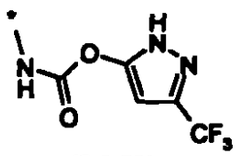
(8 0 56)



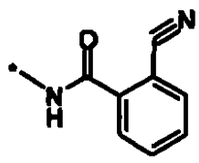
(8 0 57)



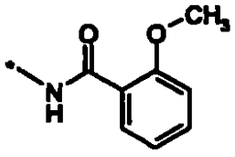
(8 0 58)



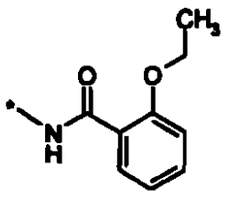
(8 0 59)



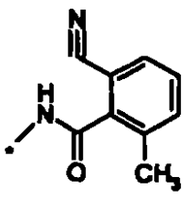
(8.0 60)



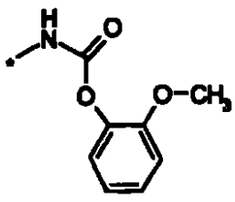
(8 0 61)



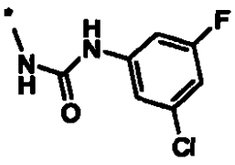
(8 0 62)



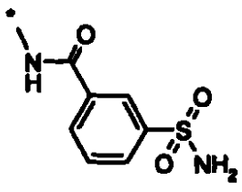
(8 0 63)



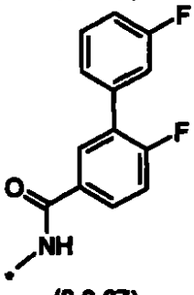
(8 0 64)



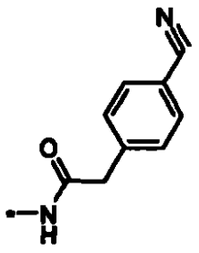
(8 0 65)



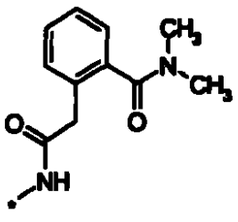
(8 0 66)



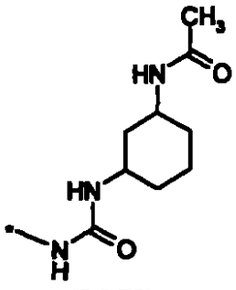
(8 0 67)



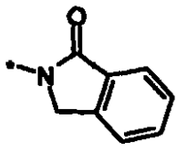
(8 0 68)



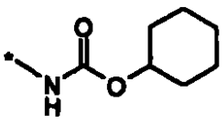
(8 0 69)



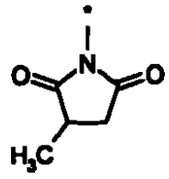
(8 0 70)



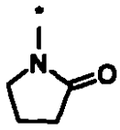
(8 0 71)



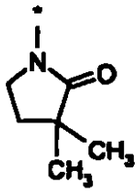
(8 0 72)



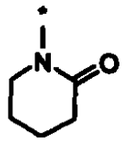
(8 0 73)



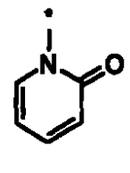
(8 0 74)



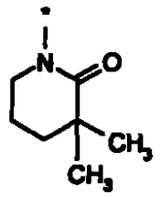
(8 0 75)



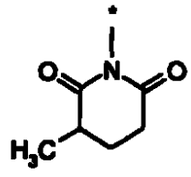
(8 0 76)



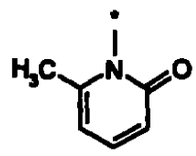
(8 0 77)



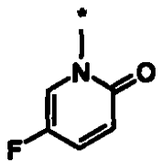
(8 0 78)



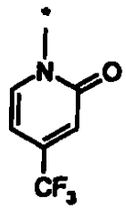
(8 0 79)



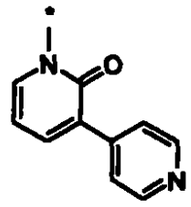
(8 0 80)



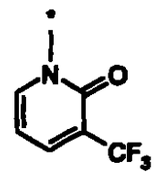
(8 0 81)



(8 0 82)



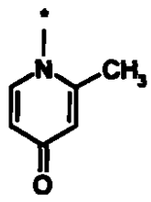
(8 0 83)



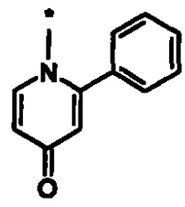
(8 0.84)



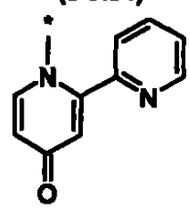
(8 0 85)



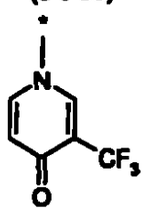
(8 0 86)



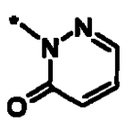
(8 0 87)



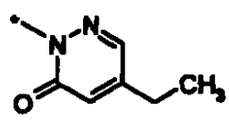
(8.0.88)



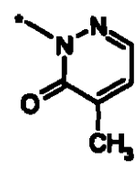
(8 0 89)



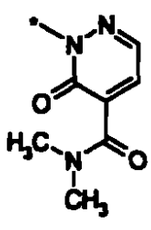
(8 0 90)



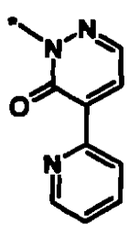
(8 0 91)



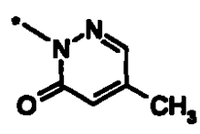
(8.0 92)



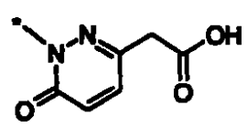
(8 0 93)



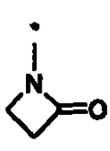
(8 0 94)



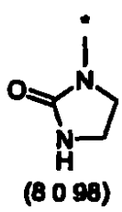
(8 0 95)



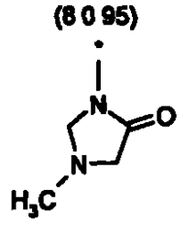
(8 0 96)



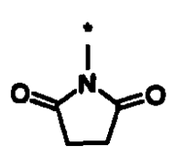
(8 0 97)



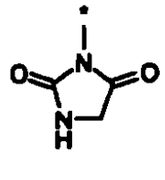
(8 0 98)



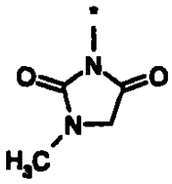
(8 0 99)



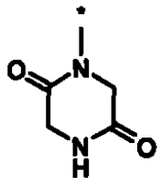
(8 0 100)



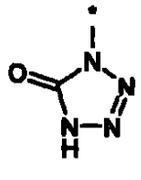
(8 0 101)



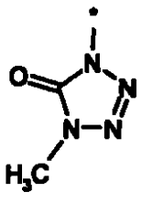
(8 0 102)



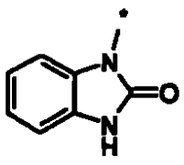
(8 0 103)



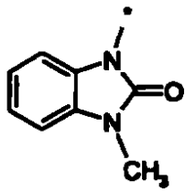
(8 0 104)



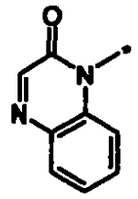
(8 0 105)



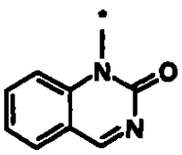
(8.0 106)



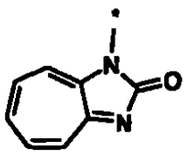
(8 0 107)



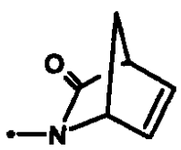
(8 0 108)



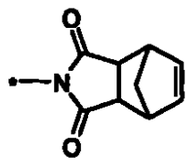
(8 0 109)



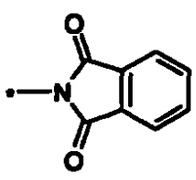
(8 0 110)



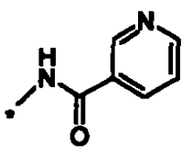
(8 0 111)



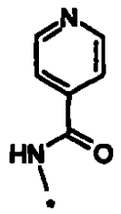
(8 0 112)



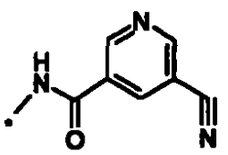
(8 0 113)



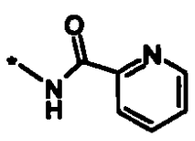
(8 0 114)



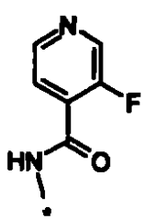
(8 0 115)



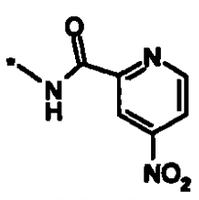
(8 0 116)



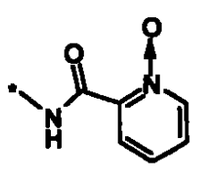
(8 0 117)



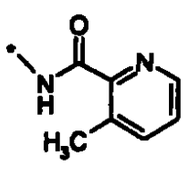
(8 0 118)



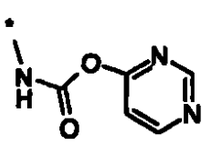
(8 0 119)



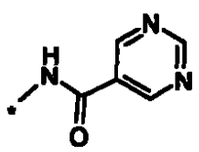
(8 0 120)



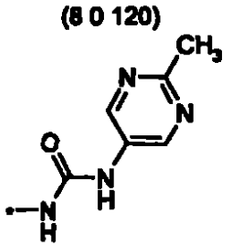
(8 0 121)



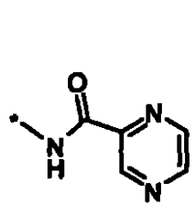
(8 0 122)



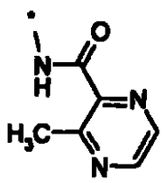
(8 0 123)



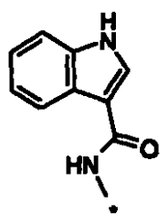
(8 0 124)



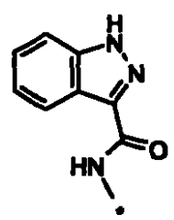
(8 0 125)



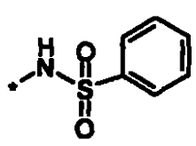
(8 0 126)



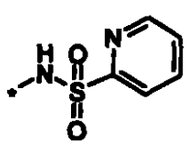
(8 0 127)



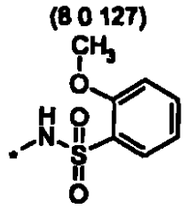
(8 0 128)



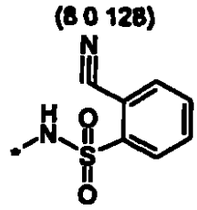
(8 0 129)



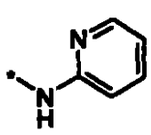
(8 0 130)



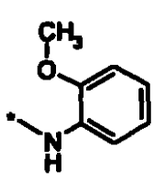
(8 0 131)



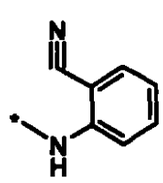
(8 0 132)



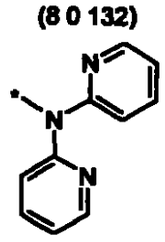
(8 0 133)



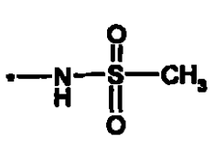
(8 0 134)



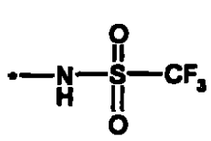
(8 0 135)



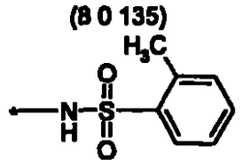
(8 0 136)



(8 0 137)



(8 0 138)

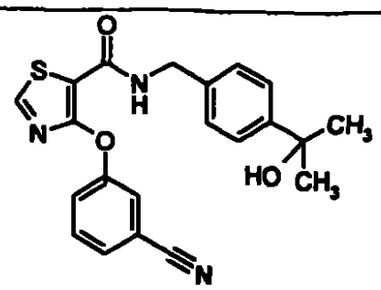
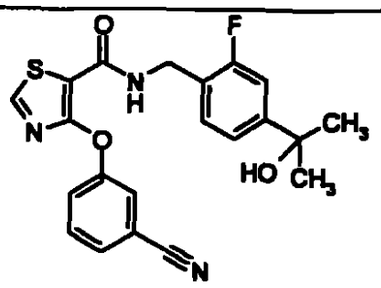
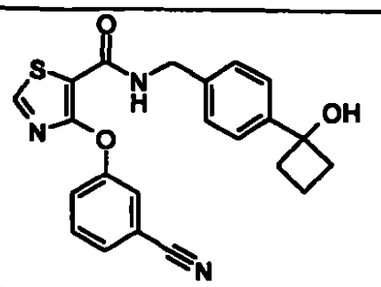
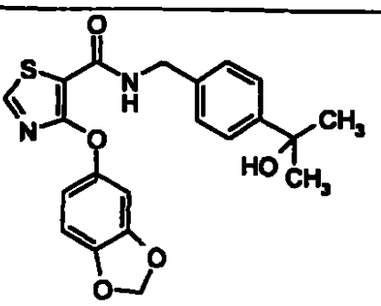
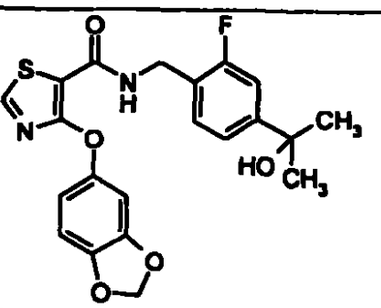


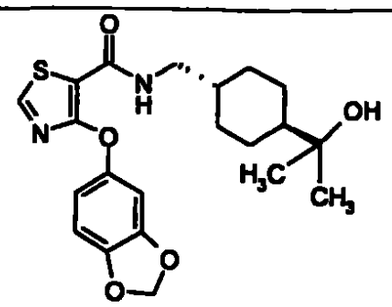
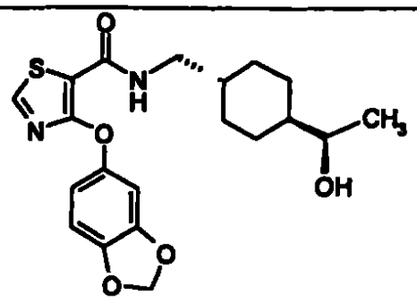
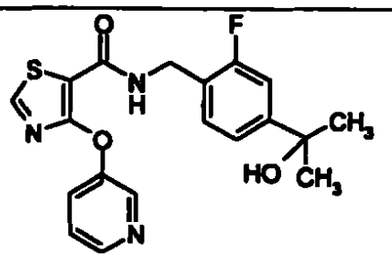
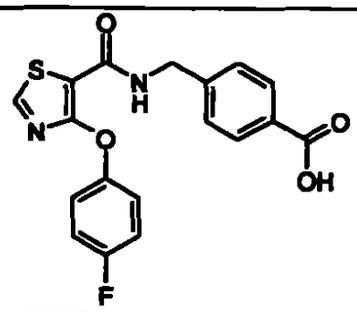
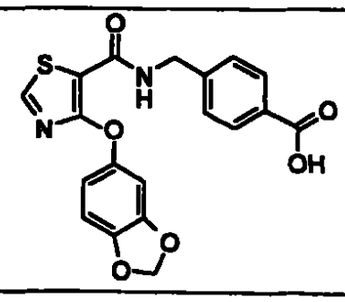
(8 0 139)

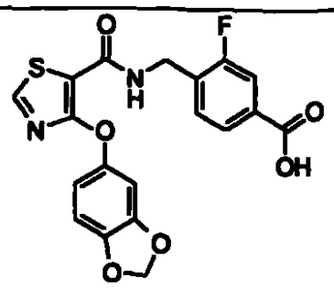
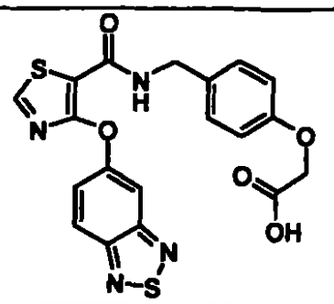
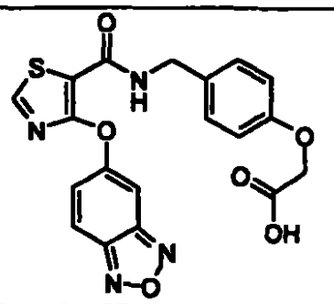
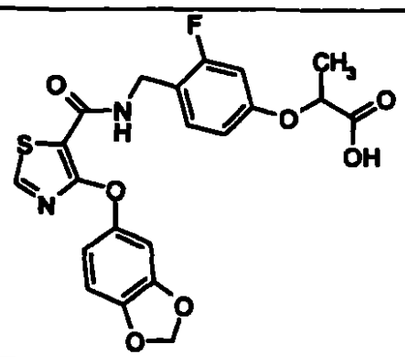
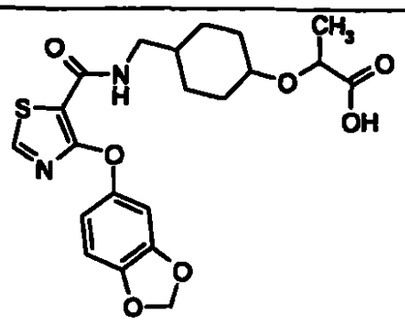
Any moiety that is a member selected from the group consisting of partial Formulas (8 0 1) through (8 0 139) depicted above, includes optional substitution thereof with respect to *(1)* any one or more carbon atoms thereof, by a substituent $R^{14}$ where $R^{14}$ has the same meaning as defined above, *(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

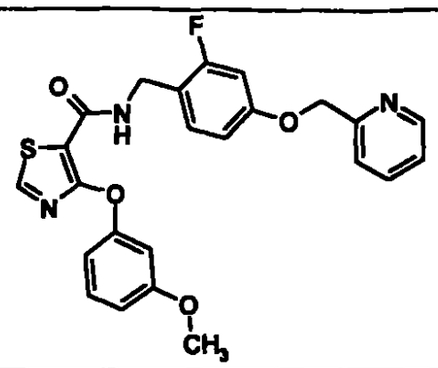
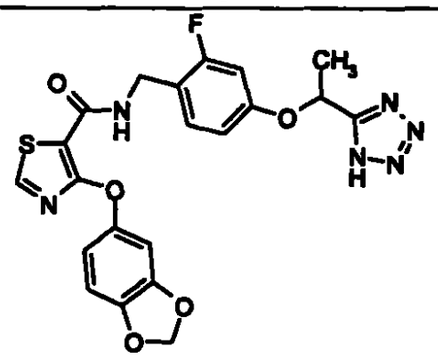
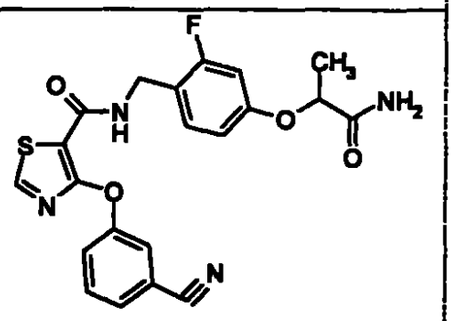
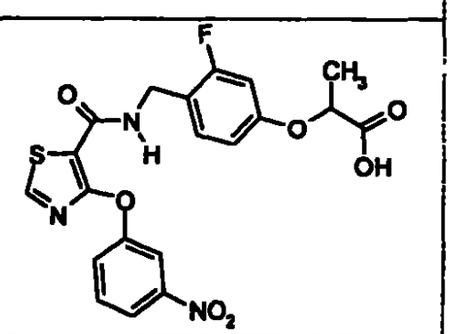
## 5.7 Representative Species of Formula (1 0.0)

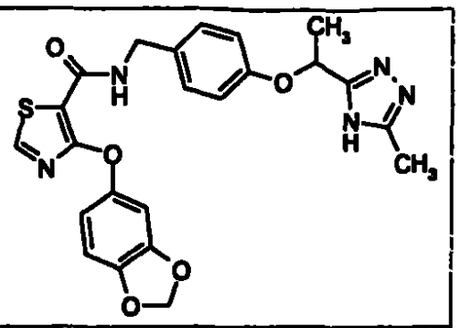
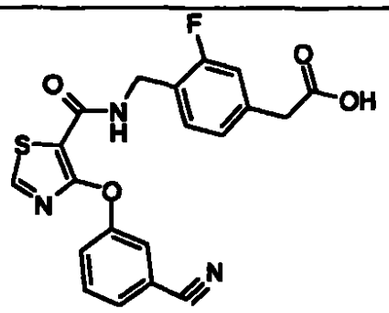
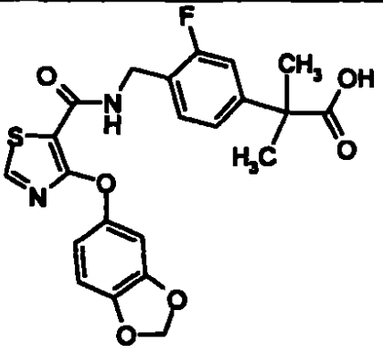
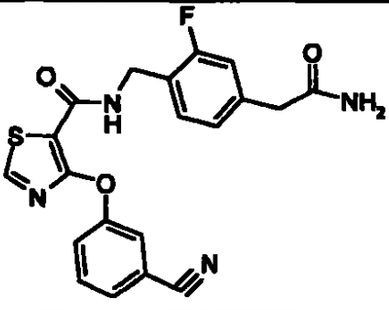
In the above description various preferred aspects of the compounds of Formula (1 0 0) have been set forth As a further demonstration of the scope and content of the present invention, specific compounds comprising embodiments of the compounds of Formula (1 0 0) are presented Such species of Formula (1 0 0) include, but are not limited to the following compounds of Formulas (8 5.1) through (8 5 44)

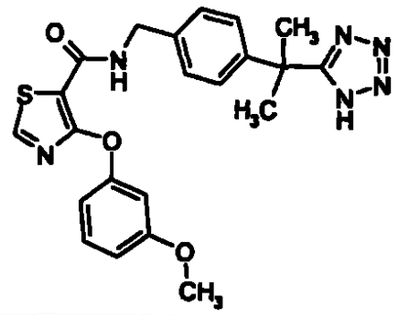
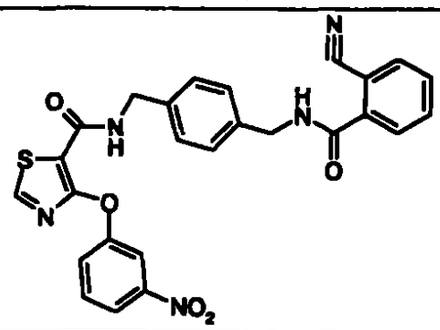
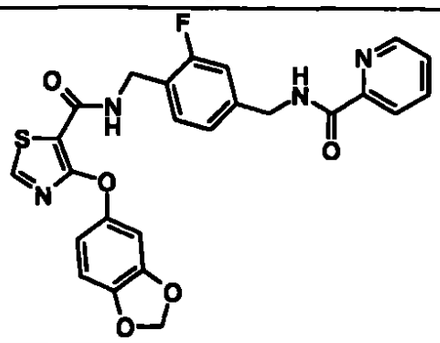
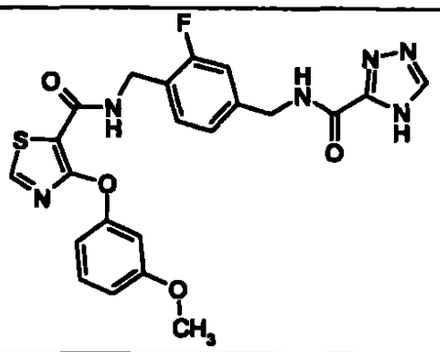
| | | |
|---|---|---|
| (8 5 1) | 4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 1), |  |
| (8 5.2) | 4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5.2), |  |
| (8 5.3) | 4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-cyclobutyl)-benzylamide of Formula (8 5 3), |  |
| (8 5 4) | 4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 4); |  |
| (8 5 5) | 4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 5), |  |

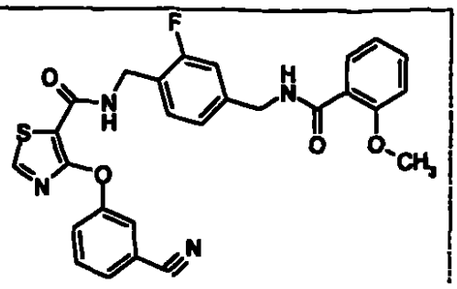
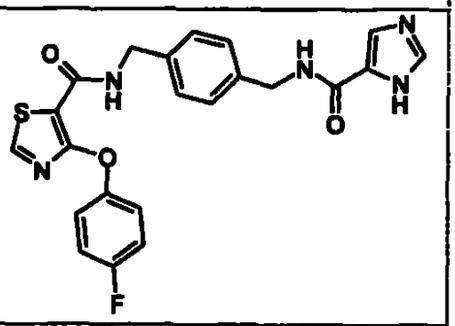
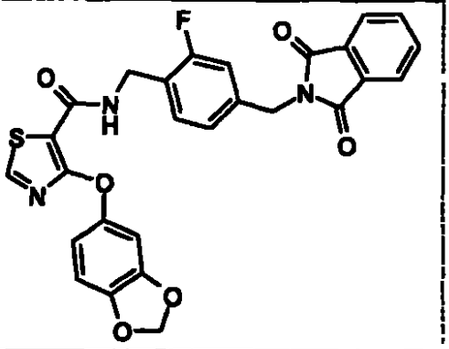
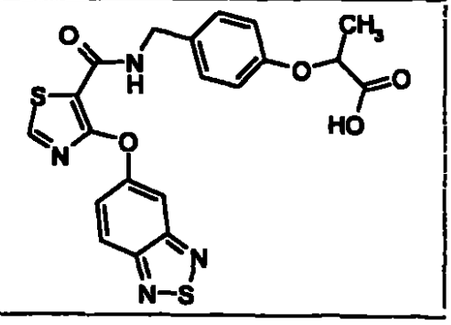
| | | |
|---|---|---|
| (8 5 6) | 4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid [4-(1-hydroxy-1-methyl-ethyl)-cyclohexylmethyl]-amide of Formula (8 5 6), |  |
| (8 5 7) | 4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid [4-(1-hydroxy-ethyl)-cyclohexylmethyl]-amide of Formula (8 5 7), |  |
| (8 5 8) | 4-(Pyridin-3-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 8), |  |
| (8 5 9) | 4-({[4-(4-Fluoro-phen-4-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-benzoic acid of Formula (8 5 9), |  |
| (8 5 10) | 4-{[(4-Benzo[1,3]dioxol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl}-benzoic acid of Formula (8 5 10), |  |

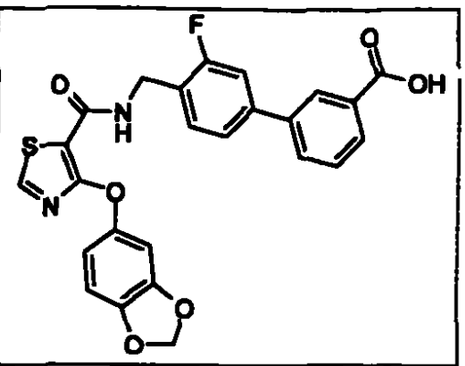
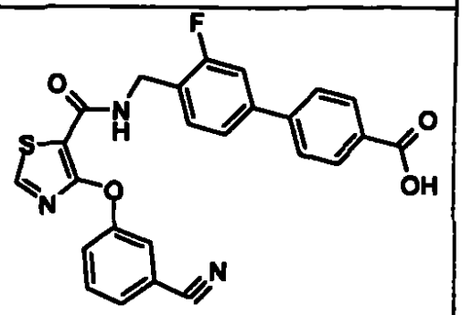
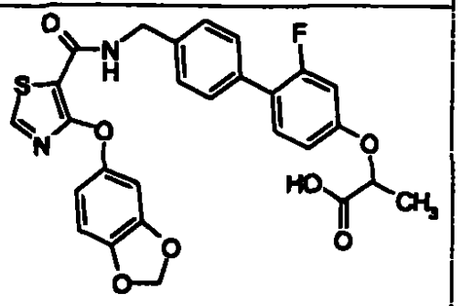
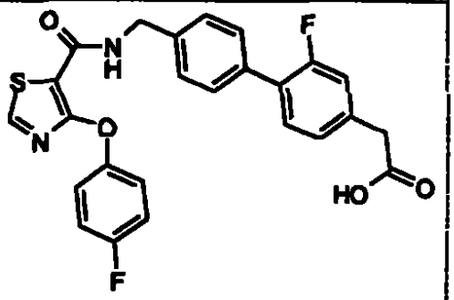
| | | |
|---|---|---|
| (8 5 11) | 4-({[4-(Benzo[1,3]dioxol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-benzoic acid of Formula (8 5 11), |  |
| (8 5 12) | [4-({[4-(Benzo[2,1,3]thiadiazol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-phen-4-yloxy]-acetic acid of Formula (8 5 12), |  |
| (8 5 13) | [4-({[4-(Benzo[2,1,3]oxadiazol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-phenyl-4-yloxy]-acetic acid of Formula (8 5 13); |  |
| (8 5 14) | (±)-2-[4-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (8 5 14), |  |
| (8 5 15) | (±)-2-[4-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (8 5 15), |  |

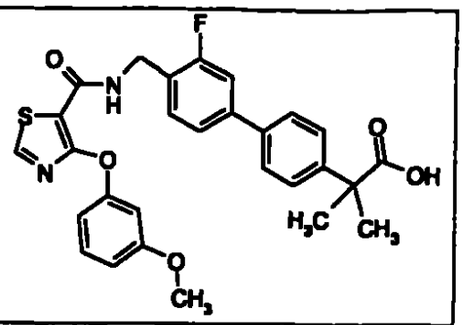
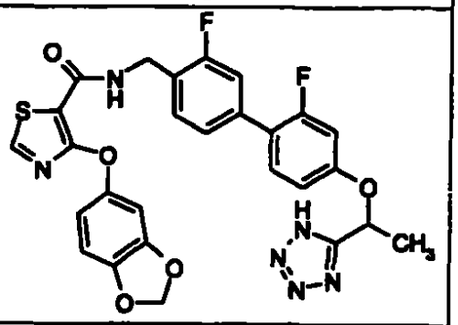
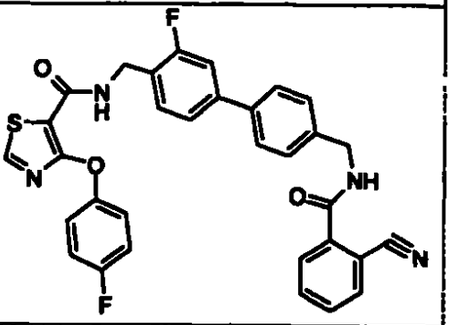
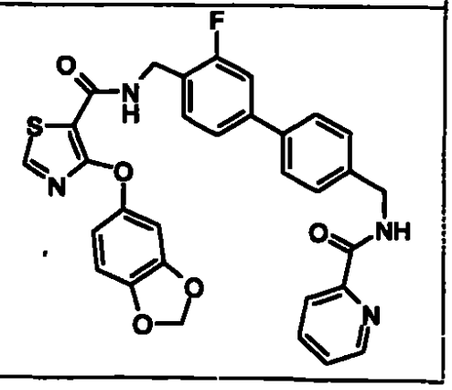
| | | |
|---|---|---|
| (8 5 16) | 4-(3-Methoxy-phenoxy)-thiazole-5-carboxylic acid 2-fluoro-4-(pyridin-2-ylmethoxy)-benzylamide of Formula (8 5 16); |  |
| (8 5 17) | (±)-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzylamide of Formula (8 5 17), |  |
| (8 5 18) | (±)-4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-carbamoyl-ethoxy)-2-fluoro-benzylamide of Formula (8 5 18), |  |
| (8 5 19) | (±)-2-[3-Fluoro-4-({[4-(3-nitro-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (8 5 19), |  |

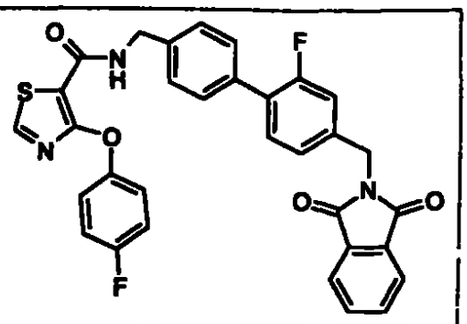
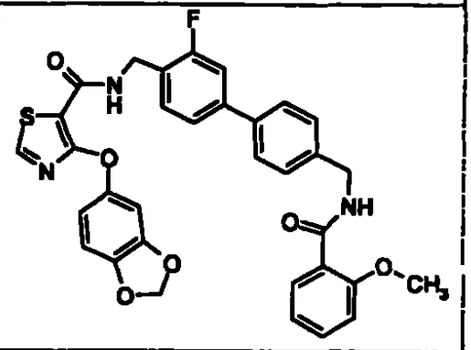
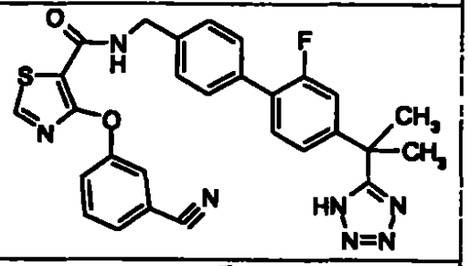
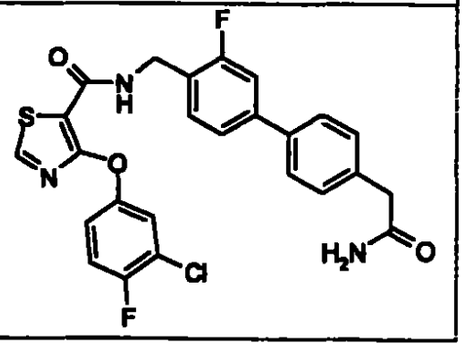
| | | |
|---|---|---|
| (8 5.20) | (±)-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzylamide of Formula (8 5 20); |  |
| (8 5 21) | [4-([[4-(3-Cyano-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-phenyl]-acetic acid of Formula (8.5.21), |  |
| (8 5 22) | 2-[4-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-phenyl]-2-methyl-propionic acid of Formula (8 5.22), |  |
| (8 5.23) | 4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-carbamoylmethyl-2-fluoro-benzylamide of Formula (8 5.23); |  |

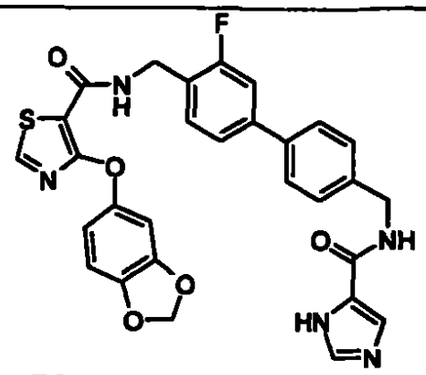
| | | |
|---|---|---|
| (8 5.24) | 4-(3-Methoxy-phenoxy)-thiazole-5-carboxylic acid 4-[1-methyl-1-(1H-tetrazol-5-yl)-ethyl]-benzylamide of Formula (8 5 24), |  |
| (8 5.25) | 4-(3-Nitro-phenoxy)-thiazole-5-carboxylic acid 4-[(2-cyano-benzoylamino)-methyl]-benzylamide of Formula (8 5.25), |  |
| (8 5 26) | Pyridine-2-carboxylic acid 4-({[4-(benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-benzylamide of Formula (8 5 26), |  |
| (8 5.27) | 4H-[1,2,4]Triazole-3-carboxylic acid 3-fluoro-4-({[4-(3-methoxy-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-benzylamide of Formula (8 5 27), |  |

| | | |
|---|---|---|
| (8 5 28) | 4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 2-fluoro-4-[(2-methoxy-benzoylamino)-methyl]-benzylamide of Formula (8 5.28), |  |
| (8 5 29) | 4-(4-Fluoro-phenoxy)-thiazole-5-carboxylic acid 4-[[(3H-imidazole-4-carbonyl)-amino]-methyl]-benzylamide of Formula (8 5 29), |  |
| (8 5 30) | 4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-fluoro-benzylamide of Formula (8 5 30), |  |
| (8 5.31) | (±)-2-[4-({[4-(Benzo[2,1,3]thiadiazol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (8 5 31), |  |

| | | |
|---|---|---|
| (8 5 32) | 4'-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8 5 32), |  |
| (8 5 33) | 4'-({[4-(3-Cyano-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-4-carboxylic acid of Formula (8 5 33), |  |
| (8 5 34) | (±)-2-[4'-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-propionic acid of Formula (8 5 34); |  |
| (8 5 35) | [2-Fluoro-4'-({[4-(4-fluoro-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-biphenyl-4-yl]-acetic acid of Formula (8 5 35), |  |

| | | |
|---|---|---|
| (8 5 36) | 2-[3'-Fluoro-4'-({[4-(3-methoxy-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-biphenyl-4-yl]-2-methyl-propionic acid of Formula (8 5 36), |  |
| (8 5 37) | (±)-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid {3,2'-difluoro-4'-[1-(1H-tetrazol-5-yl)-ethoxy]-biphenyl-4-ylmethyl}-amide of Formula (8 5 37), |  |
| (8 5 38) | 4-(4-Fluoro-phenoxy)-thiazole-5-carboxylic acid {4'-[(2-cyano-benzoylamino)-methyl]-3-fluoro-biphenyl-4-ylmethyl}-amide of Formula (8 5.38), |  |
| (8 5 39) | Pyridine-2-carboxylic acid [4'-({[4-(benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-4-ylmethyl]-amide of Formula (8 5 39), |  |

| | | |
|---|---|---|
| (8 5 40) | 4-(4-Fluoro-phenoxy)-thiazole-5-carboxylic acid [4'-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2'-fluoro-biphenyl-4-ylmethyl]-amide of Formula (8 5.40), |  |
| (8 5 41) | 4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid {3-fluoro-4'-[(2-methoxy-benzoylamino)-methyl]-biphenyl-4-ylmethyl}-amide of Formula (8 5 41), |  |
| (8 5.42) | 4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid {2'-fluoro-4'-[1-methyl-1-(1H-tetrazol-5-yl)-ethyl]-biphenyl-4-ylmethyl}-amide of Formula (8 5 42), |  |
| (8 5 43) | 4-(3-Chloro-4-fluoro-phenoxy)-thiazole-5-carboxylic acid (4'-carbamoylmethyl-3-fluoro-biphenyl-4-ylmethyl)-amide of Formula (8 5.43), |  |

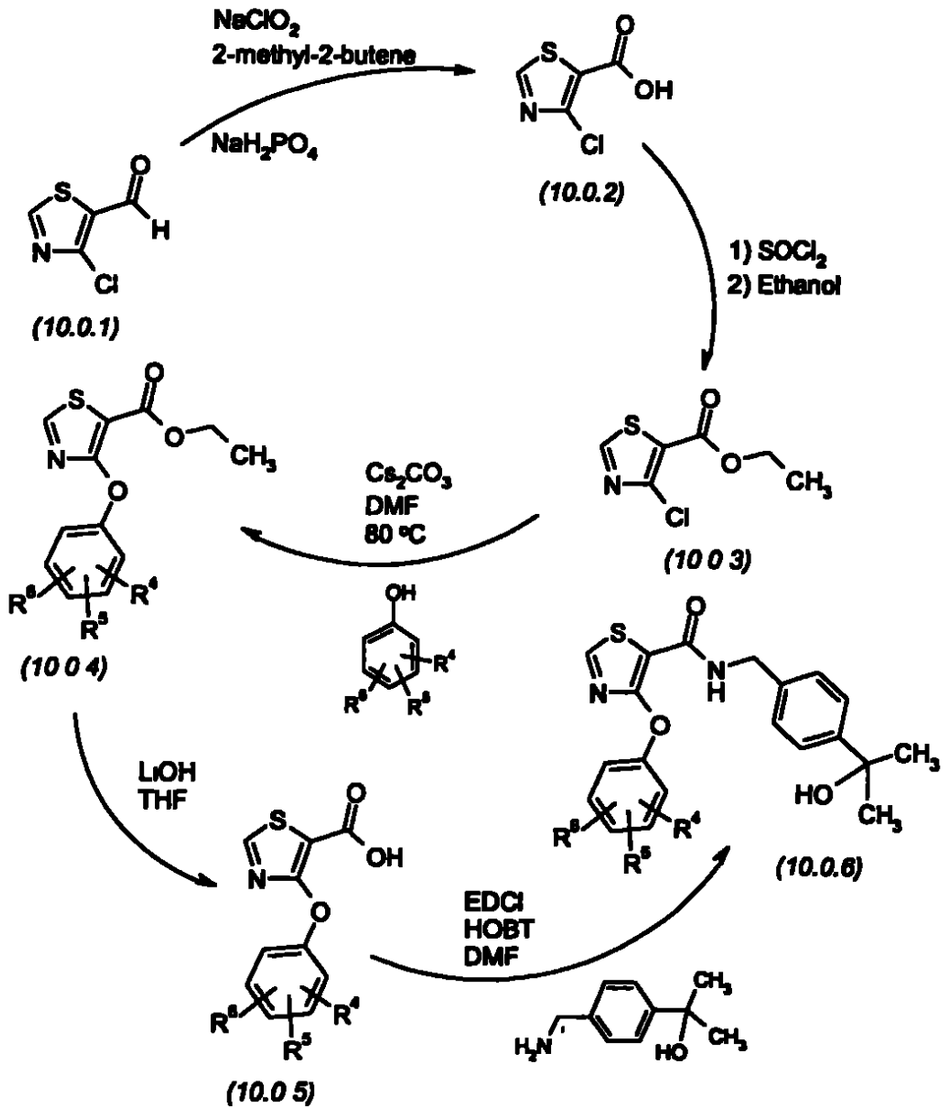
| | | |
|---|---|---|
| (8 5 44) | 4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid (3-fluoro-4'-{[(3H-imidazole-4-carbonyl)-amino]-methyl}-biphenyl-4-ylmethyl)-amide of Formula (8 5 44), |  |

## DETAILED DESCRIPTION OF THE INVENTION

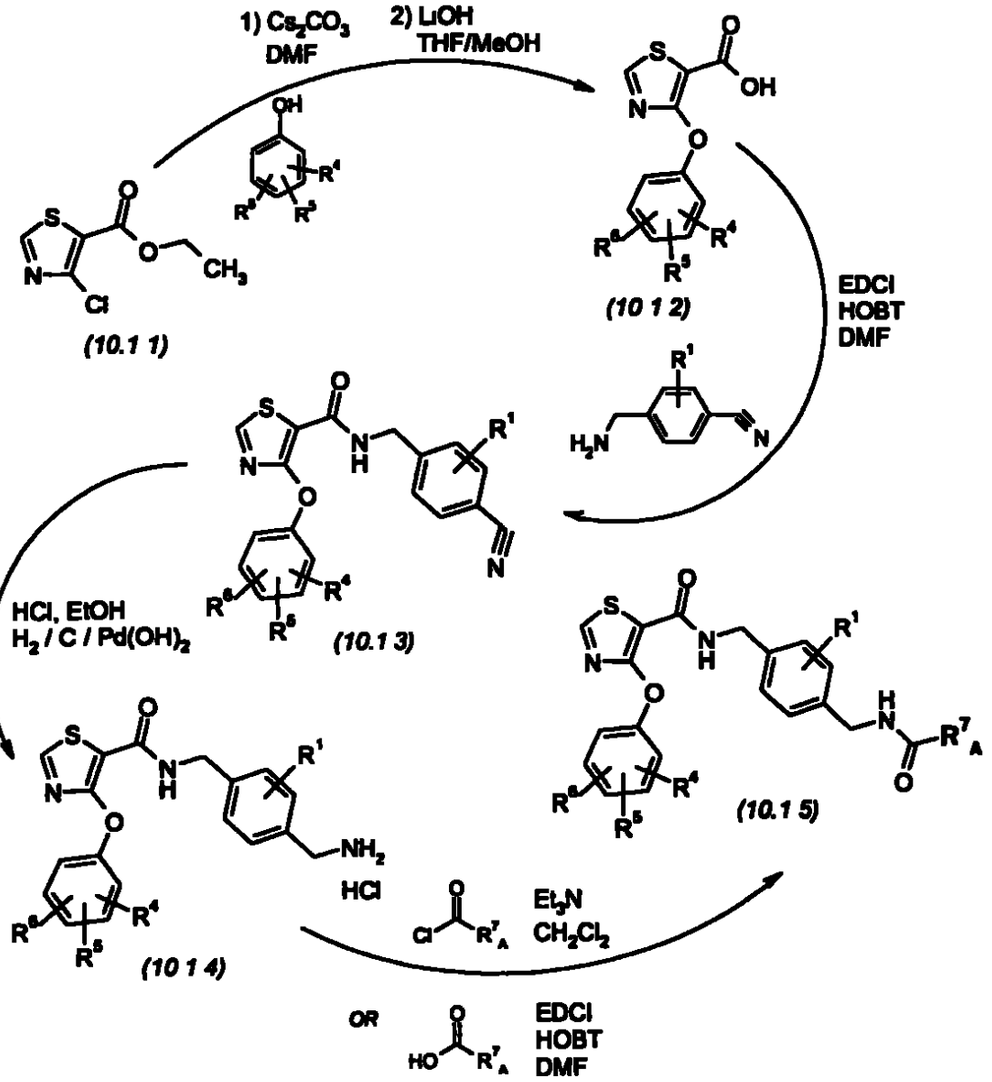
### 6.0 Processes for Making the Compounds of Formula (1.0.0)

A method suitable for preparing the compounds of Formula (1 0 0) where both the $G^1$ and $G^2$ groups are phenyl, and the E group is a moiety of partial Formula (1 1 8), is illustrated in Synthesis Scheme (10 0 0) below

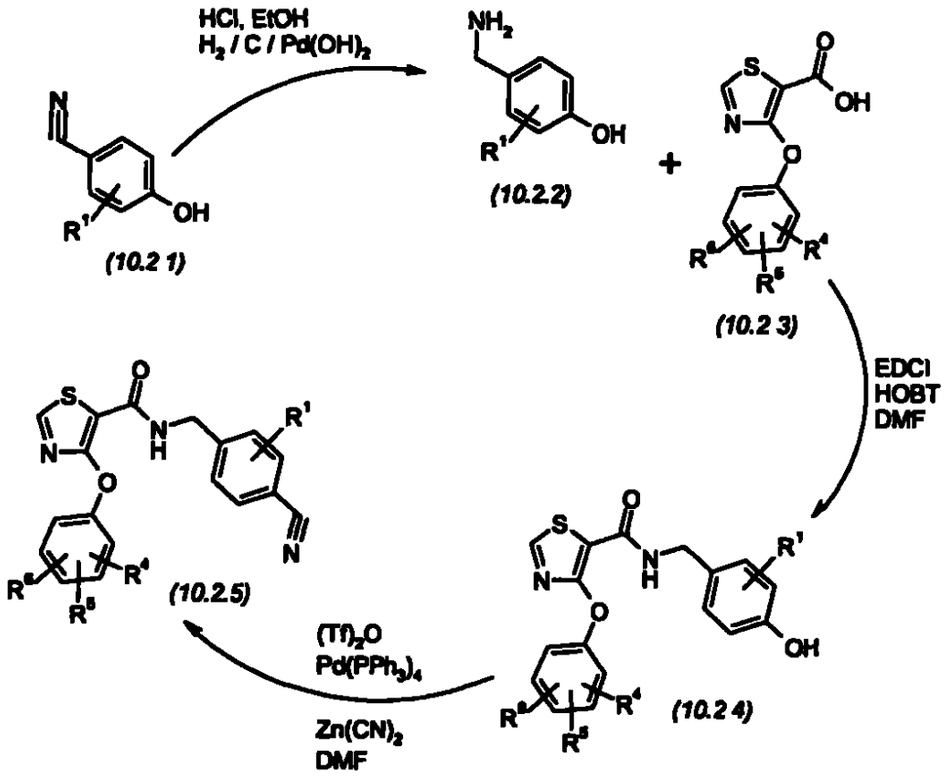
SYNTHESIS SCHEME (10.0.0)



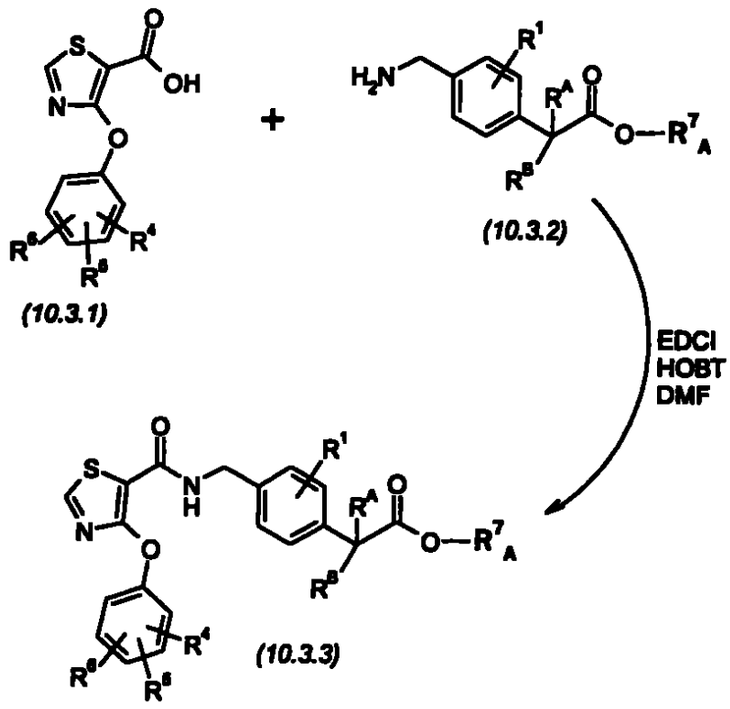
SYNTHESIS SCHEME (10.1 0)



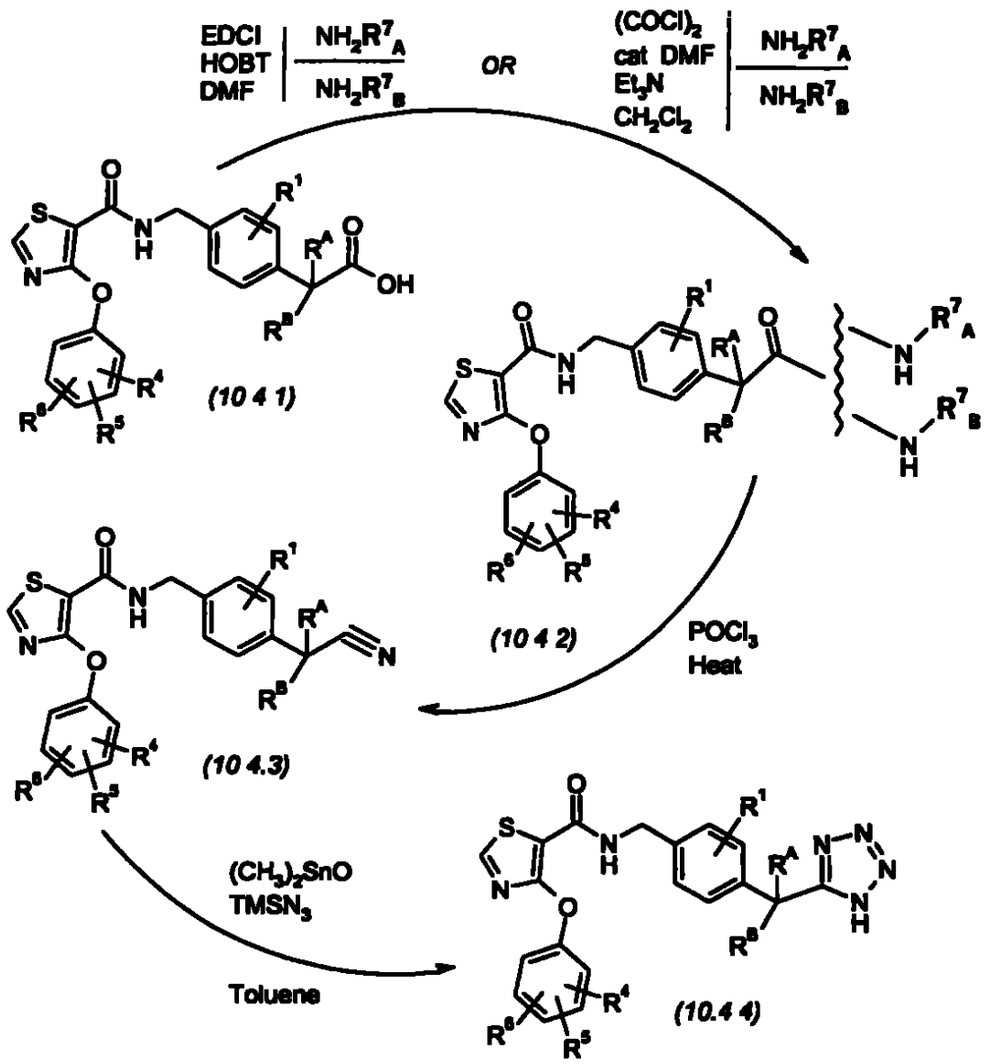
SYNTHESIS SCHEME (10.2 0)



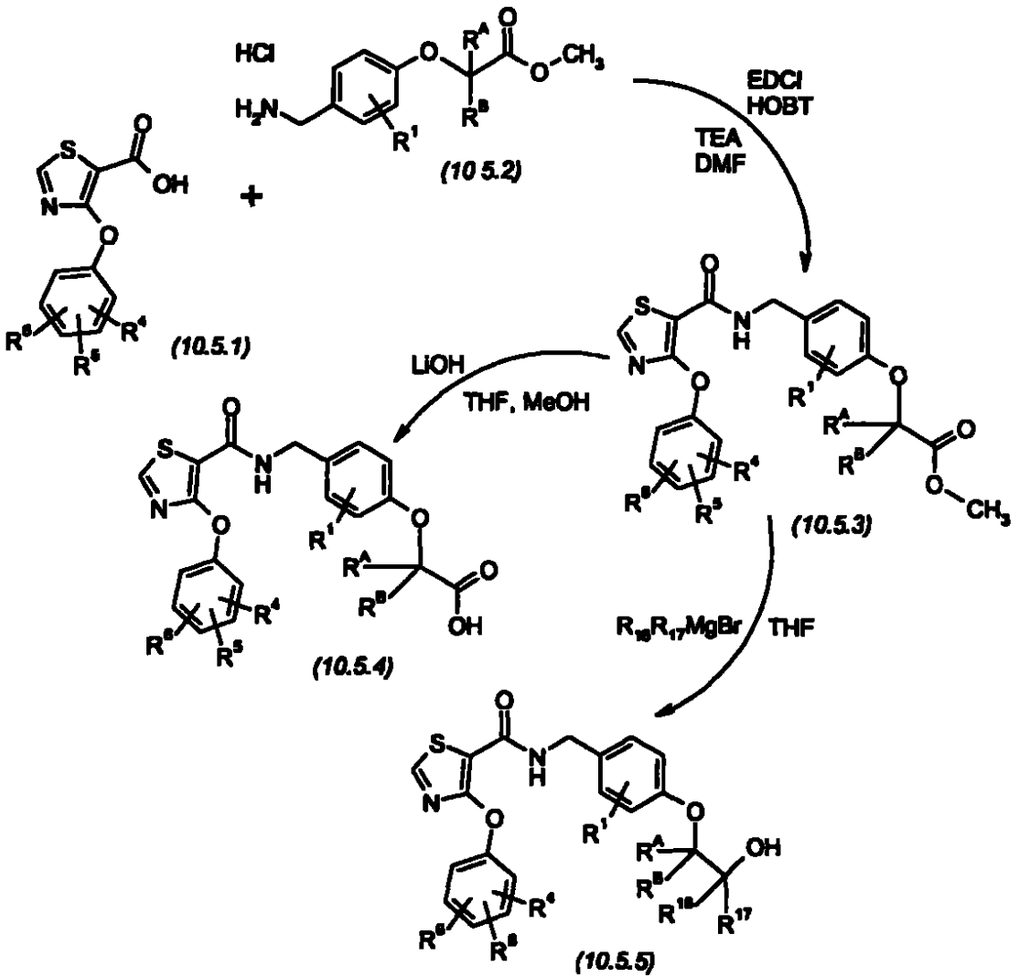
SYNTHESIS SCHEME (10.3.0)



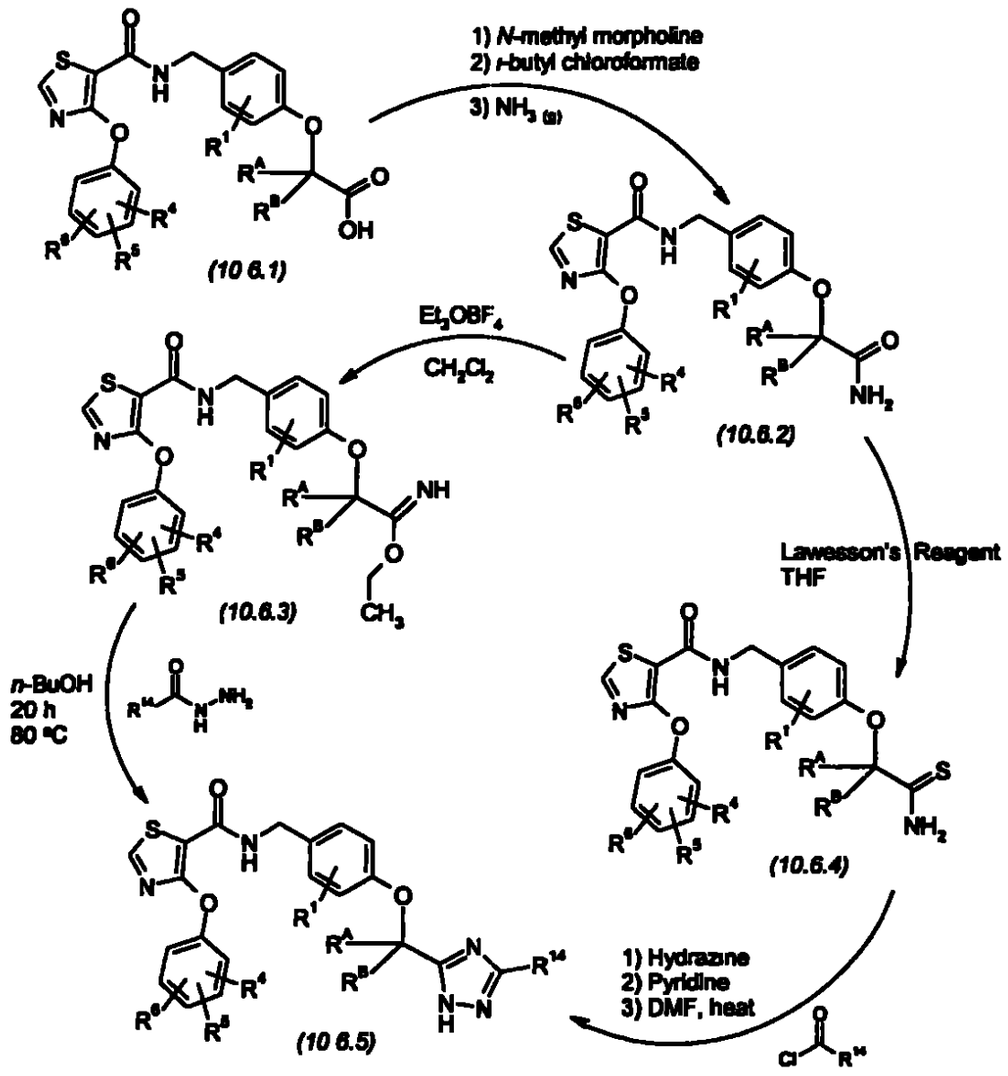
SYNTHESIS SCHEME (10.4 0)



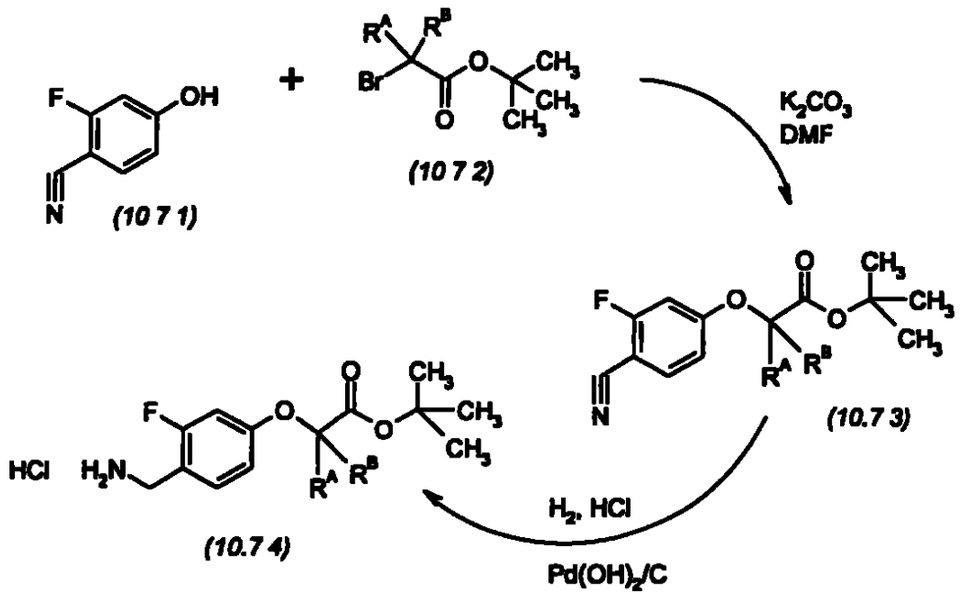
SYNTHESIS SCHEME (10.5 0)



SYNTHESIS SCHEME (10.6.0)

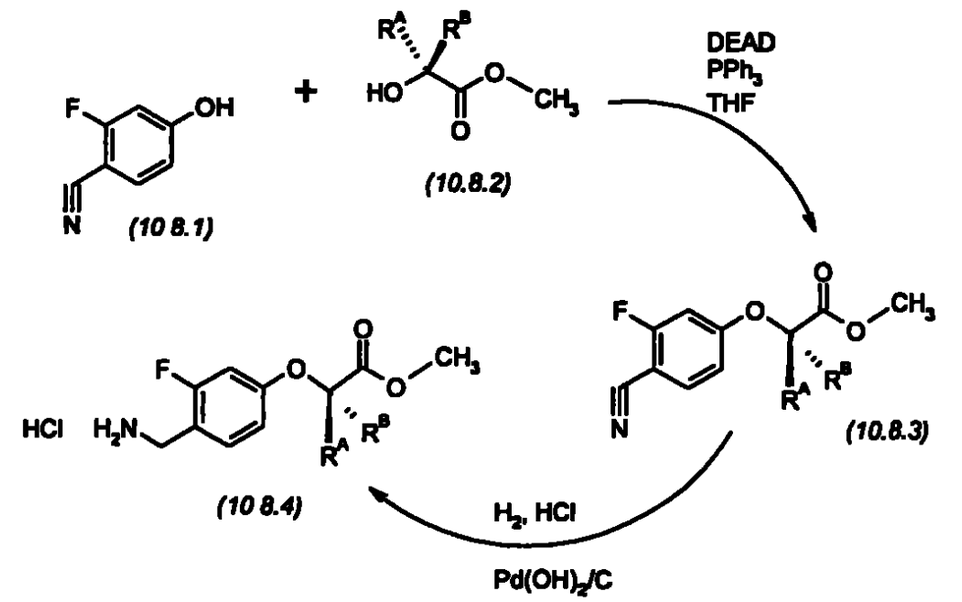


SYNTHESIS SCHEME (10.7.0)




5

SYNTHESIS SCHEME (10.8.0)



## 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 mono-arylsulfonates such as ethanesulfonate, toluenesulfonate, and benzenesulfonate, and other organic acids and their corresponding salts such as acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate, ascorbate, *etc*

Accordingly, the pharmaceutically acceptable acid addition salts of the compounds of Formula (1 0 0) include, but are not limited to acetate, adipate, alginate, arginate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, citrate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptanoate, gluconate, glutamate, 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 *Sys-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

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

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

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

Having regard to their bronchodilator activity the compounds of Formula (1 0 0) are useful as bronchodilators, *e g* , in the treatment of chronic or acute bronchoconstriction, and for the symptomatic treatment of obstructive or inflammatory airways diseases

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

In light of the above description, it may be seen that the present invention also relates to a method for the treatment of airways hyper-reactivity in mammals, to a method of effecting bronchodilation in mammals, and in particular, to a method of treating obstructive or inflammatory airways diseases, especially asthma, in a mammal subject in need thereof, which method comprises administering to said subject mammal an effective amount of a compound of Formula (1 0 0)

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

The compounds of Formula (1 0 0) are useful in the treatment of asthma of whatever type, etiology, or pathogenesis, including intrinsic asthma attributed to pathophysiologic disturbances, extrinsic asthma caused by some factor in the environment, and essential asthma of unknown or inapparent cause The compounds of Formula (1 0 0) are useful in the treatment of allergic (atopic/bronchial/IgE-mediated) asthma, and they are useful as well in the treatment of non-atopic asthma, including *e g* bronchitic, emphysematous, exercise-induced, and occupational asthma, infective asthma that is a sequela to microbial, especially bacterial, fungal, protozoal, or viral infection, and other non-allergic asthmas, *e g* , incipient asthma (wheezy infant syndrome)

The compounds of Formula (1 0 0) are further useful in the treatment of pneumoconiosis of whatever type, etiology, or pathogenesis, including, *e g*, aluminosis (bauxite workers' disease), anthracosis (miners' asthma), asbestosis (steam-fitters' asthma), chalicosis (flint disease), ptilosis caused by inhaling the dust from ostrich feathers, siderosis caused by the inhalation of iron particles, silicosis (grinders' disease); byssinosis (cotton-dust asthma), and talc pneumoconiosis

8.2 Chronic Obstructive Pulmonary Disease (COPD)

The compounds of Formula (1 0.0) are still further useful in the treatment of COPD or COAD including chronic bronchitis, pulmonary emphysema or dyspnea associated therewith COPD is characterized by irreversible, progressive airways obstruction Chronic bronchitis is associated with hyperplasia and hypertrophy of the mucus secreting glands of the submucosa in the large cartilaginous airways Goblet cell hyperplasia, mucosal and submucosal inflammatory cell infiltration, edema, fibrosis, mucus plugs and increased smooth muscle are all found in the terminal and respiratory bronchioles The small airways are known to be a major site of airway obstruction Emphysema is characterized by destruction of the alveolar wall and loss of lung elasticity A number of risk factors have also been identified as linked to the incidence of COPD The link between tobacco smoking and COPD is well established Other risk factors include exposure to coal dust and various genetic factors See Sandford *et al.*, "Genetic risk factors for chronic obstructive pulmonary disease," *Eur Respir J* 10 1380-1391, 1997. The incidence of COPD is increasing and it represents a significant economic burden on the populations of the industrialized nations COPD also presents itself clinically with a wide range of variation from simple chronic bronchitis without disability to patients in a severely disabled state with chronic respiratory failure

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

Accordingly, the use of the compounds of Formula (1 0 0) to treat COPD and its related and included obstructed airways diseases, represents a significant advance in the art. The present invention is not limited to any particular mode of action or any hypothesis as to the way in which the desired therapeutic objectives have been obtained by utilizing the

compounds of Formula (1 0 0) However, it is recognized in the art that PDE4 is the predominant PDE in neutrophils and 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

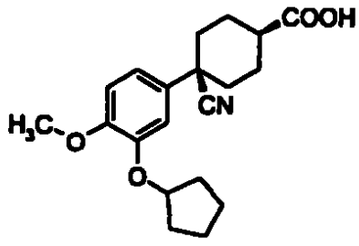
In order to provide a better understanding of the present invention, the inference is made here that the compounds of Formula (1 0 0) inhibit PDE4s in neutrophils, resulting in reduced chemotaxis, activation, adherence, and degranulation, Schudt *et al*, *Ibid*, Nelson *et al*, "Effect of selective phosphodiesterase 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* 101 502-508, 1995, and Ottonello *et al*, "Tumor necrosis factor alpha-induced oxidative burst in neutrophils adherent to fibronectin effects of cyclic AMP-elevating agents," *Br J Haematol* 91 566-570, 1995

It is further inferred that the compounds of Formula (1 0 0) inhibit CD11b/CD18 expression, Berends *et al*, "Inhibition of PAF-induced expression of CD11b and shedding of L-selectin on human neutrophils and eosinophils by the type-IV selective PDE inhibitor, rolipram," *Eur Respir J* 10 1000-1007, 1997, and Denan *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-8 release by endotoxin-stimulated macrophages," *J Immunol* 155 4909-4916, 1995

The application of PDE4 inhibitors to the treatment of COPD in human patients has been demonstrated in clinical trials Treatment with SB-207,499, represented by Formula (0 1 9) above, at a dose of 15 mg twice a day for six weeks has been shown to result in increases in $FEV_1$ and forced vital capacity (FVC), Brown, W M , "SB-207499," *Anti-Inflamm Immunomodulatory Invest Drugs* 1 39-47, 1999 The clinical efficacy of SB-207,499 has also been demonstrated in a four week trial that has provided evidence of improved $FEV_1$, and in a six week study in COPD patients receiving 15 mg twice a day that has also provided evidence of improved $FEV_1$, Brown, *Ibid* SB-207,499 has already been described further above and represented by Formula (0 1 9)




SB-207,499 (0 1 9)

8 3 Bronchitis and Bronchiectasis

In accordance with the particular and diverse inhibitory activities described above that are possessed by the compounds of Formula (1 0 0), they are useful in the treatment of bronchitis of whatever type, etiology, or pathogenesis, including, *e g*, acute bronchitis which has a short but severe course and is caused by exposure to cold, breathing of irritant substances, or an acute infection, acute laryngotracheal bronchitis which is a form of nondiphtheritic croup, arachidic bronchitis which is caused by the presence of a peanut kernel in a bronchus, catarrhal bronchitis which is a form of acute bronchitis with a profuse mucopurulent discharge, chronic bronchitis which is a long-continued form of bronchitis with a more or less marked tendency to recurrence after stages of quiescence, due to repeated

attacks of acute bronchitis or chronic general diseases, characterized by attacks of coughing, by expectoration either scanty or profuse, and by secondary changes in the lung tissue, croupus bronchitis which is characterized by violent cough and paroxysms of dyspnea, dry bronchitis which is characterized by a scanty secretion of tough sputum, infectious asthmatic bronchitis which is a syndrome marked by the development of symptoms of bronchospasm following respiratory tract infections in persons with asthma, productive bronchitis which is bronchitis associated with a productive cough, staphylococcus or streptococcal bronchitis which are caused by staphylococci or streptococci, and vesicular bronchitis in which the inflammation extends into the alveoli, which are sometimes visible under the pleura as whitish-yellow granulations like millet seeds

Bronchiectasis is a chronic dilatation of the bronchi marked by fetid breath and paroxysmal coughing with the expectoration of mucopurulent matter It may affect the tube uniformly, in which case it is referred to as cylindric bronchiectasis, or it may occur in irregular pockets, in which case it is called sacculated bronchiectasis When the dilated bronchial tubes have terminal bulbous enlargements, the term fusiform bronchiectasis is used In those cases where the condition of dilatation extends to the bronchioles, it is referred to as capillary bronchiectasis If the dilatation of the bronchi is spherical in shape, the condition is referred to as cystic bronchiectasis Dry bronchiectasis occurs where the infection involved is episodic and it may be accompanied by hemoptysis, the expectoration of blood or of blood-stained sputum During quiescent periods of dry bronchiectasis, the coughing which occurs is nonproductive Follicular bronchiectasis is a type of bronchiectasis in which the lymphoid tissue in the affected regions becomes greatly enlarged, and by projection into the bronchial lumen, may seriously distort and partially obstruct the bronchus Accordingly, the compounds of Formula (1 0 0) are useful in the beneficial treatment of the various above-described types of bronchiectasis as a direct result of their inhibition of PDE4 isozymes

The utility of the compounds of Formula (1 0 0) as bronchodilators or bronchospasmolytic agents for treating bronchial asthma, chronic bronchitis and related diseases and disorder described herein, is demonstrable through the use of a number of different *in vivo* animal models known in the art, including those described in the paragraphs below

Bronchospasmolytic Activity *In Vitro* – The ability of the compounds of Formula (1 0 0) to cause relaxation of guinea-pig tracheal smooth muscle is demonstrated in the following test procedure Guinea-pigs (350-500 g) are killed with sodium pentothal (100 mg/kg i p ) The trachea is dissected and a section 2-3 cm in length is excised The trachea is transected in the transverse plane at alternate cartilage plates so as to give rings of tissue 3-5 mm in depth The proximal and distal rings are discarded Individual rings are mounted

vertically on stainless steel supports, one of which is fixed at the base of an organ bath, while the other is attached to an isometric transducer The rings are bathed in Krebs solution (composition μM $NaHCO_3$ 25, NaCl 113, KCl 4 7, $MgSO_4$ $7H_2O$ 1 2, $KH_2PO_4$ 1.2, $CaCl_2$ 2 5, glucose 11 7) at 37°C and gassed with $O_2/CO_2$ (95 5, v/v) Rings prepared in this manner, preloaded to 1 g, generate spontaneous tone and, after a period of equilibration (45-60m), relax consistently on addition of spasmolytic drugs To ascertain spasmolytic activity, test compounds of Formula (1 0 0) are dissolved in physiological saline and added in increasing quantities to the organ bath at 5m intervals to provide a cumulative concentration-effect curve

In the above test model, compounds of Formula (1 0 0) produce concentration-related relaxation of guinea-pig tracheal ring preparations at concentrations in the range of from 0 001 to 1 0 μM

The anti-inflammatory activity of the combinations of therapeutic agents of the present invention is demonstrated by the inhibition of TNFα production in human whole blood stimulated with Lipopolysachande (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

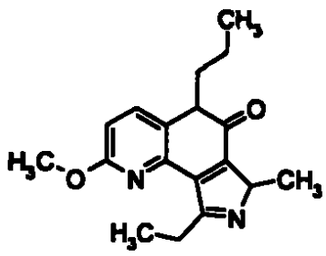
Allergic rhinitis is characterized by nasal obstruction, itching, watery rhinorrhea, sneezing and occasional anosmia Allergic rhinitis is divided into two disease categories, seasonal and perennial, in which the former is attributed to pollen or outdoor mould spores, while the latter is attributed to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

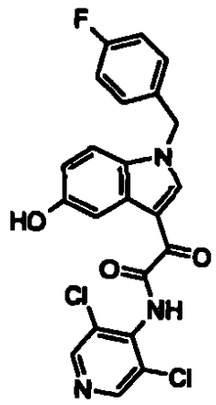
There is a recognized link between allergic rhinitis and asthma Allergic rhinitis is a frequent accompaniment to asthma, and it has been demonstrated that treating allergic rhinitis will improve asthma Epidemiologic data has also been used to show a link between severe rhinitis and more severe asthma 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)



Loteprednol (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 *et al, Ibid* Further, the ability of the compounds of Formula (1 0 0) to inhibit TNF-α release from stimulated monocytes can be correlated with animal models of inflammation in which anti-inflammatory effects can be shown to correspond to suppression of TNF-α accumulation One such animal model involves inhibition of LPS induced TNF-α release in mice by oral administration of a PDE4 inhibitor, Cheng *et al,* "The phosphodiesterase Type 4 (PDE4) inhibitor CP-80,633 elevates cyclic AMP levels and decreases TNF-α production in mice effect of adrenalectomy," *J Pharm. Exp Ther* 280 821-826, 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 a· after which the pH is brought to neutral by the addition of 1 M potassium carbonate The cAMP content of the reaction tube is measured using RIA techniques A detailed protocol for carrying out this assay is described in Brooker *et al*, "Radioimmunoassay of cyclic AMP and cyclic GMP," *Adv Cyclic Nucleotide Res.* 10 1-33, 1979

8.6 Eosinophil-Related Disorders

The ability of the PDE4 inhibitory compounds of Formula (1 0 0) to inhibit eosinophil activation as part of their overall anti-inflammatory activity has been described above Accordingly, the compounds of Formula (1 0 0) are useful in the therapeutic treatment of eosinophil-related disorders Such disorders include eosinophilia, which is the formation and accumulation of an abnormally large number of eosinophils in the blood The name of the disorder derives from "eosin", a rose-colored stain or dye comprising a bromine derivative of fluorescein which readily stains "eosinophilic leukocytes" in the blood of patients who are thus readily identified A particular eosinophilic disorder that can be treated in accordance with the present invention is pulmonary infiltration eosinophilia, which is characterized by the infiltration of the pulmonary parenchyma by eosinophils This disorder includes especially Loffler's syndrome, which is a condition characterized by transient infiltrations of the lungs, accompanied by cough, fever, dyspnea, and eosinophilia

Other eosinophilic disorders include chronic eosinophilic pneumonia, which is a chronic interstitial lung disease characterized by cough, dyspnea, malaise, fever, night sweats, weight loss, eosinophilia, and a chest film revealing non-segmental, non-migratory infiltrates in the lung periphery; tropical pulmonary eosinophilia, which is a subacute or chronic form of occult filariasis, usually involving *Brugia malayi*, *Wuchereria bancrofti*, or filariae that infect animals, occurs in the tropics, and is characterized by episodic nocturnal wheezing and coughing, strikingly elevated eosinophilia, and diffuse reticulonodular infiltrations of the lungs, bronchopneumonic aspergillosis, which is an infection of the bronchi

and lungs by *Aspergillus* funga resulting in a diseased condition marked by inflammatory granulomatous lesions in the nasal sinuses and lungs, but also in the skin, ear, orbit, and sometimes in the bones and meninges, and leading to aspergilloma, the most common type of fungus ball formed by colonization of *Aspergillus* in a bronchus or lung cavity

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

8 7 Atopic Dermatitis, Urticaria, Conjunctivitis, and Uveitis

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

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

Raven Press, New York, 1994, and O'Brien, *Mol. Medicine Today*, 369, 1997 These studies also determined that the proliferative response of HPBM from atopic dermatitis patients was more sensitive to PDE4 inhibition than was the proliferation observed in HPBM from normal subjects

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

Increased concentration of cAMP in lymphocytes and basophils has long been known to be associated with decreased mediator release from those cells, and more recently it has been reported that histamine acting on H2 receptors increases cAMP levels and inhibits IL-4 production in murine Th2 cells It is surmised accordingly, that there is present in atopic diseases such as atopic dermatitis, impaired beta-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 benefical 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, urticarogenic 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 urticarogenic 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

C0101

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 monocytosis 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

§ 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* 58 135-141, 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 patents during the course of the disease Further, a transgenic mouse overexpressing TNF-α in the central nervous system has shown signs of spontaneous demyelination, while a transgenic TNF-α knockout mouse has shown a protective effect See Probert *et al*., "Spontaneous inflammatory demyelinating disease in transgenic mice showing central nervous system-specific expression of tumor necrosis factor alpha," *Proc. Natl Acad Sci USA* 92 11294-11298, 1995, and Liu *et al*., "TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination," *Nature Med* 4 78-83, 1998

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

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

inflammatory disease Accordingly, the compounds of Formula (1 0 0) are useful in the treatment of multiple sclerosis, as discussed in detail further above

Other autoimmune/inflammatory diseases that can be treated by therapeutic agents comprising the compounds of Formula (1 0 0) include, but are not limited to, autoimmune hematological disorders such as hemolytic anemia, aplastic anemia, pure red cell anemia, and idiopathic thrombocytopenic purpura, systemic lupus erythematosus, polychondritis, scleroderma, Wegner's granulomatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Stevens-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel diseases such as ulcerative colitis and Crohn's disease; endocrin opthamopathy; Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), anterior uveitis and granulomatous (posterior) uveitis, keratoconjunctivitis sicca and epidemic keratoconjunctivitis, diffuse interstitial pulmonary fibrosis (interstitial lung fibrosis), idiopathic pulmonary fibrosis, cystic fibrosis, psoriatic arthritis, glomerulonephritis with and without nephrotic syndrome, including acute glomerulonephritis, idiopathic nephrotic syndrome, and minimal change nephropathy; inflammatory/hyperproliferative skin diseases including psoriasis and atopic dermatitis discussed in detail further above, contact dermatitis, allergic contact dermatitis, benign familial pemphigus, pemphigus erythematosus, pemphigus foliaceus, and pemphigus vulgaris

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

**8.10 Inflammatory Bowel Disease**

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

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

Current therapy for inflammatory bowel disease includes 5-aminosalicylic acid, corticosteroids, and immunomodulators such as azathioprine, 6-mercaptopurine, and methotrexate These agents have a wide range of adverse side effects and do not modify the disease itself, and there is thus an ongoing need for more effective treatment agents The compounds of Formula (1 0 0) are able to beneficially treat inflammatory bowel diseases as a result of their ability to inhibit the production of TNF-α, because TNF-α causes immune cell activation, proliferation, and mediator release in inflammatory bowel disease See Radford-Smith and Jewell, "Cytokines and Inflammatory bowel disease" *Bailleres 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 debufylline at 0 1 to 3 mg/kg i p 3x, reduces lipopolysaccharide-induced bowel erythrocyte extravasation in rats, and that denbufylline is 100-fold more potent than pentoxifylline in inhibiting lipopolysaccharide-induced mesenteric blood flow fall, without affecting renal blood flow or cardiac index See Cardelus *et al*, *Ibid*, *Eur J Pharmacol*

Renal failure is the inability of the kidney to excrete metabolites at normal plasma levels under conditions of normal loading, or the inability to retain electrolytes under conditions of normal intake In the acute form, it is marked by uremia and usually by oliguria or anuria, with hyperkalemia and pulmonary edema On the basis of the above-described activities of selective PDE4 inhibitors, it has been demonstrated that selective PDE4 inhibitors are useful in the treatment of renal failure, especially acute renal failure See Begany *et al*, "Inhibition of Type IV phosphodiesterase by Ro-20-1724 attenuates endotoxin-induced acute

renal failure," *J Pharmacol Exp. Ther* 278 37-41, 1996 See also WO 98/00135 assigned to the University of Pittsburgh Accordingly, the compounds of Formula (1 0 0) are useful in the treatment of renal failure, particularly acute renal failure

Cachexia is a profound and marked state of constitutional disorder characterized by general ill health and malnutrition Cachexia may be the end result of a number of causative factors, *e g* , it may result from infection by any one of a number of different unicellular organisms or microorganisms including bacteria, viruses, fungi, and protozoans Malarial cachexia is representative and comprises a group of signs of a chronic nature that result from antecedent attacks of severe malaria, the principal signs being anemia, sallow skin, yellow sclera, splenomegaly, and hepatomegaly Another cause of cachexia is the deprivation or deterioration of humoral or other organic functions, *e g* , hypophysial cachexia comprises a train of symptoms resulting from total deprivation of function of the pituitary gland, including phthisis, loss of sexual function, atrophy of the pituitary target glands, bradycardia, hypothermia, apathy, and coma Uremic cachexia is cachexia associated with other systemic symptoms of advanced renal failure Cardiac cachexia comprises the emaciation due to heart disease Cachexia suprarenalis, or Addison's disease, is a disorder characterized by hypotension, weight loss, anorexia, and weakness, caused by adrenocortical hormone deficiency It is due to tuberculosis- or autoimmune-induced destruction of the adrenal cortex that results in deficiency of aldosterone and cortisol

Cachexia may also be the result of disease states of various types Cancerous cachexia comprises the weak, emaciated condition seen in cases of malignant tumor Cachexia can also be a consequence of infection by the human immunodeficiency virus (HIV), and comprises the symptoms commonly referred to as acquired immune deficiency syndrome (AIDS) The compounds of Formula (1 0 0) are useful in treating cachexia of the different types described above as a result of their ability to provide down-regulation or inhibition of TNF-α release The selective PDE4 inhibitors of the present invention have a marked effect on the inhibition of TNF-α release from peripheral blood mononuclear cells after those cells have been stimulated with a wide range of mediators TNF-α release is implicated or plays a mediating role in diseases or conditions whose etiology involves or comprises morbid, *i e* , unhealthy, excessive or unregulated TNF-α release

The PDE4 inhibitory compounds of Formula (1 0 0) are further useful in the treatment of infection, especially infection by viruses wherein such viruses increase the production of TNF-α in their host, or wherein such viruses are sensitive to upregulation of TNF-α in their host so that their replication or other vital activities are adversely impacted Such viruses include, *e g* , HIV-1, HIV-2, and HIV-3, cytomegalovirus, CMV, influenza, adenoviruses, and Herpes viruses, especially *Herpes zoster* and *Herpes simplex*

The PDE4 inhibitory compounds of Formula (1 0 0) are further useful in the treatment of yeast and fungus infections wherein said yeast and fungi are sensitive to upregulation by TNF-α or elicit TNF-α production in their host A particular disease which is treatable in this way is fungal meningitis The compounds of Formula (1 0 0) also provide beneficial effects when combined with, *i.e*, administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections Such drugs of choice include, but are not limited to 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

§ 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

§ 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, endocyclitis, granulomatous uveitis, nongranulomatous uveitis, phacoantigenic uveitis, posterior uveitis, choroiditis, and chororetinitis,

– 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*, Polymyxin 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-

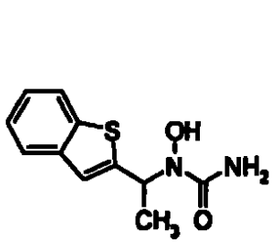
lipoxygenase (5-LO) is one of two groups of enzymes that metabolize arachidonic acid, the other group being the cyclooxygenases, COX-1 and COX-2 The 5-lipoxygenase activating protein is an 18 kDa membrane-bound, arachidonate-binding protein which stimulates the conversion of cellular arachidonic acid 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,

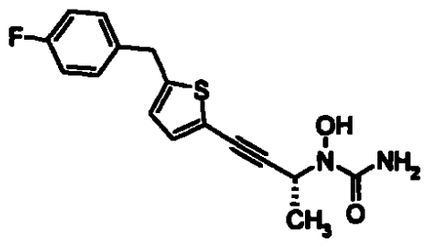
*(b)* alkylating agents and compounds which react with SH groups have been found to inhibit leukotriene synthesis *in vitro*, see Larsson *et al.*, "Effects of 1-chloro-2,4,6-trinitrobenzene on 5-lipoxygenase activity and cellular leukotriene synthesis," *Biochem Pharmacol* 55 863-71, 1998, and

*(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)



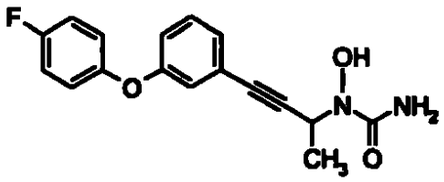
Zileuton



ABT-761

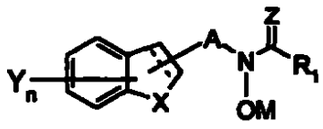
(0 1 14) (5.2 1)

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



Fenleuton (5 2.2)

Zileuton is covered by US 4,873,259 (Summers *et al*) assigned to Abbott Laboratories, which discloses indole, benzofuran, and benzothiophene containing lipoxygenase inhibiting compounds which may be represented by Formula (5.2 3)

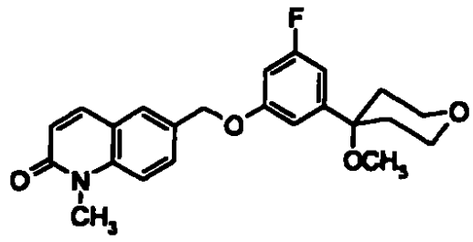


(5 2 3)

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

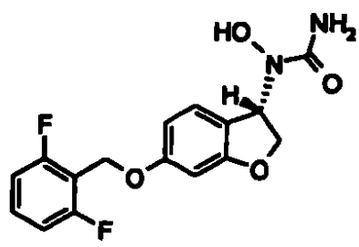
A further distinct class of 5-lipoxygenase inhibitors is that of methoxytetrahydropyrans to which Zeneca ZD-2138 belongs ZD-2138 is represented by Formula (5 2 11)



(5 2 11)

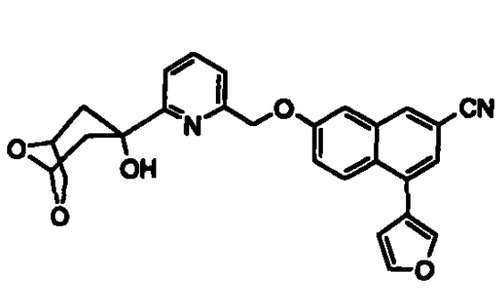
ZD-2138 is highly selective and highly active orally in a number of species and has been evaluated in the treatment of asthma and rheumatoid arthritis by oral administration Further details concerning ZD-2138 and derivatives thereof are disclosed in Crawley *et al*, *J Med Chem*, 35 2600, 1992, and Crawley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

Another distinct class of 5-lipoxygenase inhibitors is that to which the SmithKline Beecham compound SB-210661 belongs SB-210661 is represented by Formula (5 2 12)

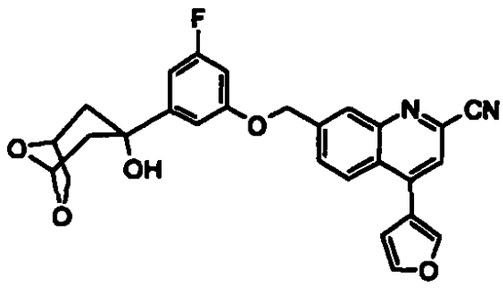


(5 2 12)

Two further distinct and related classes of 5-lipoxygenase inhibitors comprise a series of pyridinyl-substituted 2-cyanonaphthalene compounds and a series of 2-cyanoquinoline compounds discovered by Merck Frosst These two classes of 5-lipoxygenase inhibitors are exemplified by L-739,010 and L-746,530, represented by Formulas (5 2 13) and (5 2 14) respectively



L-739,010



L-746,530

(5.2 13) (5.2 14)

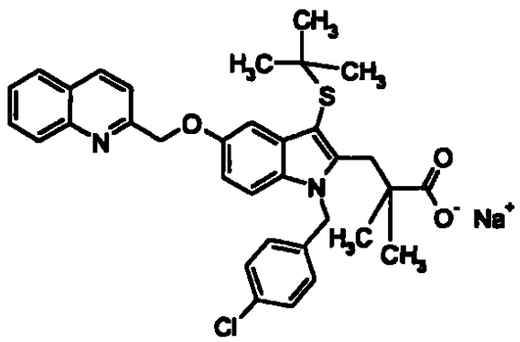
Details concerning L-739,010 and L-746,530 are disclosed in Dubé *et al*, "Quinolines as potent 5-lipoxygenase inhibitors synthesis and biological profile of L-746,530," *Bioorganic & Medicinal Chemistry* 8 1255-1260, 1998, and in WO 95/03309 (Friesen *et al.*)

The class of methoxytetrahydropyrans including Zeneca ZD-2138 of Formula (5 2 11); or the lead compound SB-210661 of Formula (5 2 12) and the class to which it belongs, or the series of pyridinyl-substituted 2-cyanonaphthalene compounds to which L-739,010 belongs, or the series of 2-cyanoquinoline compounds to which L-746,530 belongs, or any of the above-described derivatives of any of the above-mentioned classes, are combined with the compounds of Formula (1 0 0) to form embodiments of the present invention

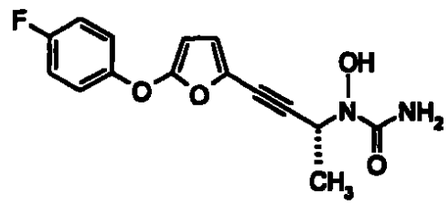
In addition to the 5-lipoxygenase enzyme, the other endogenous agent which plays a significant role in the biosynthesis of the leukotrienes is the 5-lipoxygenase activating protein (FLAP) This role is an indirect one, in contrast to the direct role of the 5-lipoxygenase enzyme Nevertheless, antagonists of the 5-lipoxygenase activating protein are employed to inhibit the cellular synthesis of leukotrienes, and as such are also used in combination with the compounds of Formula (1.0 0) to form embodiments of the present invention

Compounds which bind to the 5-lipoxygenase activating protein and thereby block utilization of the endogenous pool of arachidonic 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)



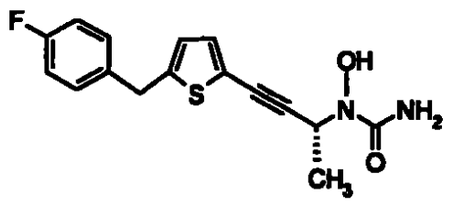
(5 2 15)



Abbott-79175 (5.2 6)

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

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

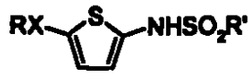


Abbott-85761 (5 2 7)

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

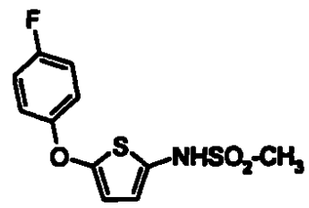
Fenleuton, Abbott-79175, Abbott-85761 or any of the above-described derivatives thereof or of tepoxalin, are combined with the compounds of Formula (1 0 0) to form embodiments of the present invention

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



(5.2 8)

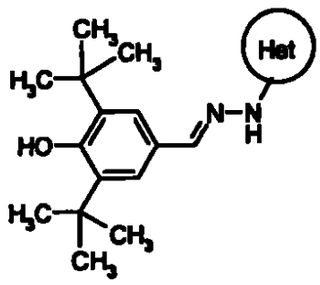
where X is O or S, R' is methyl, *iso*-propyl, *n*-butyl, *n*-octyl, or phenyl, and R is *n*-pentyl, cyclohexyl, phenyl, tetrahydro-1-naphthyl, 1- or 2-naphthyl, or phenyl mono- or di-substituted by Cl, F, Br, $CH_3$, $OCH_3$, $SCH_3$, $SO_2CH_3$, $CF_3$, or *iso*-propyl A preferred compound is that of Formula (5 2 9)



(5.2 9)

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

Another distinct class of 5-lipoxygenase inhibitors is that of the 2,6-di-*tert*-butylphenol hydrazones described in Cuadro *et al*, "Synthesis and biological evaluation of 2,6-di-*tert*-butylphenol hydrazones as 5-lipoxygenase inhibitors," *Bioorganic & Medicinal Chemistry* 6 173-180, 1998 Compounds of this type are represented by Formula (5 2 10)



(5 2 10)

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

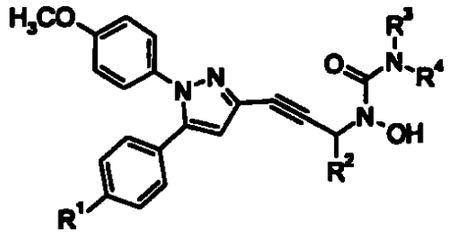
The *N*-(5-substituted)-thiophene-2-alkylsulfonamides of Formula (5.2 8), or the 2,6-di-*tert*-butylphenol hydrazones of Formula (5 2 10), or any of the above-described derivatives thereof, are combined with the compounds of Formula (1 0 0) to form embodiments of the present invention

(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

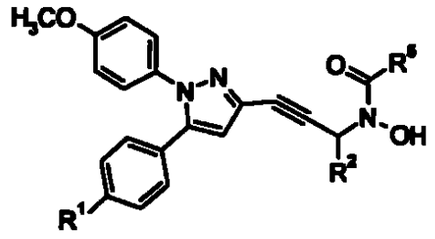
Zileuton or any of the above-described derivatives thereof are combined with the compounds of Formula (1 0 0) to form embodiments of the present invention

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 $(CH_2)_3$ 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).

The above-mentioned indole and quinoline classes of compounds and the specific compounds MK-591, MK-886, and BAY x 1005 to which they belong, or any of the above-described derivatives of any of the above-mentioned classes, are combined with the compounds of Formula (1 0 0) to form embodiments of the present invention

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

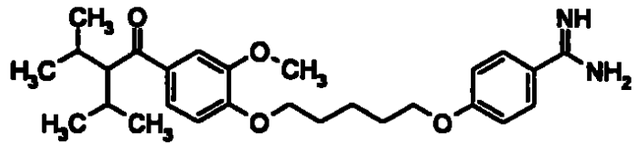
One or more compounds of Formula (1 0 0) is used in combination with receptor antagonists for leukotrienes $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$ The most significant of these leukotrienes in terms of mediating inflammatory response, are $LTB_4$ and $LTD_4$ Classes of antagonists for the receptors of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

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



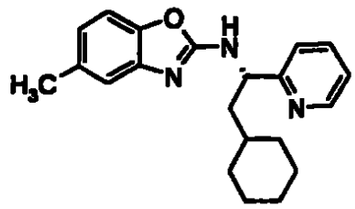

L-651,392 (5.2 16)

A class of amidino compounds that includes CGS-25019c is described in US 5,451,700 (Morrissey and Suh), US 5,488,160 (Morrissey), and US 5,639,768 (Morrissey and Suh) These receptor antagonists for $LTB_4$ are typified by CGS-25019c, which is represented by Formula (5 2 17)



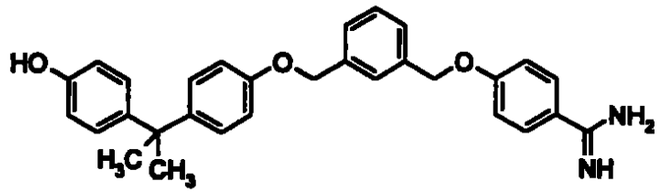

CGS-25019c (5 2 17)

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)



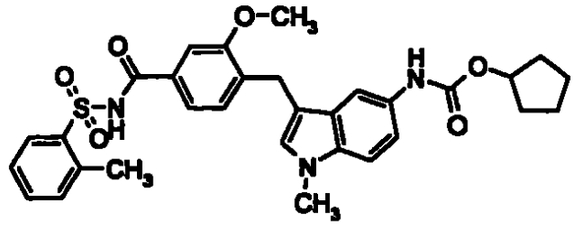
Ontazolast (5.2 18)

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)



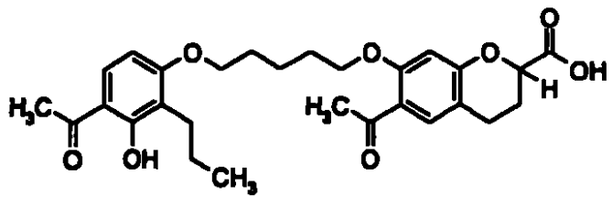
BIIL 284/260 (5.2 19)

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)



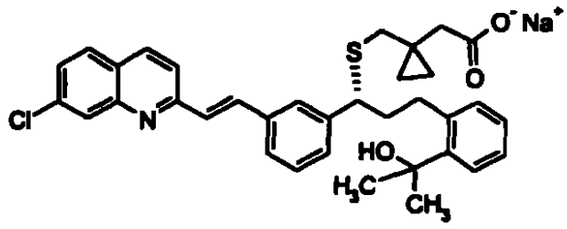
Zafirlukast (5.2 20)

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) $\alpha_1$– and $\alpha_2$–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) $\alpha_1$– and $\alpha_2$–adrenoceptor agonists in combination with inhibitors of 5-lipoxygenase (5-LO),

(i) Anticholinergic agents including ipratropium bromide,

(j) $\beta_1$– to $\beta_4$–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 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 corpons, tinea pedis, candidiasis and tinea versicolor, *e g* , griseofulvin, azoles such as miconazole, econazole, itraconazole, fluconazole, and ketoconazole, and allylamines such as naftifine and terfinafine, antiviral agents for treating cutaneous herpes simplex, herpes zoster, and chickenpox, *e g* , acyclovir, famciclovir, and valacyclovir; antihistamines for treating pruritis, atopic and contact dermatitis, *e g* , diphenhydramine, terfenadine, astemizole, loratadine, cetirizine, acrivastine, and temelastine, topical anesthetics for relieving pain, irritation and itching, *e g* , benzocaine, lidocaine, dibucaine, and pramoxine hydrochloride, topical analgesics for relieving pain and

inflammation, *e g*, methyl salicylate, camphor, menthol, and resorcinol, topical antiseptics for preventing infection, *e g*, benzalkonium chloride and povidone-iodine, and vitamins and derivatives thereof such as tocopherol, tocopherol acetate, retinoic acid and retinol

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

Emollients are agents, preferably non-oily and water-soluble, which soften and soothe the skin, especially skin that has become dry because of excessive loss of water Such agents are used with pharmaceutical compositions of the present invention which are intended for topical applications, and include,, *e g*, hydrocarbon oils and waxes, triglyceride esters, acetylated monoglycerides, methyl and other alkyl esters of $C_{10}$ -$C_{20}$ fatty acids, $C_{10}$ - $C_{20}$ fatty acids, $C_{10}$ -$C_{20}$ fatty alcohols, lanolin and derivatives, polyhydric alcohol esters such as polyethylene glycol (200-600), polyoxyethylene sorbitan fatty acid esters, wax esters, phospholipids, and sterols, emulsifying agents used for preparing oil-in-water emulsions, excipients, *e g*, laurocapram and polyethylene glycol monomethyl ether; humectants, *e g*., sorbitol, glycerin and hyaluronic acid, ointment bases, *e.g*, petrolatum, polyethylene glycol, lanolin, and poloxamer; penetration enhancers, *e g*, dimethyl isosorbide, diethyl-glycol-monoethylether, 1-dodecylazacycloheptan-2-one, and dimethylsulfoxide (DMSO); preservatives, *e g*, benzalkonium chloride, benzethonium chloride, alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, cetylpyridinium chloride, propylparaben, quaternary ammonium compounds such as potassium benzoate, and thimerosal, sequestering agents comprising cyclodextrins, solvents, *e g*, acetone, alcohol, amylene hydrate, butyl alcohol, corn oil, cottonseed oil, ethyl acetate, glycerin, hexylene glycol, isopropyl alcohol, isostearyl alcohol, methyl alcohol, methylene chloride, mineral oil, peanut oil, phosphoric acid, polyethylene glycol, polyoxypropylene 15 stearyl ether, propylene glycol, propylene glycol diacetate, sesame oil, and purified water; stabilizers, *e g*, calcium saccharate and thymol, surfactants, *e g*, lapyrium chloride, laureth 4, *i e*, α-dodecyl-ω-hydroxy-poly(oxy-1,2-ethanediyl) or polyethylene glycol monododecyl ether

Emulsifying agents, including emulsifying and stiffening agents and emulsion adjuncts, are used for preparing oil-in-water emulsions when these form the basis of the pharmaceutical compositions of the present invention Such emulsifying agents include, *e g*, non-ionic emulsifiers such as $C_{10}$ -$C_{20}$ fatty alcohols and said fatty alcohols condensed with from 2 to 20 moles of ethylene oxide or propylene oxide, ($C_8$ -$C_{12}$)alkyl phenols condensed with from 2 to 20 moles of ethylene oxide, mono- and di- $C_{10}$ -$C_{20}$ fatty acid esters of ethylene glycol, $C_{10}$ -$C_{20}$ fatty acid monoglyceride, diethylene glycol, polyethylene glycols of MW 200-6000, polypropylene glycols of MW 200-3000, and particularly sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan, hydrophilic wax esters, cetostearyl

alcohol, oleyl alcohol, lanolin alcohols, cholesterol, mono- and di-glycerides, glyceryl monostearate, polyethylene glycol monostearate, mixed mono- and distearic esters of ethylene glycol and polyoxyethylene glycol, propylene glycol monostearate, and hydroxypropyl cellulose Emulsifying agents which contain active amine groups may also be used and typically include anionic emulsifiers such as fatty acid soaps, *e g.*, sodium, potassium and triethanolamine soaps of $C_{10}$ -$C_{20}$ fatty acids, alkali metal, ammonium or substituted ammonium ($C_{10}$ -$C_{30}$)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, paraffin, synthetic paraffin, emulsifying wax, microcrystalline wax, white wax and yellow wax

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

Surfactants are employed to provide stability for multi-component pharmaceutical compositions of the present invention, enhance existing properties of those compositions, and bestow desirable new characteristics on said compositions Surfactants are used as wetting agents, antifoam agents, for reducing the surface tension of water, and as emulsifiers, dispersing agents and penetrants, and include, *e g*, lapyrium chloride, laureth 4, *i e*, α-dodecyl-ω-hydroxy-poly(oxy-1,2-ethanediyl) or polyethylene glycol monododecyl ether; laureth 9, *i e*, a mixture of polyethylene glycol monododecyl ethers averaging about 9 ethylene oxide groups per molecule; monoethanolamine, nonoxynol 4, 9 and 10, *i e*, polyethylene glycol mono(*p*-nonylphenyl) ether, nonoxynol 15, *i e*, α-(*p*-nonylphenyl)-ω-hydroxypenta-deca(oxyethylene), nonoxynol 30, *i e*, α-(*p*-nonylphenyl)-ω-hydroxytriaconta(oxyethylene), poloxalene, *i e*, nonionic polymer of the polyethylene-polypropylene glycol type, MW = approx 3000, poloxamer, referred to in the discussion of ointment bases further above, polyoxyl 8, 40 and 50 stearate, *i e*, poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, octadecanoate, polyoxyl 10 oleyl ether, *i e*, poly(oxy-1,2-ethanediyl), α-[(E)-9-octadecenyl-ω-hydroxy-, polysorbate 20, *i e*, sorbitan, monododecanoate, poly(oxy-1,2-ethanediyl), polysorbate 40, *i e*, sorbitan, monohexadecanoate, poly(oxy-1,2-ethanediyl), polysorbate 60, *i e*, sorbitan, monooctadecanoate, poly(oxy-1,2-ethanediyl), polysorbate 65,

*i.e.*, sorbitan, trioctadecanoate, poly(oxy-1,2-ethanediyl), polysorbate 80, *i.e.*, sorbitan, mono-9-monodecenoate, poly(oxy-1,2-ethanediyl), polysorbate 85, *i.e.*, sorbitan, tri-9-octadecenoate, poly(oxy-1,2-ethanediyl), sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesquioleate, sorbitan trioleate, and sorbitan tristearate

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

Where the pharmaceutical compositions of the present invention are to be in the form of emulsions, the components of the pharmaceutical composition will be brought together in accordance with the following general procedures The continuous water phase is first heated to a temperature in the range of from about 60° to about 95°C, preferably from about 70° to about 85°C, the choice of which temperature to use being dependent upon the physical and chemical properties of the components which make up the oil-in-water emulsion Once the continuous water phase has reached its selected temperature, the components of the final composition to be added at this stage are admixed with the water and dispersed therein under high-speed agitation Next, the temperature of the water is restored to approximately its original level, after which the components of the composition which comprise the next stage are added to the composition mixture under moderate agitation and mixing continues for from about 5 to about 60 minutes, preferably about 10 to about 30 minutes, depending on the components of the first two stages Thereafter, the composition mixture is passively or actively cooled to from about 20° to about 55°C for addition of any components in the remaining stages, after which water is added in sufficient quantity to reach its original predetermined concentration in the overall composition

According to the present invention, the pharmaceutical compositions may be in the form of a sterile injectable preparation, for example a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-

acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as do natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as *Rh*, HCIX or similar alcohol

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

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

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

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

carriers Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate , cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water

Pharmaceutical compositions within the scope of the present invention include those wherein the therapeutically effective amount of an active ingredient comprising a compound of the present invention required for treating or preventing diseases, disorders, and conditions mediated by or associated with modulation of PDE4, especially PDE4D activity as described herein, is provided in a dosage form suitable for systemic administration Such a pharmaceutical composition will contain said active ingredient in suitable liquid form for delivery by (1) injection or infusion which is intraarterial, intra- or transdermal, subcutaneous, intramuscular, intraspinal, intrathecal, or intravenous, wherein said active ingredient (a) is contained in solution as a solute, (b) is contained in the discontinuous phase of an emulsion, or the discontinuous phase of an inverse emulsion which inverts upon injection or infusion, said emulsions containing suitable emulsifying agents, or (c) is contained in a suspension as a suspended solid in colloidal or microparticulate form, said suspension containing suitable suspending agents, (2) injection or infusion into suitable body tissues or cavities as a depot, wherein said composition provides storage of said active ingredient and thereafter delayed-, sustained-, and/or controlled-release of said active ingredient for systemic distribution, (3) instillation, inhalation or insufflation into suitable body tissues or cavities of said pharmaceutical composition in suitable solid form, where said active ingredient (a) is contained in a solid implant composition providing delayed-, sustained-, and/or controlled-release of said active ingredient, (b) is contained in a particulate composition to be inhaled into the lungs, or (c) is contained in a particulate composition to be blown into suitable body tissues or cavities, where said composition optionally provides delayed-, sustained-, and/or controlled-release of said active ingredient, or (4) ingestion of said pharmaceutical composition in suitable solid or liquid form for peroral delivery of said active ingredient, where said active ingredient is contained in a solid dosage form, or (b) is contained in a liquid dosage form

Particular dosage forms of the above-described pharmaceutical compositions include (1) suppositories as a special type of implant, comprising bases which are solid at room temperature but melt at body temperature, slowly releasing the active ingredient with which they are impregnated into the surrounding tissue of the body, where the active ingredient becomes absorbed and transported to effect systemic administration, (2) solid peroral dosage forms selected from the group consisting of (a) delayed-release oral tablets, capsules, caplets, lozenges, troches, and multiparticulates, (b) enteric-coated tablets and capsules which prevent release and absorption in the stomach to facilitate delivery distal to the stomach of the patient being treated, (c) sustained-release oral tablets, capsules and microparticulates which provide systemic delivery of the active ingredient in a controlled

manner up to a 24-hour period, (d) fast-dissolving tablets, (e) encapsulated solutions, (f) an oral paste, (g) a granular form incorporated in or to be incorporated in the food of a patient being treated, and (h) liquid peroral dosage forms selected from the group consisting of solutions, suspensions, emulsions, inverse emulsions, elixirs, extracts, tinctures, and concentrates

Pharmaceutical compositions within the scope of the present invention include those wherein the therapeutically effective amount of an active ingredient comprising a compound of the present invention required for treating or preventing diseases, disorders, and conditions mediated by or associated with modulation of PDE4, especially PDE4D activity as described herein is provided in a dosage form suitable for local administration to a patient being treated, wherein said pharmaceutical composition contains said active ingredient in suitable liquid form for delivering said active ingredient by: (1) injection or infusion into a local site which is intraarterial, intraarticular, intrachondrial, intracostal, intracystic, intra- or transdermal, intrafascicular, intraligamentous, intramedulary, intramuscular, intranasal, intraneural, intraocular, *i.e.*, opthalmic administration, intraosteal, intrapelvic, intrapericardial, intraspinal, intrasternal, intrasynovial, intratarsal, or intrathecal, including components which provide delayed-release, controlled-release, and/or sustained-release of said active ingredient into said local site, where said active ingredient is contained (a) in solution as a solute, (b) in the discontinuous phase of an emulsion, or the discontinuous phase of an inverse emulsion which inverts upon injection or infusion, said emulsions containing suitable emulsifying agents, or (c) in a suspension as a suspended solid in colloidal or microparticulate form, said suspension containing suitable suspending agents, or (2) injection or infusion as a depot for delivering said active ingredient to said local site, wherein said composition provides storage of said active ingredient and thereafter delayed-, sustained-, and/or controlled-release of said active ingredient into said local site, and wherein said composition also includes components which ensure that said active ingredient has predominantly local activity, with little systemic carryover activity; or wherein said pharmaceutical composition contains said active ingredient in suitable solid form for delivering said inhibitor by: (3) instillation, inhalation or insufflation to said local site, where said active ingredient is contained (a) in a solid implant composition which is installed in said local site, said composition optionally providing delayed-, sustained-, and/or controlled-release of said active ingredient to said local site, (b) in a particulate composition which is inhaled into a local site comprising the lungs, or (c) in a particulate composition which is blown into a local site, where said composition includes components which will ensure that said active ingredient has predominantly local activity, with insignificant systemic carryover activity, and optionally provides delayed-, sustained-, and/or controlled-release of said active ingredient to said local site For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspension in isotonic, pH adjusted sterile

saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum

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

As already mentioned, the active ingredients of Formula (1 0 0) of the present invention may be administered systemically to a patient to be treated as a pharmaceutical composition in suitable liquid form by injection or infusion There are a number of sites and organ systems in the body of the patient which will allow the properly formulated pharmaceutical composition, once injected or infused, to permeate the entire body and all of the organ system of the patient being treated An injection is a single dose of the pharmaceutical composition forced, usually by a syringe, into the tissue involved The most common types of injections are intramuscular, intravenous, and subcutaneous By contrast, an infusion is the gradual introduction of the pharmaceutical composition into the tissue involved The most common type of infusion is intravenous Other types of injection or infusion comprise intraarterial, intra- or transdermal (including subcutaneous), or intraspinal especially intrathecal In these liquid pharmaceutical compositions, the active ingredient may be contained in solution as the solute This is the most common and most preferred type of such composition, but requires an active ingredient in a salt form that has reasonably good aqueous solubility Water (or saline) is by far the most preferred solvent for such compositions Occasionally supersaturated solutions may be utilized, but these present stability problems that make them impractical for use on an everyday basis

If it is not possible to obtain a form of some compound of Formula (1 0.0) that has the requisite degree of aqueous solubility, as may sometimes occur, it is within the skill of the artisan to prepare an emulsion, which is a dispersion of small globules of one liquid, the discontinuous or internal phase, throughout a second liquid, the continuous or external phase, with which it is immiscible The two liquids are maintained in an emulsified state by the use of emulsifiers which are pharmaceutically acceptable Thus, if the active ingredient is a water-insoluble oil, it can be administered in an emulsion of which it is the discontinuous phase Also where the active ingredient is water-insoluble but can be dissolved in a solvent which is immiscible with water, an emulsion can be used While the active ingredient would most

commonly be used as the discontinuous or internal phase of what is referred to as an oil-in-water emulsion, it could also be used as the discontinuous or internal phase of an inverse emulsion, which is commonly referred to as a water-in-oil emulsion Here the active ingredient is soluble in water and could be administered as a simple aqueous solution However, inverse emulsions invert upon injection or infusion into an aqueous medium such as the blood, and offer the advantage of providing a more rapid and efficient dispersion of the active ingredient into that aqueous medium than can be obtained using an aqueous solution Inverse emulsions are prepared by using suitable, pharmaceutically acceptable emulsifying agents well known in the art. Where the active ingredient has limited water solubility, it may also be administered as a suspended solid in colloidal or microparticulate form in a suspension prepared using suitable, pharmaceutically acceptable suspending agents The suspended solids containing the active ingredient may also be formulated as delayed-, sustained-, and/or controlled-release compositions

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

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

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

Other means of systemic administration which may utilize the active ingredients of the present invention in either liquid or solid form include transdermal, intranasal, and opthalmic routes In particular, transdermal patches prepared in accordance with well known drug delivery technology may be prepared and applied to the skin of a patient to be treated, whereafter the active agent by reason of its formulated solubility characteristics migrates across the epidermis and into the dermal layers of the patient's skin where it is taken up as part of the general circulation of the patient, ultimately providing systemic distribution of the active ingredient over a desired, extended period of time Also included are implants which are placed beneath the epidermal layer of the skin, *i e* between the epidermis and the dermis of the skin of the patient being treated Such an implant will be formulated in accordance with well known principles and materials commonly used in this delivery technology, and may be prepared in such a way as to provide controlled-, sustained-, and/or delayed-release of the active ingredient into the systemic circulation of the patient Such subepidermal (subcuticular) implants provide the same facility of installation and delivery efficiency as transdermal patches, but without the limitation of being subject to degradation, damage or accidental removal as a consequence of being exposed on the top layer of the patient's skin

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

prodrugs, and a number of established procedures are available for preparing such prodrug forms of the compounds of Formula (1 0 0)

The dosage and dose rate of the compounds of Formula (1.0.0) effective for treating or preventing a disease, disorder, or condition mediated by or associated with modulation of PDE4, especially PDE4D activity, will depend on a variety of factors, such as the nature of the inhibitor, the size of the patient, the goal of the treatment, the nature of the pathology to be treated, the specific pharmaceutical composition used, and the observations and conclusions of the treating physician

For example, where the dosage form is oral, *e g* , a tablet or capsule, suitable dosage levels of the compounds of Formula (1 0 0) will be between about 0 1 µg/kg and about 50 0 mg/kg body weight per day, preferably between about 5 0 µg/kg and about 5 0 mg/kg body weight per day, more preferably between about 10 0 µg/kg and about 1.0 mg/kg of body weight per day, and most preferably between about 20 0 µg/kg and about 0 5 mg/kg of body weight per day of the active ingredient.

Where the dosage form is topically administered to the bronchus and lungs, *e g* , by means of a powder inhaler or nebulizer, suitable dosage levels of the compounds of Formula (1 0 0) will be between about 0 001 µg/kg and about 10 0 mg/kg body weight per day, preferably between about 0 5 µg/kg and about 0 5 mg/kg body weight per day, more preferably between about 1 0 µg/kg and about 0 1 mg/kg of body weight per day, and most preferably between about 2 0 µg/kg and about 0 05 mg/kg of body weight per day of the active ingredient.

Using representative body weights of 10 kg and 100 kg in order to illustrate the range of daily aerosolized topical dosages which might be used as described above, suitable dosage levels of the compounds of Formula (1 0 0) will be between about 1 0 - 10 0 µg and 500 0 - 5000.0 mg per day, preferably between about 5 0 - 50 0 µg and 5.0 - 50 0 mg per day, more preferably between about 100 0 - 1000 0 µg and 10 0 - 100 0 mg per day, and most preferably between about 200 0 - 2000 0 µg and about 5 0 - 50 0 mg per day of the active ingredient comprising a compound of Formula (1 0 0) These ranges of dosage amounts represent total dosage amounts of the active ingredient per day for a given patient The number of times per day that a dose is administered will depend upon such pharmacological and pharmacokinetic factors as the half-life of the active ingredient, which reflects its rate of catabolism and clearance, as well as the minimal and optimal blood plasma or other body fluid levels of said active ingredient attained in the patient which are required for therapeutic efficacy

Numerous other factors must also be considered in deciding upon the number of doses per day and the amount of active ingredient per dose that will be administered Not the least important of such other factors is the individual response of the patient being treated Thus, for example, where the active ingredient is used to treat or prevent asthma, and is administered topically *via* aerosol inhalation into the lungs, from one to four doses consisting of acuations of a dispensing device, *i e* , "puffs" of an inhaler, will be administered each day, each dose containing from about 50 0 µg to about 10 0 mg of active ingredient

## DETAILED DESCRIPTION OF THE INVENTION

### 11.0 Preparations and Working Examples

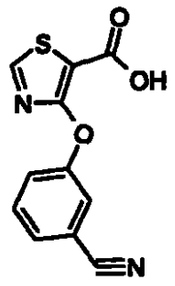
There follows a description of numerous Preparations by which intermediates used in preparing specific compounds of Formula (1 0 0) were made There also follows numerous Examples showing preparation of specific compounds of Formula (1 0 0). These Preparations and Examples are intended to further illustrate 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-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid of Formula (9 0 1)




(9 0 1)

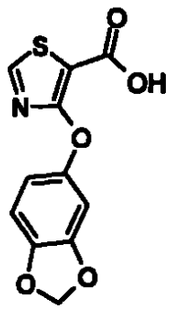
A mixture of 375mg (1 4mmol) 4-(3-cyano-phenoxy)-thiazole-5-carboxylic acid ethyl ester, 1 4ml 1M LiOH, and 10mL of THF was stirred for 18 hours at room temperature The mixture was concentrated via rotary evaporation to yield yellow oil The oil was diluted with 1N HCl (30mL) precipitating a white solid The solid was filtered then dried in a drying pistol giving 265mg of white powder

APCI M/S (m/z $M^+$-1) 245

The compounds of Preparations 1a-1b were prepared according to the procedure of Preparation 1 substituting the corresponding oxy-thiazole-5-carboxylic acid ethyl ester The duration of reaction was between 1 and 24 hours

**Preparation 1a**

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid of Formula (9 0.2)

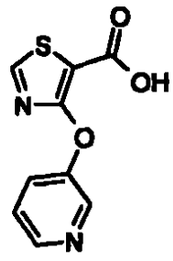


(9 0 2)

APCI M/S (m/z $M^+$+1) 266

**Preparation 1b**

4-(Pyridin-3-yloxy)-thiazole-5-carboxylic acid of Formula (9 0.3)

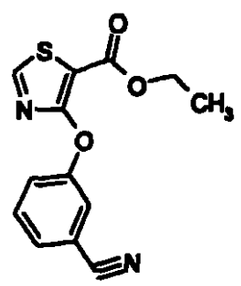


(9 0 3)

APCI M/S (m/z $M^+$+1) 221

**Preparation 2**

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid ethyl ester of Formula (9 0 4)



(9 0.4)

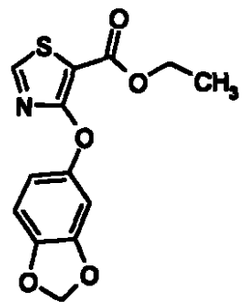
A stirred of 665mg (3 5mmol) 4-chloro-thiazole-5-carboxylic acid ethyl ester, 415mg (3 5mmol) 3-cyanophenol, 2 4g (7 3mmol) $Cs_2CO_3$ and 60mL dimethylformamide was warmed to 80° C in an oil bath for 72 hours The mixture was then cooled, poured into 70mL water, and extracted with ethyl acetate (3 X 40mL) The combined extracts were washed with water (2X50mL), brine (1x50mL), dried over $Na_2SO_4$, and concentrated via rotary evaporation The resulting oil was chromatographed on a Biotage Flash 40S® silica column, loaded with methylene chloride and eluted with 20% ethyl acetate/ 80% hexanes to give 375mg of a light yellow oil

APCI M/S (m/z $M^+$+1) 275

The compounds of Preparations 2a-2b were prepared according to the procedure of Preparation 1 substituting the corresponding phenol The duration of reaction was between 1 and 72 hours

**Preparation 2a**

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid ethyl ester of Formula (9 0 5)

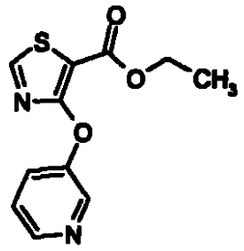


(9 0 5)

Crude material carried on

**Preparation 2b**

4-(Pyridin-3-yloxy)-thiazole-5-carboxylic acid ethyl ester of Formula (9.0 6)

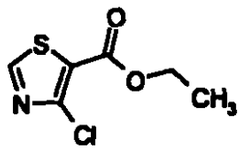


(9 0 6)

APCI M/S (m/z $M^+$+1) 251

**Preparation 3**

4-Chloro-thiazole-5-carboxylic acid ethyl ester of Formula (9 0 7)



(9 0 7)

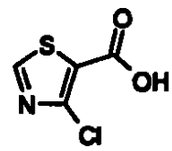
A mixture of 2 0g (12 2mmol) 4-chloro-thiazole-5-carboxylic acid and 6.24mL (85 6mmol) $SOCl_2$ was stirred at reflux for 2 hours The mixture was then concentrated via rotary evaporation and pumped under high-vac for 2 hours Next, the material was diluted with ethanol and heated at reflux for 18 hours The mixture was concentrated *via* rotary

evaporation and diluted with methylene chloride Eluted through a silica plug with methylene chloride and concentrated via rotary evaporation to give 1 49g of a light yellow solid

MP 43-45°C

**Preparation 4**

4-Chloro-thiazole-5-carboxylic acid of Formula (9 0 8)



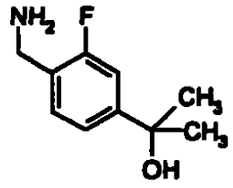
(9 0 8)

To a stirring mixture of 10 3g (69 8mmol) 4-chloro-thiazole-5-carbaldehyde (*Journal of the Chemical Society, Perkins Transactions*, 1992, 973-976), 296ml (2792mmol) 2-methyl-2-butene, and 200mL tertiary butanol was added a solution of 50 5g (558mmol) $NaClO_2$, 50 2g (419mmol) $NaH_2PO_4$ in 300mL of water, dropwise over 20 minutes The reaction was stirred for 1 hour then concentrated to 1/3 volume via rotary evaporation The remaining solution was acidified with 6N HCl with rapid stirring The precipitated solid was filtered and air dried under high vacuum overnight to give 10 6g of white solid

MP 235-240°C (decomposition)

**Preparation 5**

2-(4-Aminomethyl-3-fluoro-phenyl)-propan-2-ol of Formula (9 0 9)



(9 0 9)

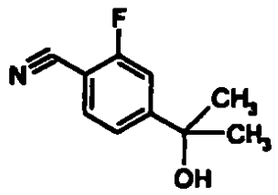
To a stirred solution of 1 95g (0 011mol) 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzonitrile in 30mL anhydrous THF at 0°C was added dropwise 34mL (0 034mol) 1 0M $LiAlH_4$ The mixture was warmed to room temperature then heated to reflux for 30 minutes The mixture was then cooled to 0°C and quenched with 20mL MeOH added dropwise Next, it was diluted with 700mL $CHCl_3$ and washed with 100mL water The resulting suspension was filtered

through Celite and the organic layer dried over $MgSO_4$ and concentrated to give 1 6g of an amber oil

APCI M/S (m/z $M^+$+1) 183

**Preparation 6**

2-Fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzonitrile of Formula (9 0 10)



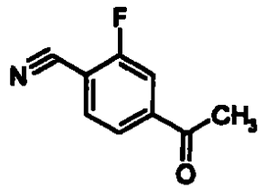
(9 0 10)

To a stirred suspension of 4 7g (0 019mol) anhydrous $CeCl_3$ in 30mL anhydrous THF at 0°C was added 6mL of 3 0M $CH_3MgCl$ dropwise Stirred at 0°C for 45 minutes Next a solution of 2 5g (0 015mol) 4-Acetyl-2-fluoro-benzonitrile in 200mL anhydrous THF was added dropwise at 0°C Stirred at 0°C for 1 hour, then quenched with 2N acetic acid added dropwise The mixture was poured into 200mL water and acidified to pH 2 with 2N acetic acid The aqueous layer was extracted with ethyl acetate (2 X 200mL) The ethyl acetate extracts were combined, washed with water (2 X 40mL), brine (1 X 40mL), dried over MgSO4 and concentrated to give an oil, which was then chromatographed on silica gel eluted with 50% ethyl acetate/ 50% hexanes to give 1 95g of an amber oil

APCI M/S (m/z $M^+$+1) 179

**Preparation 7**

4-Acetyl-2-fluoro-benzonitrile of Formula (9 0 11)



(9 0 11)

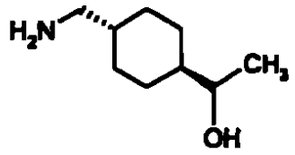
A mixture of 5 0g (0 02mol) 4-bromo-2-fluorobenzonitrile, 6ml TEA, 906mg (0 0022mol) dppp, 5 8g (0 04mol) TlOAc, and 448mg (0 002mol) $Pd(OAc)_2$ in 50ml DMF was deaired under a stream of $N_2$ The mixture was heated to 90°C for 7 hours The reaction was cooled to room

temperature and 25mL 2N HCl was added and stirred to 30 minutes The mixture was poured into 300ml water and extracted with $Et_2O$ (2 X 300mL) The combined organics were washed with water (2 X 80mL), brine (1 X 80mL), dried over $MgSO_4$ and concentrated to give an oil, which was then chromatographed on silica gel eluted with 30% ethyl acetate/ 70% hexanes to give 2 5g of a yellow/orange oil

APCI M/S (m/z $M^+$+1) 164

**Preparation 8**

*Trans*-(-)-1-(4-Aminomethyl-cyclohexyl)-ethanol of Formula (9 0 12)



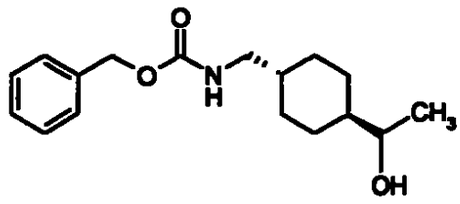
(9 0 12)

A 500mL Parr bottle was charged with 400mg $Pd(OH)_2$, 7 0g (24 1mol) *trans*-(-)-[4-(1-hydroxy-ethyl)-cyclohexylmethyl]-carbamic acid benzyl ester, 125mL ethyl acetate and 125ml MeOH The bottle was placed under 50 psi $H_2$ and shaken for 2 hours The suspension was then filtered through Celite and concentrated to give 3 8g of a white solid

APCI M/S (m/z $M^+$+1) 158

**Preparation 9**

*Trans*-(-)-[4-(1-Hydroxy-ethyl)-cyclohexylmethyl]-carbamic acid benzyl ester of Formula (9 0 13)



(9 0 13)

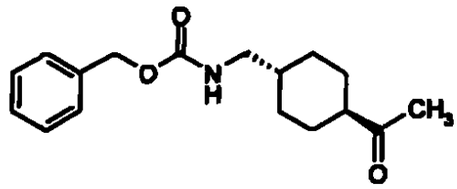
A flame dried 250mL flask was charged with 7 95g (27 5mmol) *trans*-(4-acetyl-cyclohexylmethyl)-carbamic acid benzyl ester, 60mL anhydrous THF and 2 7mL (2 7mmol) 1M (S)-2-methyl-CBS-oxazoborolidine The mixture was heated to 50°C then 11mL (22mmol) 2M BH3•DMS was added dropwise over 10 minutes, the reaction mixture was stirred for an additional 30 minutes at 50°C and then cooled The reaction was quenched with 25mL

MeOH and concentrated to give an oil The material was diluted with water and extracted with ethyl acetate (3 X 40mL) The combined organics were washed with water (1 X 100mL), brine (1 X 100mL), dried over $Na_2SO_4$ and concentrated to give a white solid, which was then chromatographed on silica gel eluted with 50% ethyl acetate/ 50% hexanes to give 7 0g of a white solid

MP 83-84°C

**Preparation 10**

*Trans*-(4-Acetyl-cyclohexylmethyl)-carbamic acid benzyl ester of Formula (9 0 14)



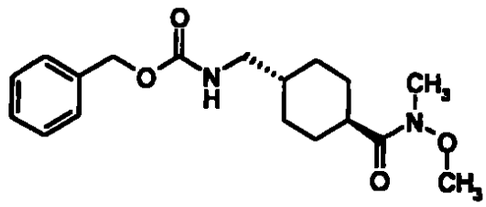
(9 0 14)

A 500mL flask was charged with 15.2g (45 4mmol) *trans*-[4-(methoxy-methyl-carbamoyl)-cyclohexylmethyl]-carbamic acid benzyl ester and 350mL anhydrous THF The solution was cooled to 0°C then 33 3mL (99 9mmol) 3M $CH_3MgCl$ was added dropwise over 10 minutes The reaction mixture was then stirred for 1 hour at 0°C then quenched with 20mL 2N acetic acid and poured into 300mL water The aqueous was extracted with ethyl acetate (3 X 200mL) and the combined organics were washed with 0 5M HCl (1 X 100mL), water (1 X 100mL), brine (1 X 100mL), dried over $Na_2SO_4$ and concentrated to a solid The solid was recrystalized from IPE and filtered to give 5 5g of a white solid

MP 66-67°C

**Preparation 11**

*Trans*-[4-(Methoxy-methyl-carbamoyl)-cyclohexylmethyl]-carbamic acid benzyl ester of Formula (9 0 15)



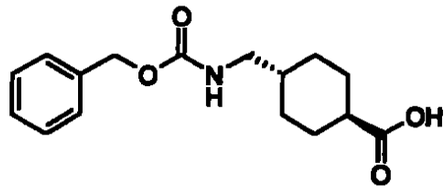
(9 0 15)

A 1L flask was charged with 25 02g (85 9mmol) *trans*-4-(benzyloxycarbonylamino-methyl)-cyclohexanecarboxylic acid, 9,21g (94 5mmol) O,N-dimethylhydroxyl amine HCl, 41 8g (94 5mmol) BOP, 750mL methylene chloride and 75mL diisopropylethyl amine The reaction mixture was then stirred under nitrogen overnight The solution was then washed with water, 5% citric acid (2 X 300mL), saturated sodium bicarbonate (2 X 300mL), brine (1X 300mL) and dried over $Na_2SO_4$ and concentrated to an oil The oil was chromatographed on silica gel eluted with 50% ethyl acetate/ 50% hexanes to give 27.2g of a clear oil that solidified on standing

PBMS (m/z $M^+$+1) 335

**Preparation 12**

*Trans*-4-(Benzyloxycarbonylamino-methyl)-cyclohexanecarboxylic acid of Formula (9 0 16)



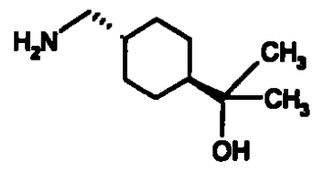
(9 0 16)

A 1L 3-neck flask was charged with 25 09 (160mmol) *trans*-4-aminomethyl-cyclohexanecarboxylic acid, 77 4g (560 mmol) $K_2CO_3$, 250mL dioxane and 250mL water The suspension was stirred, then 28 5mL (200 mmol) benzylchloroformate was added dropwise The reaction mixture was then stirred at room temperature for 6 5 hours then poured into 800mL water and acidified (slowly) with 1N HCl The resulting white precipitate was filtered and dried - 45 6g

PBMS (m/z $M^+$+1) 292

**Preparation 13**

*Trans*-2-(4-Aminomethyl-cyclohexyl)-propan-2-ol of Formula (9 0 17)



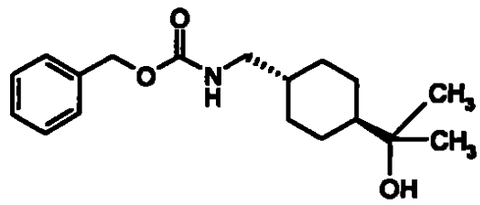
(9 0 17)

A 500mL Parr bottle was charged with 150mg $Pd(OH)_2$, 3 3g (10 7mmol) *trans*-[4-(1-hydroxy-1-methyl-ethyl)-cyclohexylmethyl]-carbamic acid benzyl ester, 100mL ethyl acetate and 100mL MeOH The bottle was placed under 50 psi $H_2$ and shaken for 1 hour The material was filtered through Celite and concentrated to give 1 57g of a white solid

PBMS (m/z $M^+$+1) 172

**Preparation 14**

*Trans*-[4-(1-Hydroxy-1-methyl-ethyl)-cyclohexylmethyl]-carbamic acid benzyl ester of Formula (9 0 18)



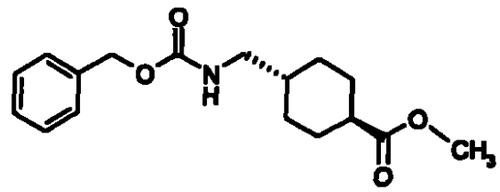
(9 0 18)

A 1L 3-neck flask was charged with 7.2g (29 2mmol) $CeCl_3$ and 100mL anhydrous THF The suspension was heated to reflux for 15 minutes then cooled to 0°C and a solution of 8 10g (26 5mmol) *trans*-benzyloxycarbonylamino-methyl)-cyclohexanecarboxylic acid methyl ester in 200mL anhydrous THF was added Next, 29mL (87 5mmol) 3M $CH_3MgCl$ was added dropwise over 30 minutes The reaction mixture was stirred for an additional 2 hoursat 0°C then quenched and diluted with 2N acetic acid to pH 2 The material was extracted with ethyl acetate (3 X 100mL) The combined extracts were washed with saturated sodium bicarbonate (1 X 100mL), brine (1 X 100mL), dried over $Na_2SO_4$ and concentrated to an amber oil The oil was chromatographed on a Biotage Flash 40S® silica column + SIM eluted with 40% ethyl acetate/ 60% hexanes to give 3 3g of a light yellow solid

PBMS (*m/z* $M^+$+1) 306

**Preparation 15**

*Trans*-Benzyloxycarbonylamino-methyl)-cyclohexanecarboxylic acid methyl ester of Formula (9 0 19)



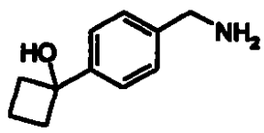
(9 0 19)

A 500mL flask was charged with 7 0g (24 1mmol) *trans*-4-(benzyloxycarbonylamino-methyl)-cyclohexanecarboxylic acid,, 8 32g (60.2mmol) $K_2CO_3$, 200mL DMF and 1 95mL (31 3mmol) methyl iodide The reaction mixture was stirred at room temperature overnight then diluted with water and extracted with ethyl acetate (3 X 60mL) The combined ethyl acetate extracts were washed with water (1 X 100mL), brine (1 X 100mL), dried over $Na_2SO_4$ and concentrated to 8.1g of a light yellow oil that solidified on standing

PBMS (m/z $M^+$+1). 306

**Preparation 16**

1-(4-Aminomethyl-phenyl)-cyclobutanol of Formula (9.0 20)



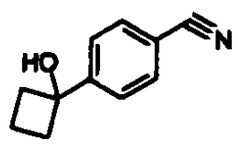
(9 0 20)

A 250mL flask was charged with 4 1g (23 5mmol) 4-(1-hydroxy-cyclobutyl)-benzonitrile and 100mL anhydrous THF then cooled to 0°C Next, 70 5mL (70 5mmol) 1M $LiAlH_4$ was added dropwise The reaction mixture was stirred at 0°C for 10 minutes then heated to reflux for 30 minutes, then cooled to 0°C and quenched with MeOH Diluted with methylene chloride and washed with water (2 X 100mL) The organic was filtered through Celite and concentrated to give 2g of a yellow solid

GC/MS (m/z) 177

**Preparation 17**

4-(1-Hydroxy-cyclobutyl)-benzonitrile of Formula (9 0 21)



(9 0.21)

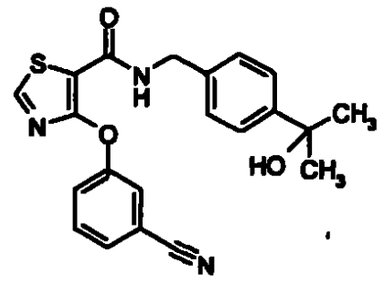
A 500mL flask was charged with 10.8g (59 4mmol) 4-bromo-benzonitrile and 150mL anhydrous THF The solution was cooled to -78°C and 26 1mL (65.3mmol) 2 5M *n*-butyl lithium was added dropwise The reaction mixture was stirred at -78°C for an additional 10 minutes, then 5 0g (71 3mmol) cyclobutanone was added dropwise The reaction mixture was stirred for an additional 10 minutes at -78°C then the bath was removed and the reaction stirred for an additional 1 hour The material was poured into 300mL water and extracted with ethyl acetate (3 X 100mL). The combined organics were washed with water (2 X 100mL), brine (1 X 100mL), dried over $Na_2SO_4$ and concentrated to a light brown oil The oil was chromatographed on a Biotage Flash 40S® silica column + SIM eluted with 10% ethyl acetate/ 90% hexanes to give 4 1g of a light yellow oil

APMS (m/z $M^+$-1) 172

---

**Example 1**

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 1)



(8 5 1)

A stirred mixture of 93 8mg (0 38mmol) 4-(3-cyano-phenoxy)-thiazole-5-carboxylic acid 5, 63 0mg (0 40mmol) 2-(4-Aminomethyl-phenyl)-propan-2-ol, 56 6mg (0 42mmol) HOBT and 87 6mg (0 46mmol) EDCI in 15mL dimethylformamide was stirred at room temperature for 18 hours The mixture was then poured into water and extracted with ethyl acetate (3 X 50mL) The organic extracts were combined and washed with 1N NaOH (1 X30mL), water (1 X 30mL), brine (1 X 30mL), dried over $Na_2SO_4$ and concentrated to give a yellow oil

Chromatography on a Biotage Flash 12S® silica column, loaded with methylene chloride and eluted with 40% ethyl acetate/ 60% hexanes to give 10 8mg of a clear oil that solidified on standing

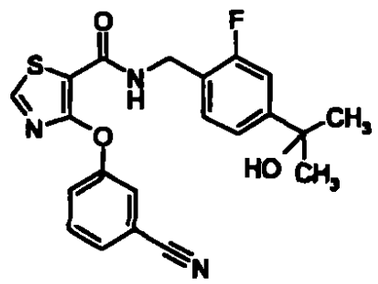
APCI M/S (m/z $M^+$-1) 392

$^1$H NMR (400MHz,$CDCl_3$) δ 1 53 (6H, s), δ 4 6 (2H, d), δ 7 2-7 5 (6H, m), δ 8 6 (1H, s)

The compounds of Example 2-8 were prepared according to the procedure of Example 1 substituting the corresponding amine for 2-(4-Aminomethyl-phenyl)-propan-2-ol The duration of reaction was between 1 and 24 hours

**Example 2**

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzyl-amide of Formula (8 5 2)



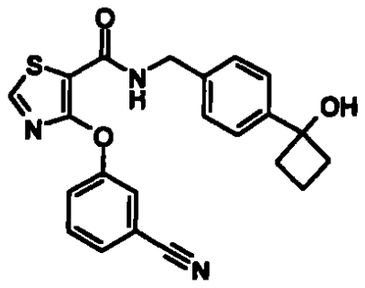
(8 5.2)

APCI M/S (m/z $M^+$-1) 410

$^1$H NMR (400MHz, $CDCl_3$) δ 1 53 (6H, s), δ 4 6 (2H, d), δ 7 1-7 6 (7H, m), δ 8 6 (1H, s)

**Example 3**

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-cyclobutyl)-benzylamide of Formula (8 5 3)



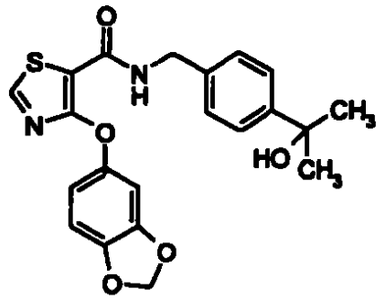
(8 5.3)

APCI M/S (m/z $M^+$-1)$^-$ 404

$^1$H NMR (400MHz, $CDCl_3$) δ 1 95 (2H, m), δ 2 3 (2H, m), δ 2 5 (2H, m), δ 4 6 (2H, d), δ 7.2-7 6 (8H, m), δ 8 6 (1H, s)

**Example 4**

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 4)



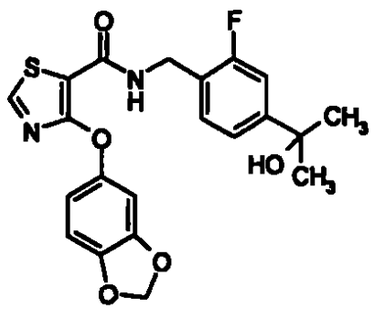
(8 5 4)

APCI M/S (m/z $M^+$+1)$^-$ 413

$^1$H NMR (400MHz, $CDCl_3$) δ 1 53 (6H, s), δ 4 6 (2H, d), δ 5 9 (2H, s) δ 6 6 (1H, d), δ 6 63 (1H, s), δ 6 75 (1H, d), δ 7 3 (2H, d), δ 7 42 (2H, d), δ 8 6 (1H, s)

**Example 5**

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 5)



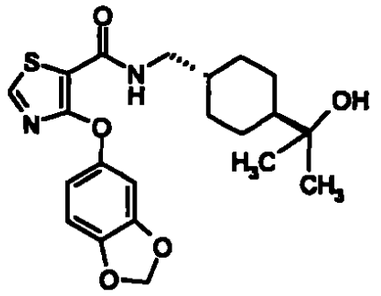
(8 5 5)

APCI M/S (m/z $M^+$+1): 431

MP 117-118°C

Example 6

*Trans*-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid [4-(1-hydroxy-1-methyl-ethyl)-cyclo-hexylmethyl]-amide of Formula (8 5 6)



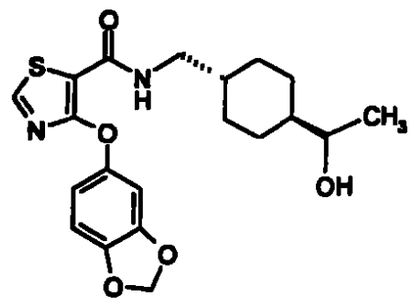
(8 5 6)

APCI M/S (m/z $M^+$+1-$H_2O$) 401

$^1$H NMR (400MHz, $CDCl_3$) δ 1 0 (6H, m), δ 1 9 (6H, s), δ 1 5 (2H, m), δ 1 9 (2H, d), δ 3 4 (2H, t), δ 6 0 (2H, s), δ 6 8 (3H, m), δ 7.2 (1H, b),δ 8 6 (1H, s)

Example 7

*Trans*-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid [4-(1-hydroxy-ethyl)-cyclohexylmethyl]-amide of Formula (8 5 7)



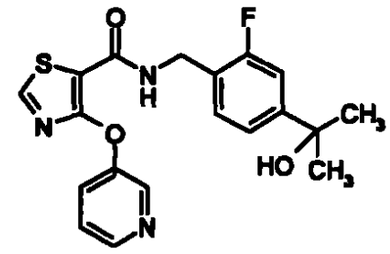
(8 5 7)

APCI M/S (m/z $M^+$+1) 405

$^1$H NMR (400MHz, $CDCl_3$) δ 1.0-1 9 (12H, m), δ 3 3 (2H, t), δ 3 5 (1H, m), δ 6 0 (2H, s), δ 6 6 (1H, dd), δ 6 7 (1H, s), δ 6 8 (1H, dd), δ 7 1 (1H, b), δ 8 55 (1H, s)

**Example 8**

4-(Pyridin-3-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzyl-amide of Formula (8 5 8)



(8 5 8)

APCI M/S (m/z $M^+$+1) 388

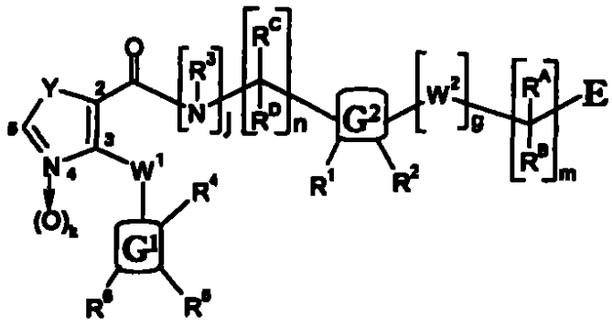
$^1$H NMR (400MHz, $CDCl_3$) δ 1 5 (6H, s), δ 4 6 (2H, d), δ 7 3 (7H, m), δ 8 6 (1H, s)

127

CB130

## 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, 2, or 3,

-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 $-CR^{29}R^{30}-$,

— 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 $-S(=O)_t-$, where t is 0, 1, or 2, –O–, $-[N\Rightarrow(O)_k]-$ or $-N(R^3)-$, where k is 0 or 1 and $R^3$ has the same meaning as defined below, or $-CH(R^1{}_a)-$, where $R^1{}_a$ has the same meaning as defined below;

— 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 $-NR^{16}R^{17}$,

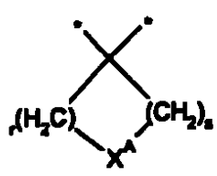
— and —

$—R^{16}$ 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, $–(C_3-C_8)$ 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)

00191



(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 $G^2$ 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 $G^1$ 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 $R^9$ 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, -C(=O)$R^{16}$; –O$R^{16}$, –($C_1$-$C_4$) alkyl–O$R^{16}$, -C(=O)O$R^{16}$, -($C_1$-$C_2$) alkyl-C(=O)O$R^{16}$, –C(=O)N$R^{16}R^{17}$, –($C_1$-$C_4$) alkyl, –($C_2$-$C_4$) alkenyl, –$(CH_2)_u$–($C_3$-$C_7$) cycloalkyl where u is 0, 1 or 2, phenyl, benzyl, pyridyl, and quinolinyl, wherein said alkyl, alkenyl, alkoxy, cycloalkyl, phenyl, benzyl, pyridyl or quinolinyl is substituted with 0 to 3 substituents $R^{12}$; where $R^{16}$ and $R^{17}$ have the same meanings as defined above, and

— where —

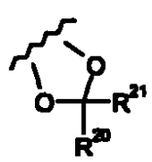
—$R^{12}$ is a member independently selected from the group consisting of –F, –Cl, -$CO_2R^{18}$, –O$R^{18}$, –CN, –C(=O)N$R^{18}R^{19}$, –N$R^{18}R^{19}$, –N$R^{18}$C(=O)$R^{19}$, -N$R^{18}$C(=O)O$R^{19}$, -N$R^{18}$S(=O)$_p$$R^{19}$, –S(=O)$_p$N$R^{18}R^{19}$, where p is 1 or 2, –($C_1$-$C_4$) alkyl, and -($C_1$-$C_4$) alkoxy in the case where $R^{12}$ has the meaning of –O$R^{16}$ 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 —

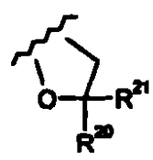
——$R^{18}$ and $R^{19}$ are independently selected from the group consisting of –H, -($C_1$-$C_4$) alkyl, and phenyl, where said alkyl or phenyl is substituted by 0-3 of –F, or –Cl,

— or in the case where $G^1$ is phenyl —

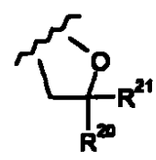
*-(d)* $R^5$ and $R^6$ are taken together to form a moiety which is a member selected from the group consisting of partial Formulas (1.3 1) through (1 3 15)



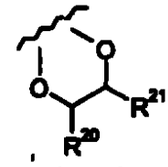
(1.3 1)



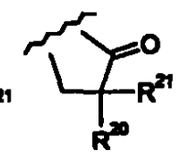
(1 3.2)



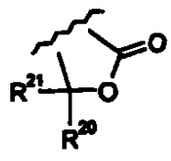
(1 3.3)



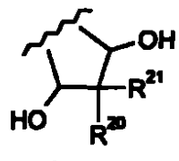
(1 3.4)



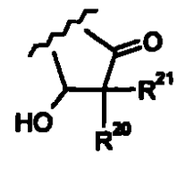
(1 3 5)



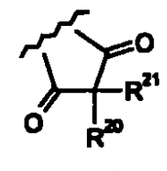
(1 3 6)



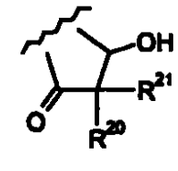
(1 3 7)



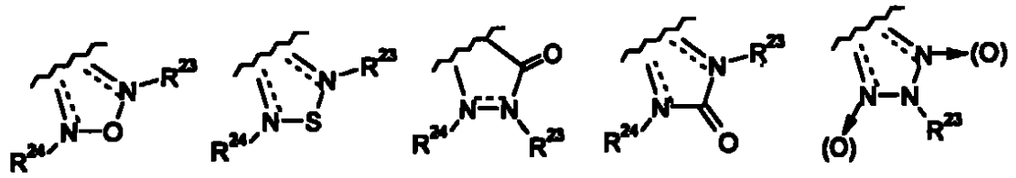
(1 3 8)



(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,

$G^1$ 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 $G^1$ is not a discontinuous or restricted biaryl moiety as defined under $G^2$ 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 $G^1$ is substituted on any ring or rings thereof by $R^4$, $R^5$ and $R^6$, which have the same meaning as defined above,

$G^2$ is 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, or that is a 7- to 18-membered discontinuous or restricted biaryl moiety, wherein for each of the carbon ring systems recited, 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,

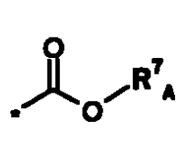
— wherein —

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

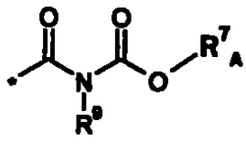
E is a member independently selected from the group consisting of

— the following —

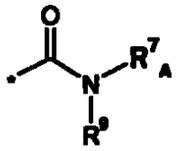
-(a) the group consisting of partial Formulas (1 1 1) through (1 1 15)



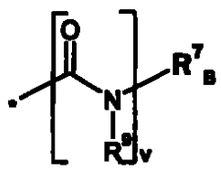
(1 1 1)



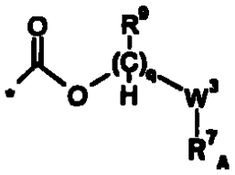
(1 1 2)



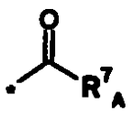
(1 1 3)



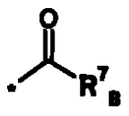
(1 1 4)



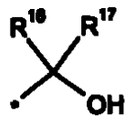
(1 1 5)



(1 1 6)



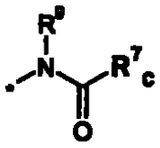
(1 1 7)



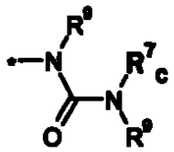
(1 1 8)



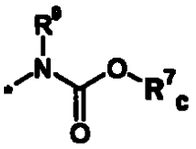
(1 1 9)



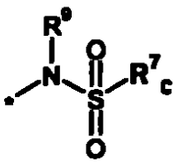
(1 1 10)



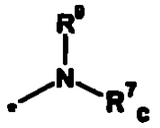
(1 1 11)



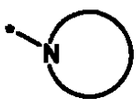
(1 1 12)



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

$-R^7$ 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 $E$ is further selected from —

*-(b)* a moiety comprising a member selected from the group consisting of $-O-P(=O)(OH)_2$ (phosphono), $-PH(=O)OH$ (phosphinic), $-P(=O)(OH)_2$ (phosphonic), $-[P(=O)(OH)-O(C_1-C_4)$ alkyl] (alkylphosphono), $-P(=O)(OH)-O(C_1-C_4)$ alkyl) (alkylphosphinyl), $-P(=O)(OH)NH_2$ (phosphoramido), $-P(=O)(OH)NH(C_1-C_4)$ alkyl and $-P(=O)(OH)NHR^{25}$ (substituted phosphoramido), $-O-S(=O)_2OH$ (sulfuric); $-S(=O)_2OH$

(sulfonic), $-S(=O)_2NHR^{28}$ or $-NHS(=O)_2R^{28}$ (sulfonamido) where $R^{28}$ is $-CH_3$, $-CF_3$, or *o*-toluyl, and acylsulfonamido selected from the group consisting of $-C(=O)NHS(=O)_2R^{25}$; $-C(=O)NHS(=O)_2NH_2$, $-C(=O)NHS(=O)_2(C_1-C_4)$ alkyl, $-C(=O)NHS(=O)_2NH(C_1-C_4)$ alkyl, $-C(=O)NHS(=O)_2N[(C_1-C_4)\text{ alkyl}]_2$, $-S(=O)_2NHC(=O)(C_1-C_4)$ alkyl, $-S(=O)_2NHC(=O)NH_2$, $-S(=O)_2NHC(=O)NH(C_1-C_4)$ alkyl, $-S(=O)_2NHC(=O)N[(C_1-C_4)\text{ alkyl}]_2$, $-S(=O)_2NHC(=O)R^{25}$, $-S(=O)_2NHCN$, $-S(=O)_2NHC(=S)NH_2$, $-S(=O)_2NHC(=S)NH(C_1-C_4)$ alkyl, $-S(=O)_2NHC(=S)N[(C_1-C_4)\text{ alkyl}]_2$, and $-S(=O)_2NHS(=O)_2R^{25}$;

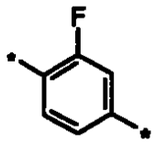
— where —

$-R^{25}$ is –H, $-(C_1-C_4)$ alkyl, phenyl, or $-OR^{15}$, where $R^{15}$ has the same meaning as defined above,

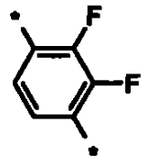
— or —

a pharmaceutically acceptable salt thereof

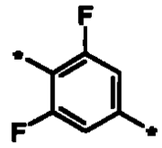
2 A compound according to Claim 1 wherein the group $G^2$ and the substituents $R^1$ and $R^2$ attached thereto are selected in such a way that the resulting portion of a compound of Formula (1 0 0) is represented by partial Formulas (2 5 1) through (2 5 50)



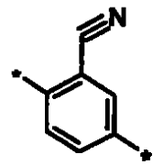
(2 5 1)



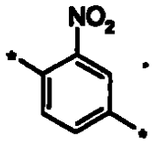
(2 5.2)



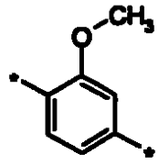
(2 5.3)



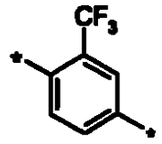
(2 5 4)



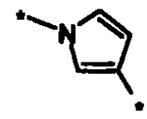
(2 5 5)



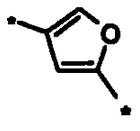
(2 5 6)



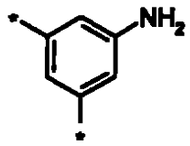
(2 5 7)



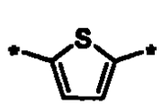
(2.5.8)



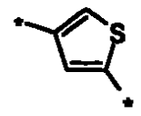
(2 5 9)



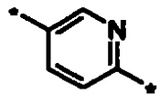
(2 5 10)



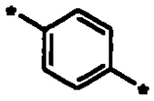
(2 5 11)



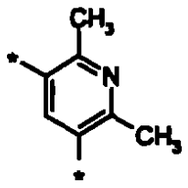
(2 5 12)



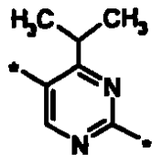
(2 5 13)



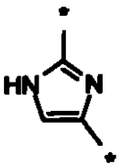
(2 5 14)



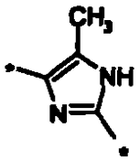
(2 5 15)



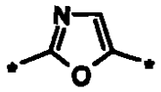
(2 5 16)



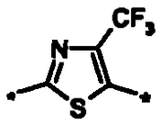
(2 5 17)



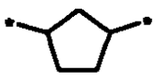
(2 5 18)



(2 5 19)



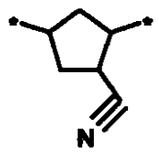
(2 5.20)



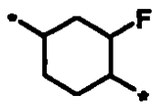
(2 5.21)



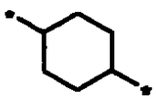
(2 5 22)



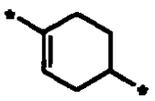
(2 5 23)



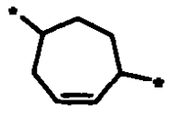
(2.5.24)



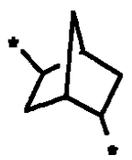
(2 5.25)



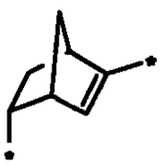
(2 5 26)



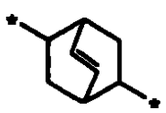
(2 5 27)



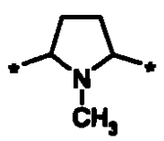
(2 5 28)



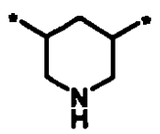
(2 5 29)



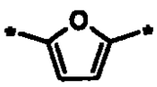
(2 5 30)



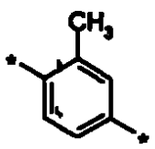
(2 5.31)



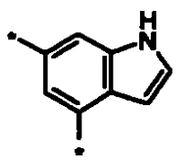
(2 5 32)



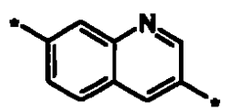
(2 5 33)



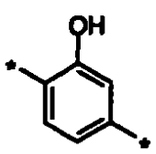
(2 5 34)



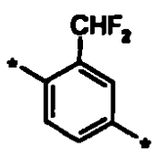
(2 5 35)



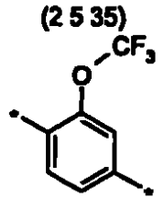
(2 5 36)



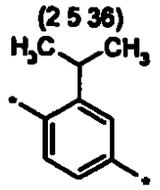
(2 5 37)



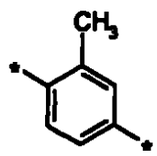
(2 5 38)



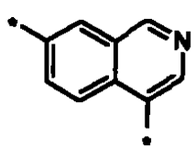
(2 5 39)



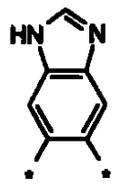
(2 5 40)



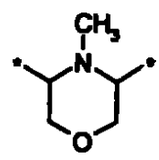
(2 5.41)



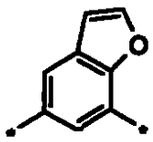
(2 5 42)



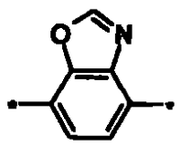
(2 5 43)



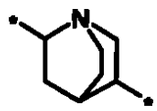
(2 5 44)



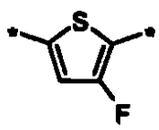
(2 5 45)



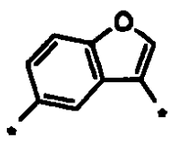
(2 5.46)



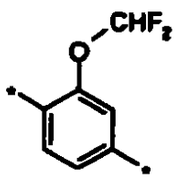
(2.5.47)



(2 5 48)

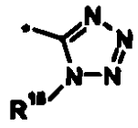


(2 5 49)



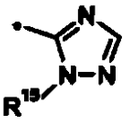
(2 5 50)

3 A compound according to Claim 1 wherein E compnses partial Formulas (1 1 4) and (1 1 10) through (1 1 14), and the meaning of $R^7$a 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 32)



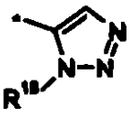
Tetrazol-5-yl

(1 4 1)



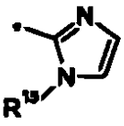
1,2,4-triazol-3-yl

(1 4.2)



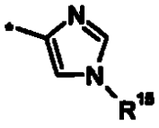
1,2,3-triazol-5-yl

(1.4.3)



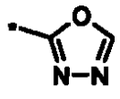
imidazol-2-yl

(1.4.4)



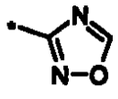
Imidazol-4-yl

(1 4 5)



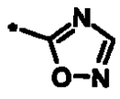
1,3,4-oxadiazolyl

(1 4 6)



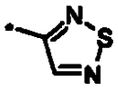
1,2,4-oxadiazol-3-yl

(1 4 7)



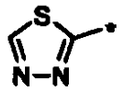
1,2,4-oxadiazol-5-yl

(1 4 8)



1,2,5-thiadiazol-2-yl

(1 4 9)



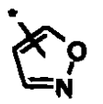
1,3,4-thiadiazolyl

(1 4 10)



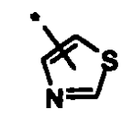
oxazolyl

(1 4 11)



isoxazolyl

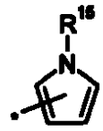
(1 4 12)



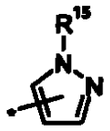
Thiazolyl
(1 4 13)



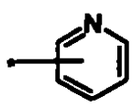
isothiazolyl
(1.4 14)



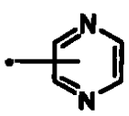
pyrrolyl
(1.4 15)



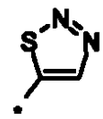
pyrazolyl
(1 4 16)



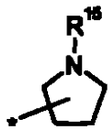
Pyridyl
(1 4 17)



pyrazinyl
(1 4 18)



1,2,3-thiadiazol-5-yl
(1.4 19)



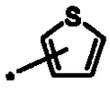
pyrrolidinyl
(1.4.20)



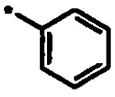
Furanyl
(1 4.21)



tetrahydrofuranyl
(1.4.22)



thienyl
(1 4.23)



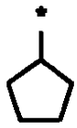
phenyl
(1 4.24)



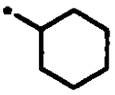
Cyclopropyl
(1 4.25)



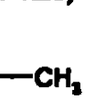
cyclobutyl
(1.4 26)



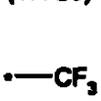
cyclopentyl
(1 4 27)



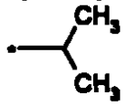
cyclohexyl
(1 4.28)



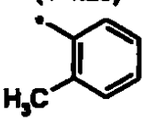
Methyl
(1 4.29)



trifluoromethyl
(1 4 30)



*iso*-propyl
(1.4.31)

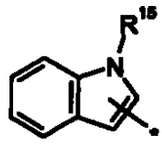


o-toluyl
(1 4 32)

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

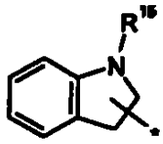
5

4 A compound according to Claim 1 wherein E comprises partial Formulas (1 1 4) and (1 1 9) through (1 1 13) 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)



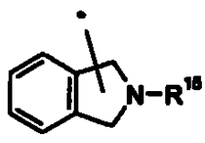
Indolyl

(1 5 1)



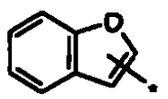
Indolinyl

(1 5 2)



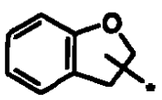
isoindolinyl

(1 5 3)



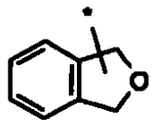
benzo[*b*]furanyl

(1 5 4)



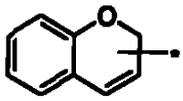
2,3-dihydrobenzo-furanyl

(1 5 5)



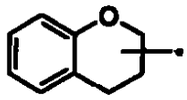
1,3-dihydroisobenzo-furanyl, phthalanyl

(1 5 6)



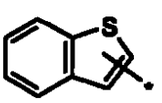
2*H*-1-benzopyranyl

(1 5 7)



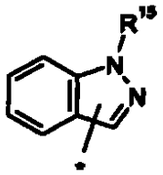
chromanyl

(1 5.8)



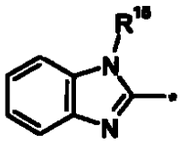
Benzothienyl

(1 5.9)



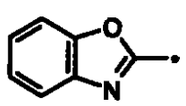
1*H*-indazolyl

(1 5 10)



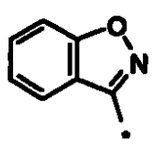
benzimidazolyl

(1 5 11)



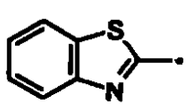
benzoxazolyl

(1 5 12)



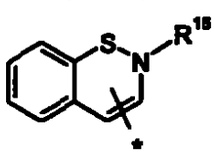
Benzisoxazolyl

(1 5.13)



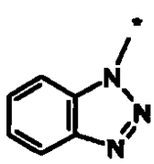
benzothiazolyl

(1 5 14)



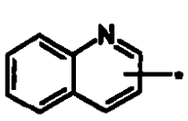
2*H*-1,2-benzothiazinyl

(1 5 15)



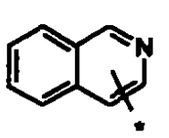
benzotriazolyl

(1 5 16)



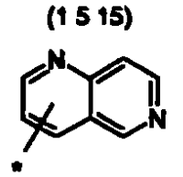
Quinolinyl

(1 5 17)



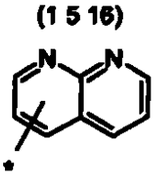
isoquinolinyl

(1 5 18)



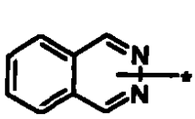
1,6-naphthyridinyl

(1 5 19)



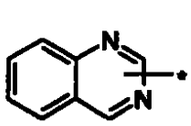
1,8-naphthyridinyl

(1 5.20)



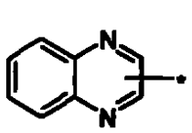
Phthalazinyl

(1 5.21)



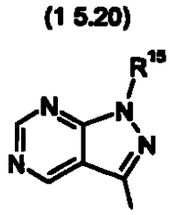
quinazolinyl

(1 5 22)



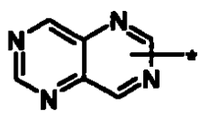
quinoxalinyl

(1 5.23)



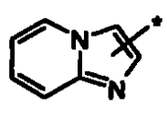
1*H*-pyrazolo[3,4-*d*]-pyrimidinyl

(1 5.24)



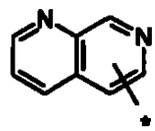
Pyrimido[5,4-*d*]-pyrimidinyl

(1 5.25)



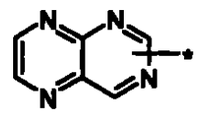
imidazo-[1,2-*a*]-pyridinyl

(1 5 26)



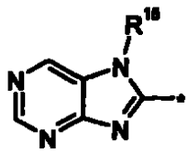
1,7-naphthyridinyl

(1 5 27)



ptendinyl

(1 5 28)



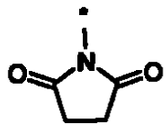
1*H*-purinyl

(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

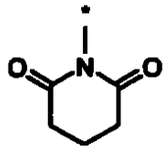
5

5 A compound according to Claim 1 wherein E comprises partial Formula (1 1 15) and is a member selected from the group consisting of partial Formulas (1 7 1) through (1 7 46)



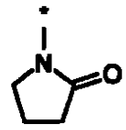
Succinimid-1-yl

(1 7 1)



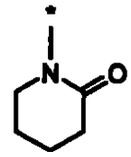
glutarimid-1-yl

(1 7 2)



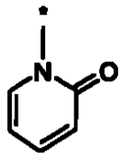
pyrrolidin-2-on-1-yl

(1 7.3)



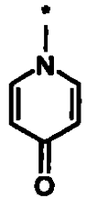
piperid-2-on-1-yl

(1 7.4)



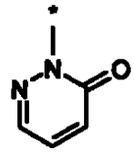
Pyrid-2-on-1-yl

(1 7.5)



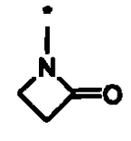
pyrid-4-on-1-yl

(1 7 6)



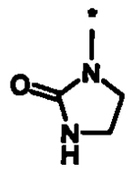
pyridazin-3-on-2-yl

(1 7 7)



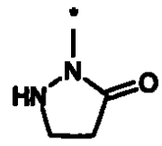
azetidin-2-on-1-yl

(1 7 8)



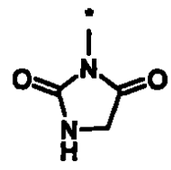
Imidazolidin-2-on-1-yl

(1 7 9)



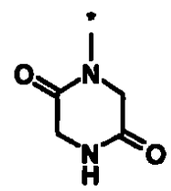
pyrazol-5-on-1-yl

(1 7 10)



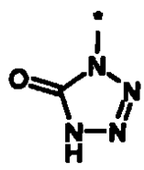
imidazolidin-2,4-dion-1-yl

(1 7 11)



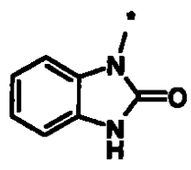
piperazin-2,5-dion-1-yl

(1 7 12)



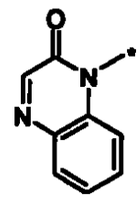
4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl

(1 7 13)



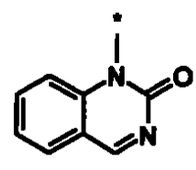
benzimidazolin-2-on-1-yl

(1 7 14)



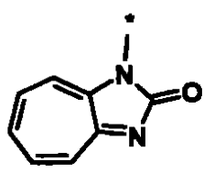
1*H*-quinoxalin-2-on-1-yl

(1 7 15)



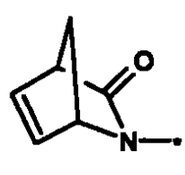
1*H*-quinazolin-2-on-1-yl

(1 7 16)



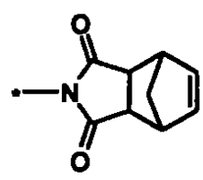
1H-cycloheptimidazol-2-on-1-yl

(1 7 17)



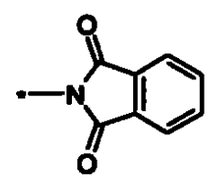
2-azabicyclo[2 2 1]-hept-5-en-3-on-1-yl

(1 7 18)



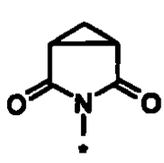
norborn-5-en-2,3-dicarboximid-1-yl

(1 7 19)



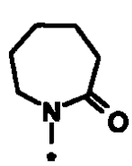
phthalimid-1-yl, 1*H*-isoindole-1,3(2*H*)-dion-1-yl

(1 7.20)



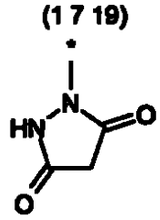
3-azabicyclo[3 1 0]-hexane-2,4-dion-3-yl

(1 7.21)



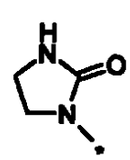
2*H*-azepin-2-on-1-yl

(1 7 22)



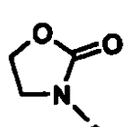
pyrazolidin-3,5-dion-1-yl

(1 7.23)



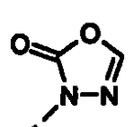
imidazolidin-2-on-1-yl

(1 7 24)



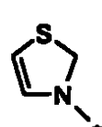
Oxazolidin-2-on-1-yl

(1 7.25)



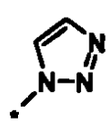
1,3,4-oxadiazol-2(3*H*)-on-3-yl

(1 7.26)



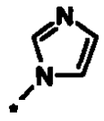
thiazol-3-yl

(1 7.27)



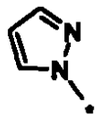
1*H*-1,2,3-triazol-1-yl

(1 7.28)



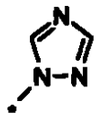
Imidazol-1-yl

(1 7 29)



pyrazol-1-yl

(1 7 30)



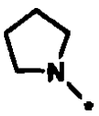
1*H*-1,2,4-triazol-1-yl

(1 7.31)



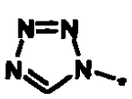
azetidin-1-yl

(1 7.32)



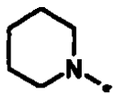
Pyrrolidin-1-yl

(1 7 33)



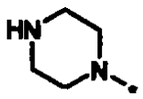
tetrazol-1-yl

(1 7.34)



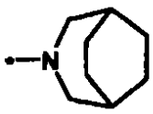
piperidin-1-yl

(1 7 35)



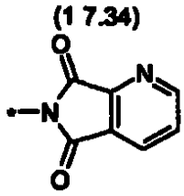
piperazin-1-yl

(1 7.36)



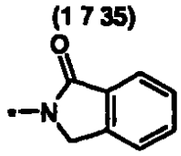
3-azabicyclo[3 2 2]-non-3-yl

(1 7.37)



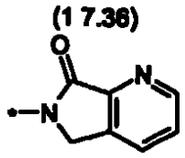
pyrrolo[3,4-*b*]pyridin-5,7-dion-6-yl

(1 7.38)



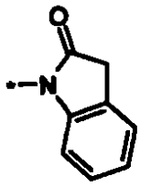
2,3-dihydro-*iso*-indol-1-on-2-yl

(1 7 39)



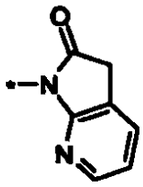
pyrrolo[3,4-*b*]pyridin-7-on-6-yl

(1 7.40)



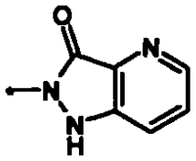
1,3-dihydro-indol-2-on-1-yl

(1 7.41)



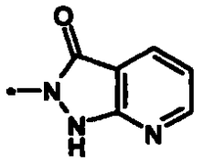
pyrrolo[4,5-*b*]pyridin-3-on-2-yl

(1 7.42)



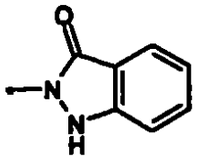
1*H*-pyrazolo[4,5-*e*]pyridin-7-on-2-yl

(1 7 43)



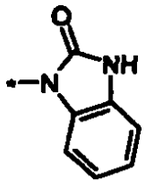
1*H*-pyrazolo[4,5-*b*]pyridin-4-on-2-yl

(1 7 44)



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

(1 7 45)



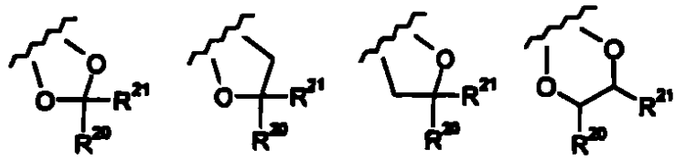
1*H*-benzimidazol-2-on-3-yl

(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

5

6 A compound according to Claim 1 wherein m is 1, n is 1, $W^1$ is -O-, $W^2$ is absent, Y is $=C(R^1_a)-$, $R^1_a$ is -H, -F, -Cl, $-CH_3$, $-CF_3$, or $-OCH_3$, $R^A$ 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; $R^C$ and $R^D$ are both -H, and $R^5$ and $R^6$ are taken together to form a moiety selected from the group consisting of partial Formulas (1 3 1) through (1 3 4), (1 3 11), (1 3 12), (1 3 14), and (1 3 15)



(1 3 1) (1 3 2) (1 3 3) (1 3 4)



(1 3 11) (1 3 12) (1 3 14) (1 3 15)

where $R^{20}$ and $R^{21}$ are each independently -H, -F, $-CH_3$, or $-OCH_3$, and $R^{23}$ and $R^{24}$ are each independently -H, $-CH_3$, $-OCH_3$, or absent, in which case the dashed line - - - - represents a double bond

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

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 1),

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 2),

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-cyclobutyl)-benzylamide of Formula (8 5 3),

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 4);

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 5),

*Trans*-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid [4-(1-hydroxy-1-methyl-ethyl)-cyclohexylmethyl]-amide of Formula (8 5 6),

*Trans*-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid [4-(1-hydroxy-ethyl)-cyclohexylmethyl]-amide of Formula (8 5 7),

4-(Pyridin-3-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-(1-hydroxy-1-methyl-ethyl)-benzylamide of Formula (8 5 8),

4-({[4-(4-Fluoro-phen-4-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-benzoic acid of Formula (8 5 9);

4-{[(4-Benzo[1,3]dioxol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl}-benzoic acid of Formula (8 5 10);

4-({[4-(Benzo[1,3]dioxol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-benzoic acid of Formula (8 5 11);

[4-({[4-(Benzo[2,1,3]thiadiazol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-phen-4-yloxy]-acetic acid of Formula (8 5 12),

[4-({[4-(Benzo[2,1,3]oxadiazol-5-yloxy)-[1,3]thiazole-5-carbonyl]-amino}-methyl)-phenyl-4-yloxy]-acetic acid of Formula (8 5 13),

(±)-2-[4-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-phenoxy]-propionic acid of Formula (8.5 14),

(±)-2-[4-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-cyclohexyloxy]-propionic acid of Formula (8 5 15),

4-(3-Methoxy-phenoxy)-thiazole-5-carboxylic acid 2-fluoro-4-(pyridin-2-ylmethoxy)-benzylamide of Formula (8 5 16),

(±)-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 2-fluoro-4-[1-(1H-tetrazol-5-yl)-ethoxy]-benzylamide of Formula (8 5 17),

(±)-4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-(1-carbamoyl-ethoxy)-2-fluoro-benzylamide of Formula (8 5 18),

(±)-2-[3-Fluoro-4-({[4-(3-nitro-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (8 5 19),

(±)-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 4-[1-(5-methyl-4H-[1,2,4]triazol-3-yl)-ethoxy]-benzylamide of Formula (8 5 20),

[4-({[4-(3-Cyano-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-phenyl]-acetic acid of Formula (8 5 21),

2-[4-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-phenyl]-2-methyl-propionic acid of Formula (8 5 22),

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 4-carbamoylmethyl-2-fluoro-benzylamide of Formula (8 5 23);

4-(3-Methoxy-phenoxy)-thiazole-5-carboxylic acid 4-[1-methyl-1-(1H-tetrazol-5-yl)-ethyl]-benzylamide of Formula (8 5 24),

4-(3-Nitro-phenoxy)-thiazole-5-carboxylic acid 4-[(2-cyano-benzoylamino)-methyl]-benzylamide of Formula (8 5 25);

Pyridine-2-carboxylic acid 4-({[4-(benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3-fluoro-benzylamide of Formula (8 5 26),

4H-[1,2,4]Triazole-3-carboxylic acid 3-fluoro-4-({[4-(3-methoxy-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-benzylamide of Formula (8 5 27),

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid 2-fluoro-4-[(2-methoxy-benzoylamino)-methyl]-benzylamide of Formula (8 5 28),

4-(4-Fluoro-phenoxy)-thiazole-5-carboxylic acid 4-[[(3H-imidazole-4-carbonyl)-amino]-methyl]-benzylamide of Formula (8 5.29),

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid 4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-fluoro-benzylamide of Formula (8 5 30);

(±)-2-[4-({[4-(Benzo[2,1,3]thiadiazol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-phenoxy]-propionic acid of Formula (8 5 31),

4'-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-3-carboxylic acid of Formula (8 5 32);

4'-({[4-(3-Cyano-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-4-carboxylic acid of Formula (8 5 33),

(±)-2-[4'-({[4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-2-fluoro-biphenyl-4-yloxy]-propionic acid of Formula (8 5 34),

[2-Fluoro-4'-({[4-(4-fluoro-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-biphenyl-4-yl]-acetic acid of Formula (8 5 35),

2-[3'-Fluoro-4'-({[4-(3-methoxy-phenoxy)-thiazole-5-carbonyl]-amino}-methyl)-biphenyl-4-yl]-2-methyl-propionic acid of Formula (8 5 36),

(±)-4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid {3,2'-difluoro-4'-[1-(1H-tetrazol-5-yl)-ethoxy]-biphenyl-4-ylmethyl}-amide of Formula (8 5 37),

4-(4-Fluoro-phenoxy)-thiazole-5-carboxylic acid {4'-[(2-cyano-benzoylamino)-methyl]-3-fluoro-biphenyl-4-ylmethyl}-amide of Formula (8 5 38),

Pyridine-2-carboxylic acid [4'-({[4-(benzo[1,3]dioxol-5-yloxy)-thiazole-5-carbonyl]-amino}-methyl)-3'-fluoro-biphenyl-4-ylmethyl]-amide of Formula (8 5 39),

4-(4-Fluoro-phenoxy)-thiazole-5-carboxylic acid [4'-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2'-fluoro-biphenyl-4-ylmethyl]-amide of Formula (8 5 40),

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid {3-fluoro-4'-[(2-methoxy-benzoylamino)-methyl]-biphenyl-4-ylmethyl}-amide of Formula (8 5 41),

4-(3-Cyano-phenoxy)-thiazole-5-carboxylic acid {2'-fluoro-4'-[1-methyl-1-(1H-tetrazol-5-yl)-ethyl]-biphenyl-4-ylmethyl}-amide of Formula (8 5 42),

4-(3-Chloro-4-fluoro-phenoxy)-thiazole-5-carboxylic acid (4'-carbamoylmethyl-3-fluoro-biphenyl-4-ylmethyl)-amide of Formula (8 5.43), and

4-(Benzo[1,3]dioxol-5-yloxy)-thiazole-5-carboxylic acid (3-fluoro-4'-[[(3H-imidazole-4-carbonyl)-amino]-methyl]-biphenyl-4-ylmethyl)-amide of Formula (8 5 44)

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 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, characterized in that 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;

— pneumoconioses 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, urticarogenic 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, 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, imidazoles, clotrimazole, econazole, miconazole, and ketoconazole, triazoles, fluconazole and itranazole, and amphotericins, Amphotencin B and liposomal Amphotencin 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

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-746,530 belongs, the classes of indole and quinoline compounds to which MK-591, MK-886, and BAY x 1005 belong;

(b) Receptor antagonists for leukotrienes $LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$ selected from the group consisting of the phenothiazin-3-one class of compounds to which L-651,392 belongs, the class of amidino compounds to which CGS-25019c belongs, the class of benzoxaolamines to which ontazolast belongs, the class of benzenecarboximidamides to which BIIL 284/260 belongs, and the classes of compounds to which zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195 belong,

(c) PDE4 inhibitors including inhibitors of the isoform PDE4D,

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

(e) Dual inhibitors of 5-lipoxygenase (5-LO) and antagonists of platelet activating factor (PAF),

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

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

(h) Gastroprotective $H_2$ receptor antagonists,

(i) $\alpha_1$— and $\alpha_2$—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) $\alpha_1$— and $\alpha_2$—adrenoceptor agonists in combination with inhibitors of 5-lipoxygenase (5-LO),

(k) Anticholinergic agents including ipratropium bromide,

(l) $\beta_1$— to $\beta_4$—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 (TNF□) 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 AMIDA DE ACIDO TIAZOLILICO, OXAZOLILICO, PIRROLILICO E IMIDAZOLILICO UTILES COMO INHIBIDORES DE LAS ISOZIMAS PDE4

## 1.0 REFERENCIA A SOLICITUDES DE PATENTE EN TRAMITACION JUNTO CON LA PRESENTE

Se hace referencia a la solicitud internacional y a la solicitud U.S. basada en ésta, en tramitación junto con la presente, nº de serie PCT/IB98/00315, presentadas ambas el 10 de marzo de 1998 (expediente de agente Nº PC9762A), y publicadas como WO 98/45268 el 15 de octubre de 1998; que reivindica prioridad de la solicitud nº de serie 60/043403, presentada el 4 de abril de 1997 (expediente de agente Nº PC9762), ahora abandonada; que describe derivados de nicotinamida con actividad biológica como inhibidores selectivos de la isozima PDE4D, útiles así en el tratamiento de enfermedades y afecciones inflamatorias, respiratorias y alérgicas. Nada de lo descrito en las solicitudes anteriormente indicadas explicaría a una persona de conocimiento medio de la técnica pertinente los nuevos compuestos de la presente invención, o el nivel inesperadamente alto de selectividad inhibitoria por la isozima PDE4D que poseen los citados nuevos compuestos.

Se hace referencia también a la solicitud en tramitación junto con la presente de nº de serie 09/345.185, presentada el 30 de junio de 1999 (expediente de agente Nº PC10096A); que

reivindica prioridad sobre la solicitud de n° de serie 60/105.120, presentada el 21 de octubre de 1998 (expediente de agente N° PC10096), que describe compuestos y procedimientos para la preparación de derivados de nicotinamida N-sustituidos. Sin embargo, los compuestos y procedimientos descritos no son los mismos que los de la presente invención.

Se hace referencia además a las solicitudes en tramitación junto con la presente presentadas con la misma fecha con la presente solicitud, expedientes de agente n° PC11712, PC11848, PC11893, PC11895, PC11896 y PC11897, que implican otras clases de derivados de nicotinamida útiles como inhibidores de isozimas PDE4. Las descripciones de todas las citadas solicitudes en tramitación junto con la presente se incorporan a la presente como referencia en su totalidad.

## 2.0 ANTECEDENTES DE LA INVENCION

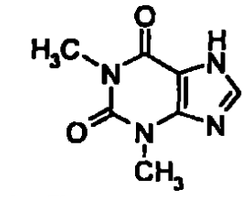
Las fosfodiesterasas de nucleótido 3',5'-cíclico (PDE) comprenden una gran clase de enzimas divididas en al menos once familias diferentes, que son estructural, bioquímica y farmacológicamente distintas entre sí. Las enzimas de cada familia se denominan habitualmente como isoenzimas, o isozimas. Se incluye en esta clase más de quince productos génicos, y resulta una diversidad adicional por ayuste diferencial y procesamiento post-traducción de esos productos génicos. La

presente invención se refiere principalmente a los cuatro productos génicos de la cuarta familia de las PDE, es decir, PDE4A, PDE4B, PDE4C y PDE4D. Estas enzimas se representan colectivamente como isoformas o subtipos de la familia de isozimas PDE4. Más adelante se encontrará una discusión más detallada de la organización genómica, estructura molecular y actividad enzimática, ayuste diferencial, regulación transcripcional y fosforilación, distribución y expresión e inhibición selectiva de los subtipos de isozima PDE4.

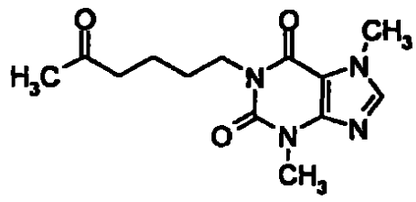
Las PDE4 se caracterizan por una degradación selectiva hidrolítica de alta afinidad del nucleotido cíclico segundo mensajero monofosfato 3',5'-cíclico de adenosina (AMPc), y por la sensibilidad ante la inhibición por rolipram. Se han descubierto una serie de inhibidores selectivos de las PDE4 en los últimos años, y se han mostrado los efectos farmacológicos beneficiosos resultantes de esa inhibición en una variedad de modelos de enfermedad. Véanse, por ejemplo, Torphy et al., *Environ. Health Perspec.* **102**, supl. 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 y 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 KF-19514, a phosphodiesterase 4 and 1 inhibitor", *Eur J. Pharmacol.* **332**, 97-107, 1997; y Ukita et al. "Novel, potent and selective phosphodiesterase-4 inhibitors as antiasthmatic agents: synthesis and biological activities of a series of 1-pyridylnaphtalene derivatives", *J. Med. Chem* , **42**, 1088-1099, 1999. Consiguientemente, continúa habiendo un interés considerable en la técnica con respecto del descubrimiento de inhibidores selectivos de PDE4.

La presente invención se refiere también al uso de inhibidores selectivos de PDE4 para un tratamiento terapéutico mejorado de una serie de enfermedades y afecciones inflamatorias, respiratorias y alérgicas, pero especialmente para el tratamiento de asma, enfermedad pulmonar obstructiva crónica (EPOC), incluyendo bronquitis crónica, enfisema y bronquiectasis; rinitis crónica; y sinusitis crónica. Sin embargo, hasta el momento en la técnica, la terapia de primera línea para el tratamiento de asma y otras enfermedades obstructivas de las vías aéreas ha sido el inhibidor de PDE no selectivo teofilina, así como pentoxilina e IBMX, que pueden representarse por las fórmulas (0.0.1), (0.0.2) y (0.0.3), respectivamente.



teofilina
(0 0 1)

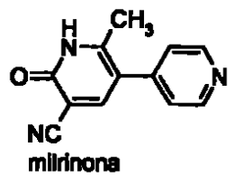


pentoxifilina
(0 0 2)

La teofilina, que tiene a las PDE como una de sus dianas bioquímicas, además de su bien caracterizada actividad broncodilatadora, afecta a la vasculatura de pacientes con una presión arterial pulmonar aumentada, suprime las respuestas celulares inflamatorias e induce la apoptosis de eosinófilos. Sin embargo, los sucesos adversos de la teofilina, lo más frecuentemente disrritmias cardiacas y naúsea, están también mediados por la inhibición de PDE, lo que conduce a la búsqueda de inhibidores más selectivos de PDE que sean capaces de suprimir tanto las funciones celulares inmunes in vitro, como la inflamación pulmonar alérgica in vivo, teniendo al mismo tiempo perfiles mejorados de efectos secundarios. En las vías aéreas de los pacientes que padecen asma y otras enfermedades obstructivas de las vías aéreas, la PDE4 es la más importante de las isozimas de PDE como diana de descubrimiento de fármacos debido a su distribución en músculo liso de las vías aéreas y en células inflamatorias. Se han diseñado así varios inhibidores de PDE4

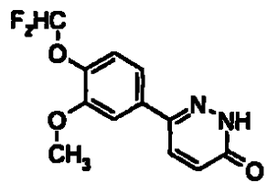
introducidos en la técnica para tener un índice terapéutico mejorado respecto de los efectos secundarios cardiovasculares, gastrointestinales y del sistema nervioso central de las xantinas no selectivas anteriormente citadas.

La obstrucción del flujo de aire y la inflamación de las vías aéreas son características del asma, así como de la EPOC. Aunque el asma bronquial se caracteriza principalmente por una inflamación eosinófila, los neutrófilos parecen desempeñar un papel importante en la patogénesis de la EPOC. Así, las PDE que están implicadas en la relajación del músculo liso y que se encuentran también en eosinófilos, así como neutrófilos, constituyen probablemente un elemento esencial de la progresión de ambas enfermedades. Las PDE implicadas incluyen las PDE3, así como las PDE4, y se han descubierto inhibidores de broncodilatación que son inhibidores selectivos de PDE3 e inhibidores selectivos duales de PDE3/4. Son ejemplos de estos, milrinona, un inhibidor selectivo de PDE3, así como zardaverina y benafentrina, ambos inhibidores selectivos duales de PDE3/4, que pueden representarse por las fórmulas (0.0.4), (0.0.5) y (0.0.6), respectivamente:



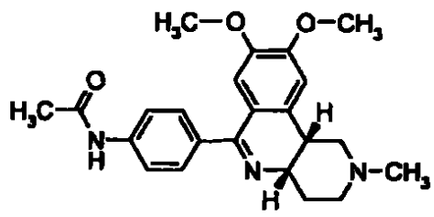
milrinona

(004)



zardaverina

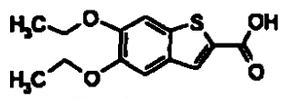
(005)



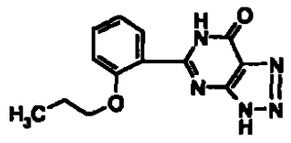
benafentrina

(006)

Sin embargo, la benafentrina da como resultado boncodilatación sólo cuando se administra por inhalación, y la zardaverina produce sólo una broncodilatación modesta y de corta vida. La milrinona, un agente cardiotónico, induce una broncodilatación de corta vida, y un ligero grado de protección frente a la broncoconstricción inducida, pero tiene sucesos adversos importantes, por ejemplo, taquicardia e hipotensión. Se han obtenido también resultados insatisfactorios con un inhibidor débilmente selectivo de PDE4, tibenelast, y un inhibidor selectivo de PDE5, zaprinast, que pueden representarse por las fórmulas (0.0.7) y (0.0.8):




tibenelast
(0.0 7)



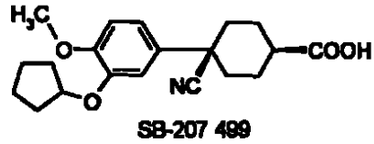

zaprinast
(0 0.8)

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

In vivo, los inhibidores de PDE4 reducen la entrada de eosinófilos a los pulmones de animales infectados con alergenos, mientras que reduce también la broncoconstricción y aparece una elevada respuesta bronquial después de la aplicación de la infección del alergeno. Los inhibidores de PDE4 suprimen también la actividad de las células inmunes, incluyendo linfocitos T $CD4^+$, monocitos, mastocitos y basófilos, reducen el edema pulmonar; inhiben la neurotransmisión no colinérgica no adrenérgica excitatoria (eNANC), potencian la neurotransmisión no colinérgica no adrenérgica inhibitoria (iNANC); reducen la mitogénesis en músculo liso de las vías aéreas; e inducen la broncodilatación. Los inhibidores de PDE4 suprimen también la actividad de una serie de células inflamatorias asociadas con la patofisiología de la EPOC, incluyendo monocitos/macrófagos, linfocitos T $CD8^+$ y neutrófilos. Los inhibidores de PDE4 reducen también la mitogénesis de músculo liso vascular e interfieren potencialmente con la capacidad de las células epiteliales de

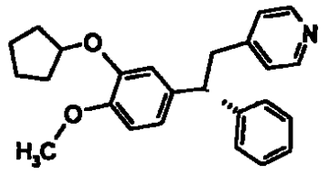
las vías aéreas de generar mediadores proinflamatorios. Mediante la liberación de proteasas neutras e hidrolasas ácidas de sus gránulos, y la generación de especies de oxígeno reactivas, los neutrófilos contribuyen a la destrucción del tejido asociada a la inflamación crónica, y están implicados también en la patología de afecciones tales como enfisema.

Los inhibidores selectivos de PDE4 que se han descubierto hasta ahora que proporcionan ventajas terapéuticas incluyen SB-207.499, identificado como ARIFLO(R), que puede representarse por la fórmula (0.1.9):




SB-207 499 (0 1 9)

SB-207.499 administrado oralmente a dosificaciones de 5, 10 y 15 mg b.i.d. ha producido aumentos significativos del $FEV_1$ mínimo (volumen expiratorio forzado en 1 segundo) respecto del placebo en la semana 2 de un estudio que implicaba un gran número de pacientes. Otro potente inhibidor selectivo de PDE4, CDP840, ha mostrado la supresión de reacciones tardías ante alergeno inhalado después de 9,5 días de administración oral a dosis de 15 y 30 mg en un grupo de pacientes con asma bronquial. El CDP840 puede representarse por la fórmula (0.0.9):

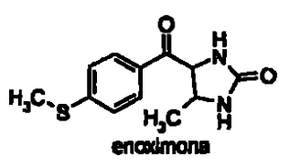



CDP840 (009)

Las PDE se han investigado también como terapia potencial para enfermedades obstructivas pulmonares, incluyendo EPOC. En un amplio estudio de SB-207.499 en pacientes con EPOC, el grupo de pacientes que recibió 15 mg b.i.d. ha experimentado una mejora progresiva del $FEV_1$ mínimo, alcanzando una diferencia media máxima, en comparación con el placebo, de 160 ml en la semana 6, lo que representa una mejora del 11%. Véase Compton et al., "The efficacy of Ariflo (SB207499), a second generation, oral PDE4 inhibitor, in patients with EPOC", *Am. J. Respir. Crit. Care Med.* **159**, 1999. Se ha observado que los pacientes con EPOC graves tienen hipertensión pulmonar, y se han conseguido reducciones de la presión arterial pulmonar media en condiciones clínicas mediante la administración oral de los inhibidores selectivos de PDE3 milrinona y enoximona. Se ha mostrado también que la enoximona reduce la resistencia de las vías aéreas en pacientes hospitalizados con EPOC descompensada. Véase Leeman et al., *Chest* **91**, 662-666, 1987. Utilizando una inhibición selectiva de PDE3 por motapizona y una inhibición selectiva de PDE5 por zaprinast, se ha mostrado que la inhibición combinada de PDE3 y 5 ejerce una relajación de los anillos arteriales

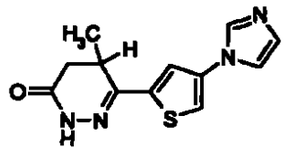
pulmonares que se corresponde ampliamente con el patrón de las isozimas de PDE encontrado en músculo liso arterial pulmonar. Véase Rabe et al., *Am. J Physiol.* **266** (LCMP 10); L536-L543, 1944. Se han mostrado anteriormente las estructuras de milrinona y zaprinast como fórmulas (0.0.4) y (0.0.8), respectivamente.

Las estructuras de enoximona y motapizona pueden representarse por las fórmulas (0.0.10) y (0.0.11), respectivamente:




enoximona

(0 0 10)

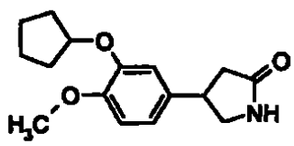



motapizona

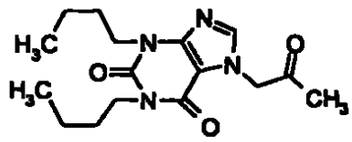
(0.0 11)

Pueden utilizarse los efectos de los inhibidores de PDE4 sobre diversas respuestas celulares inflamatorias como base para el perfilado y la selección de inhibidores para un estudio adicional. Estos efectos incluyen la elevación del nivel de AMPc y la inhibición de la producción de superóxido, desgranulación, quimiotaxia y liberación del factor de necrosis tumoral alfa (TNFα) en eosinófilos, neutrófilos y monocitos. Los inhibidores de PDE4 pueden inhibir la émesis, es decir, naúsea y vómitos que, como se espera, son un efecto adverso. El efecto adverso de la émesis se hizo evidente cuando se investigaron por primera vez los inhibidores de PDE4 para indicaciones del SNC tales como depresión, cuando se utilizaron rolipram y denbufilina en

ensayos clínicos. El rolipram y la denbufilina pueden representarse por las fórmulas (0.0.12) y (0.0.13), respectivamente:

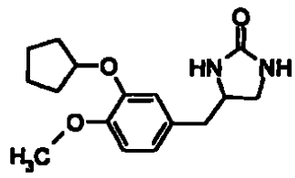



Rolipram
(0 0 12)




denbufilina
(0 0 13)

El (los) mecanismo(s) por el(los) que los inhibidores de PDE4 pueden inducir potencialmente la émesis es (son) incierto(s), pero un estudio de inhibidor de PDE4, Ro-20-1724, sugiere que náusea y vómitos están mediados al menos en parte por los centros de émesis del cerebro. Los sucesos adversos gastrointestinales pueden estar causados por efectos locales, por ejemplo, el rolipram es un estimulador muy potente de la secreción ácida de las células parietales gástricas, y el ácido en exceso resultante, al producir una irritación local, puede exacerbar las molestias gastrointestinales. El Ro-20-1724 puede representarse por la fórmula (0.0.14):

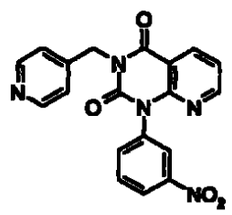



Ro-20-1724
(0 0 14)

Los esfuerzos por minimizar o eliminar los sucesos adversos

anteriormente citados, asociados a veces a los inhibidores de PDE4, han incluido crear inhibidores que no penetran en el sistema nervioso central, y administrar inhibidores de PDE4 por inhalación en vez de por vía oral.

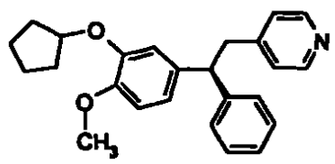
Con respecto a los subtipos de PDE4 A, B, C y D, se ha encontrado que la PDE4C es habitualmente menos sensible a todos los inhibidores, mientras que, con respecto a los subtipos A, B y D, no existe hasta ahora una evidencia clara de especificidad de inhibidor, que se define como una diferencia de 10 veces en los valores de $CI_{50}$. Aunque la mayoría de los inhibidores, especialmente el RS-25.344, son más potentes frente a PDE4D, esto no cuenta para la selectividad. El RS-25.344 puede representarse por la fórmula (0.0.15).



RS-25 344 (0 0 15)

Por otro lado, existe un efecto esteroselectivo sobre la elevación del nivel de AMPc en una goma de tipos celulares, lo que se ha demostrado con los resultados de una investigación de CDP840, mostrado anteriormente como la fórmula (0.0.9), y su enantiómero menos activo CT-1731, que se representa por la

fórmula (0.0.16):



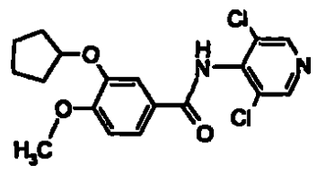
CT-1731 (0 0 16)

Se sabía desde hace tiempo que el rolipram tenía la capacidad de interactuar con un sitio de unión de alta afinidad en las membranas celulares, y se estableció después en la técnica que este sitio de unión de alta afinidad de rolipram ($S_r$), que es distinto del sitio catalítico ($S_c$), existe en una PDE4A recombinante truncada y en una PDE4B recombinante de longitud completa. Más recientemente, se ha identificado $S_r$ en los cuatro subtipos de PDE4. Véase Hughes et al., *Drug Discovery Today* **2(3)** 89-101, 1997. La presencia de $S_r$ parece tener un profundo efecto sobre la capacidad de ciertos inhibidores tales como rolipram y RS-25.344 de inhibir la actividad catalítica de las isozimas PDE4.

El impacto de los residuos sobre la unión del inhibidor es también significativo. Se ha mostrado que una simple sustitución de aminoácido (aspartato por alanina) en la región catalítica de PDE4B es crítica para la inhibición por rolipram, y esto parece ser un efecto de clase, porque los inhibidores relacionados RP-

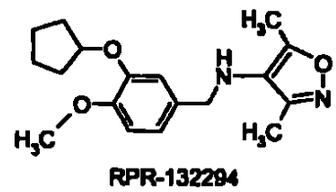
73.401 y Ro-20-1724, pierden también potencia en la enzima mutante. Sin embargo, el papel de la unión de los inhibidores a $S_c$ ó a $S_r$ en términos de elevación del nivel de AMPc e inhibición de las respuestas celulares no se comprende totalmente en la actualidad

El RP-73,401, en estudios de conejillos de indias, se ha encontrado que es activo en (1) la inhibición de la eosinofilia en pulmón inducida por antígeno y de la peroxidasa de eosinófilo (EPO), Banner, K.H. "The effect of selective phosphodiesterase inhibitors in comparison with other anti-asthma drugs on allergen-induced eosinophilia in guinea-pigs airways", *Pulm. Pharmacol.* **8**, 37-42, 1995; (2) la eosinofilia por lavado broncoalveolar (LBA) inducida por antígeno, 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) la eosinofilia de las vías aéreas inducida por antígeno, el factor activante de plaquetas (PAF) y la hiperrespuesta de las vías aéreas inducida por ozono (AHR), Karlsson et al., "Anti-inflammatory effects of the novel phosphodiesterase IV inhibitor RP73401", *Int. Arch. Allergy Immunol.* **107**, 425-426, 1995; y (4) la eosinofilia pleural inducida por IL-5. Se ha abandonado el desarrollo de RP-73.401, piclamilast. El piclamilast puede representarse por la fórmula (0.0.17):



piclamilast (RP-73 401) (0 0 17)

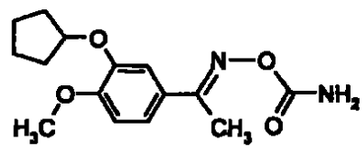
Se representa una serie relacionada de compuestos por RPR-132294 y RPR-132703, que se ha demostrado en estudios en rata que tienen actividad de inhibición de broncoespaSmo inducido por antígeno; Escott et al., "Pharmacological profiling of phosphodiesterase 4 (PDE4) inhibitors and analysis of the therapeutic ratio in rats and dogs", *Br. J. Pharmacol.* **123** (proc. supl.) 40P, 1998; y 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. La estructura del RPR-132294 puede representarse por la fórmula (0.0.18):



RPR-132294

(0 0 18)

Otro compuesto cuyo desarrollo se ha abandonado es el WAY-PDA-641, filaminast, que se ha encontrado en estudios en perro que es activo en la inhibición de la broncoconstricción inducida por seratonina. El filaminast puede representarse por la fórmula (0.0.19):

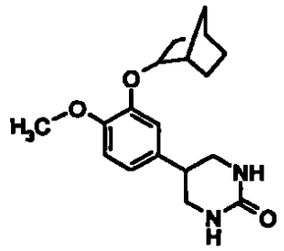



Filaminast (WAY-PDA-641)

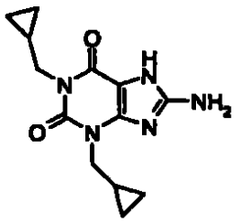
(0 0 19)

Se ha sugerido en la técnica que los inhibidores de PDE4 que tienen una alta afinidad en $S_r$ pueden estar correlacionados con la émesis y con un aumento de la secreción de ácidos gástricos. RS-23.544, RP-73.401 y CP-80.633 desencadenan la émesis y tienen una alta afinidad en $S_r$. CDP840 y SB-207.499 tienen una afinidad comparativamente baja en $S_r$, pero CDP840 tiene una potencia significativamente superior en $S_c$ que SB-207.499. Se ha demostrado que CDP840 proporciona una inhibición significativa de la respuesta de fase tardía en el tratamiento del asma sin ningún suceso adverso de naúsea ni dolor de cabeza. Otro inhibidor de PDE4 que se ha mostrado que tiene sucesos adversos de náusea y vómitos es BRL-61.063, también designado

como cipamfilina, que se describe más adelante. El desarrollo de CDP840 se ha abandonado, mientras que CP-80.633, atizoram, ha avanzado hasta los estudios clínicos. CP-80.633 y BRL-61.063 pueden representarse por las fórmulas (0.0.20) y (0.1.12), respectivamente:

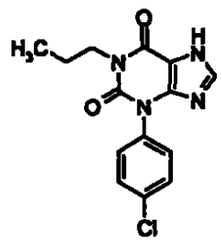



Atizoram (CP-80 633)
(0 0 20)




cipamfilina (BRL-61 063)
(0 1 12)

Otro compuesto que está en desarrollo es LAS-31205, arofilina, que en estudios en conejillos de indias se ha encontrado que es activo en la inhibición de la broncoconstricción inducida por antígeno, Beleta. B. J. "Characterization of LAS31205: a new selective PDE IV inhibitor for bronchial asthma"; *Third. Int. Conf. On Cyclic Nucleotide Phosphodiesterase. From Genes to Therapies*, Glasgow, R.U., 1996, Resumen 73. El LAS-31205, arofilina, puede representarse por la fórmula (0.0.21):



arofilina (LAS-31025)

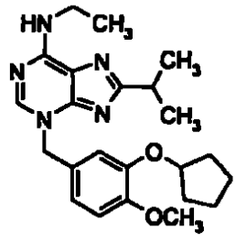
(0 0.21)

Una serie de inhibidores de PDE4 han avanzado 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 aleatorizado de doble ciego controlado por placebo, y se ha encontrado que una dosis oral de 300 mg es eficaz en la reducción de los niveles de TNF y de la proliferación de linfocitos; Landells et al., "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 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

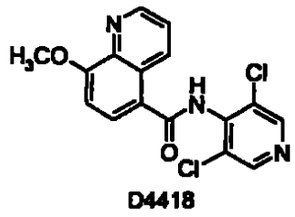
Se ha administrado el compuesto D4418 a voluntarios sanos en un estudio de dosis sencilla en aumento, aleatorizado, controlado por placebo de fase I; Montana et al., "Activity of D4418, a novel phosphodiesterase 4 (PDE4) inhibitor, effects in

cellular and animal models of asthma and early clinical studies", *Am. J. Respir. Crit. Care Med.* **159** A108, 1999. El D4418 es un inhibidor moderadamente potente de PDE4 con una $CI_{50}$ de 200 nM. Tiene una buena absorción oral; una dosis de 200 mg proporciona una $C_{máx}$ en plasma de 1,4 µg/ml. Se ha abandonado el desarrollo de D4418 debido a su potencia moderada, y se ha reemplazado por el candidato de desarrollo preclínico D4396.

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




V-11294A
(0 0 22)

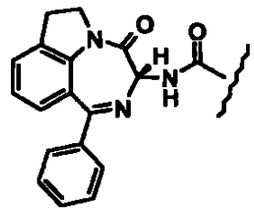



D4418

(0 0 23)

Se ha evaluado otro compuesto, CI-1018, en 54 sujetos y no se ha informado de ningún suceso adverso a dosis de hasta 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-04-06, 1999. Se ha demostrado que CI-1018 tiene una buena biodisponibilidad oral (57% en rata) y una buena potencia oral,

con una $DE_{50}$ de 5 mg/kg en la 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 a CI-1018 como, o asociado como de estructura estrechamente relacionada con, PD-168787, que en estudios en rata ha demostrado tener actividad en la inhibición de eosinofilia inducida por antígeno; 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, EE.UU., MEDI 50, 1997. Las estructuras deducidas para CI-1018 y PD-168787 pertenecen a una clase de diazepinonas cuyo núcleo puede representarse por la fórmula (0.0 24).

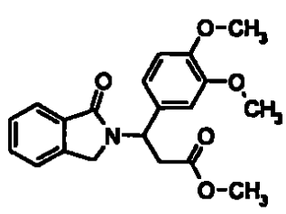


(0 0 24)

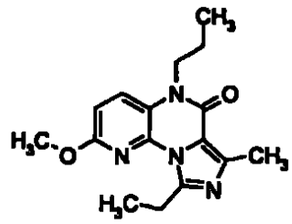
Se han evaluado también los compuestos citados anteriormente en modelos animales que demuestran su actividad de inhibición de PDE4. Por ejemplo, se ha encontrado que V-11294A, en estudios en conejillos de indias, es activo en la inhibición de la broncoconstricción inducida por antígeno; Cavalla et al., "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. Se ha encontrado que D4418, en estudios en conejillos de indias, es activo en la inhibición de la broncoconstricción de fase temprana y tardía inducida por antígeno y en eosinofilia por LBA; Montana et al., ibid. Se ha encontrado que CI-1018, en estudios en ratas, es activo en la inhibición de eosinofilia inducida por antígeno; Burnouf, et al., "Pharmacology of the novel phosphodiesterase Type 4 inhibitor, CI-1018", *215th ACS Nat. Meeting*, MEDI 008, 1998.

Otros compuestos que han avanzado en su desarrollo incluyen CDC-3052, D-22888, YM-58997 y roflumilast, que pueden representarse por las fórmulas (0.0.27), (0.0.28), (0.0.29) y (0.0.30), respectivamente·

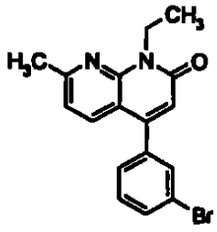


CDC-3052
(0 0 27)

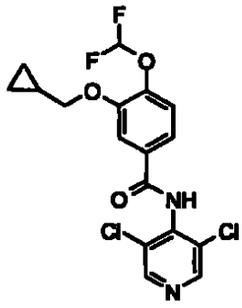


D-22888

(0 0 28)



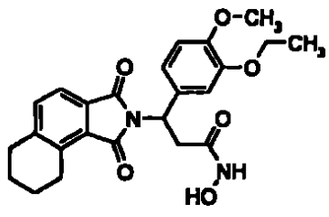
YM-58977
(0.0 29)



Roflumilast

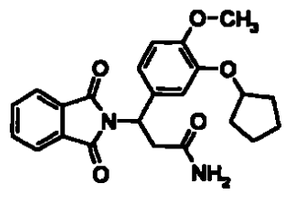
(0 0.30)

Se ha abandonado el desarrollo de CDC-3052, pero se ha tenido éxito con inhibidores muy potentes de PDE4, tales como el compuesto representado por la fórmula (0.0.31) y con el compuesto antiinflamatorio CDC-801, representado por la fórmula (0.0.32), respectivamente:



(0 0.31)

CDC-801

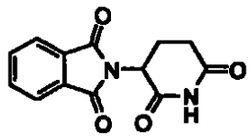


(0 0.32)

Se ha informado de que el compuesto de fórmula (0.0.32) tiene

valores de $CI_{50}$ de 42 pM y 130 nM como inhibidor de PDE4 y de la producción de TNF, respectivamente, Muller et al., "N-Phtaloyl beta-aryl-beta-amino derivatives· Potent TNF-alpha and PDE4 inhibitors", *217th American Chemical* Society, Annheim, Alemania, MEDI 200, 1999, y Muller et al., "Thalidomide analogs and PDE4 inhibition", *Bioorg. Med. Chem Letts* 8, 2669-2674, 1998.

El CDC-801 es uno de una serie de compuestos basados en talidomida y se ha desarrollado principalmente para mejorar la actividad inhibidora de TNF-α de la talidomida para el tratamiento de enfermedades autoinmunes. La talidomida puede representarse por la fórmula (0.0.33)



talidomida

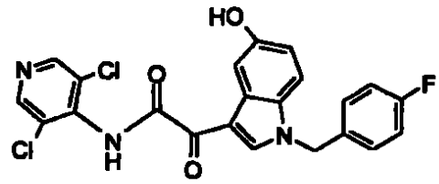
(0.0.33)

Se ha estudiado también CDC-810 para el tratamiento de enfermedad de Crohn, una enfermedad inflamatoria granulomatosa crónica de etiología desconocida que implica habitualmente el íleon terminal, con cicatrización y espesamiento de la pared intestinal, que conducen frecuentemente a obstrucción intestinal y a formación de fístula 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 frente a la PDE4; Takayama et al., "Synthetic studies on selective Type IV phosphodiesterase (PDE IV) inhibitors", *214th American Chemical Society*, Las Vegas, EE.UU., MEDI 245, 1997. YM-58997 tiene una estructura de 1,8-naftiridin-2-ona, como YM-976.

Se ha estudiado el roflumilast para el tratamiento tanto de EPOC como de asma, y tiene un valor de $CI_{50}$ de 3,5 nM en modelos de conejillo de indias estándares in vitro de asma. Se ha descrito también el uso de roflumilast y un tensioactivo para el tratamiento de síndrome de distrés respiratorio en adultos (SDRA).

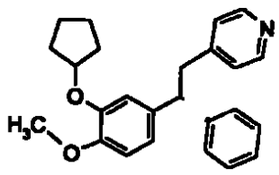
Se ha mostrado que AWD-12.281, que se designa actualmente como loteprednol, es activo en un modelo de rata de rinitis alérgica, como se describe más adelante en una sección que trata de la rinitis alérgica y del uso de inhibidores de PDE4 para tratarla. El AWD-12.281 puede representarse por la fórmula (0.3.34):



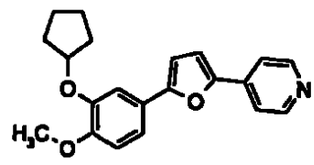

Loteprednol (AWD-12 281)

(0 0 34)

Los compuestos de estructura relacionada con CDP840, mostrados anteriormente como de fórmula (0.0.9), incluyen L-826.141, que se ha informado que tiene actividad en un modelo de rata de bronquitis, 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. Otro de dichos compuestos tiene una estructura relacionada con las informadas por Perrier et al., "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)

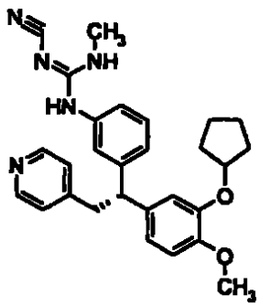


CDP840
(009)

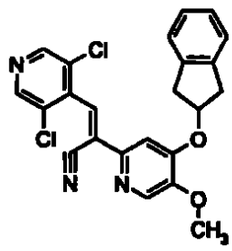


(0035)

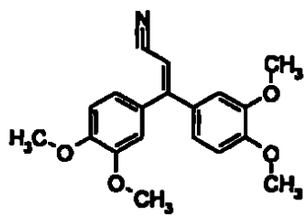
Otros compuestos que se encontró que eran muy potentes inhibidores de PDE4 son aquellos representados por las fórmulas (0.0.36), (0.0.37) y (0.0.38).



(0 0.36)

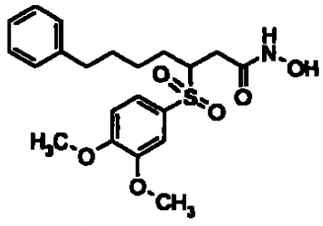


(0 0 37)

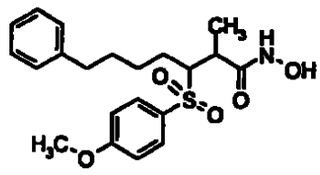


(0 0.38)

Se han creado compuestos que combinan la actividad inhibitoria de PDE4 y metaloproteinasas de matriz (MMP) en una sola molécula; 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. Se representan dos ejemplos de dichos compuestos por las fórmulas (0.0.39) y (0.0.40):



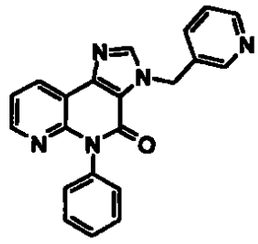
(0.0 39)



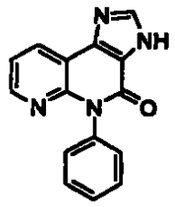
(0 0.40)

Los valores respectivos de $CI_{50}$ para los compuestos de fórmulas (0.1.36) y (0.1.37) utilizando un ensayo de PDE4 de macrófago de conejillo de indias fueron 1 nM y 30 nM.

Los compuestos identificados como KF19514 y KF17625 han mostrado en estudios en conejillos de indias tener actividad en la inhibición de lo siguiente: broncoconstricción inducida por histamina e inducida por antígeno; eosinofilia pulmonar inducida por PAF y eosinofilia por LBA inducida por antígeno; AHR inducida por acetilcolina (ACh); eosinofilia y neutrofilia por LBA inducidas por PAF; broncoespasmo inducido por antígeno; y broncoconstricción anafiláctica; 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]naphtyridin-4(5H)-ones", *J. Med. Chem.* **35** 4866-4874, 1992; Matsuura et al., "Substituted 1,8-naphtyridin-2(1H)-ones as selective phosphodiesterase IV inhibitors", *Biol. Pharm. Bull.* **17**(4), 498-503, 1994; y Manabe et al., "Pharmacological properties of a new bronchodilator, KF 17625", *Jpn. J. Pharmacol.* **58** (Supl. 1), 238P, 1992. KF19514 y KF17625 pueden representarse por las fórmulas (0.0.41) y (0.0.42):

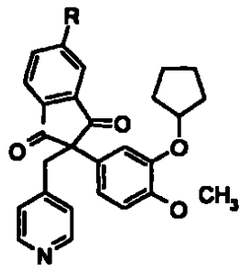


KF19514
(0 0.41)



KF17625
(0 0 42)

La potencia y falta de émesis informadas de una serie de indandionas sugieren que la hipótesis que ha relacionado los efectos secundarios, tales como émesis, con la relación de afinidad por la enzima PDE4 respecto del sitio de unión de rolipram de alta afinidad (HARBS) es errónea. Dichas indandionas pueden representarse por las fórmulas (0 0.43) y (0.0.44)·



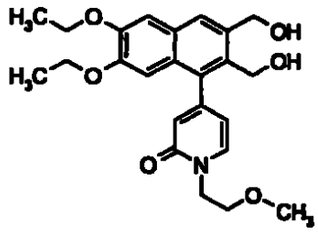
R = benciloxi (0 0.43)

R = [1,4']-piperidinil-1'-carboniloxi (0 0.44)

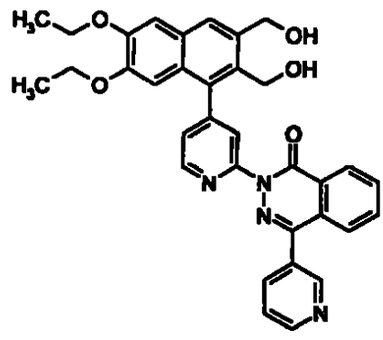
Los inhibidores de PDE4 que se han creado hasta la fecha entran dentro de un número significativo de diferentes clases en términos de sus estructuras químicas. Dichas clases han sido tan

120
00174

distintas como fenantridinas y naftiridinas. Una clase de inhibidores de PDE4 son los lignanos, tales com T-440, que se ha demostrado que tiene actividad en la inhibición de lo siguiente: broncoconstricción de fase temprana inducida por antígeno, histamina, LTD4, U-46619, Ach, neurocinina A y endotelina-1, broncoconstricción de fase temprana y fase tardía y eosinofilia LBA inducidas por alergeno; AHR y daño epitelial de las vías aéreas inducidos por ozono. La optimización de la potencia inhibidora de PDE4 de dichos compuestos ha conducido al descubrimiento de T-2585, uno de los inhibidores de PDE4 más potentes descritos hasta la fecha, con un valor de $CI_{50}$ de 0,13 nM frente a PDE4 de pulmón de conejillo de indias. T-440 y T-2585 pueden representarse por las fórmulas (0.0.45) y (0.0.46):



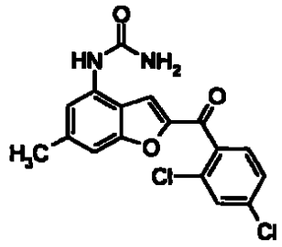
T-440
(0.0.45)



T-2585
(0.0.46)

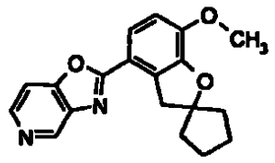
Otra clase de inhibidores de PDE4 está constituida por benzofuranos y benzotiofenos. Particularmente se han utilizado

anillos furano y cromano como sustitutos del ciclopentiléter del farmacóforo de rolipram. Un ejemplo de dicho compuesto es uno de estructura aparentemente relacionada con BAY 19-8004, y que puede representarse por la fórmula (0.0.47):



(0.0.47)

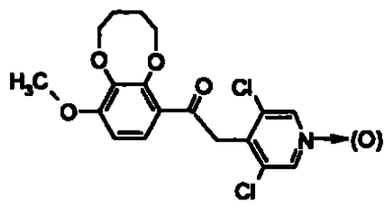
Se ha informado de que otro compuesto de tipo benzofurano tiene un valor de $CI_{50}$ de 2,5 nM, y puede representarse por la fórmula (0.0.48):



(0.0.48)

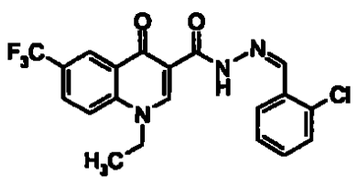
Un compuesto con una estructura relacionada, que sin embargo no es un benzofurano, se caracteriza por un anillo dioxicina condensado y se ha informado de que produce una inhibición casi completa de la PDE4 traqueal canina a 100 nM.

Este compuesto puede representarse por la fórmula (0.0.49):

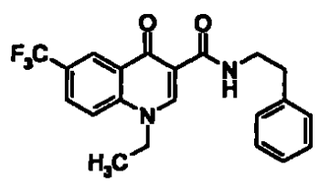


(0049)

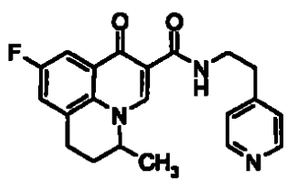
Las quinolinas y quinolonas son otra clase de estructuras inhibidoras de PDE4, y sirven como sustitutos del resto catecol del rolipram. Este compuesto, y dos compuestos de estructura similar, pueden representarse por las fórmulas (0.0.50), (0.0.51) y (0.0.52).



(0050)

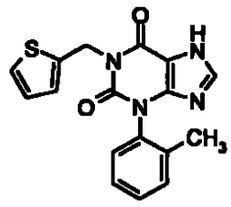


(0051)



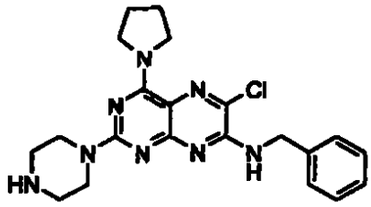
(0052)

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 la que pertenece la teofilina, Montana et al., "PDE4 inhibitors, new xanthine analogues", *Bioorg. Med. Chem. Letts.* **8**, 2925-2930, 1998. El compuesto de xantina puede representarse por la fórmula (0.0.54):



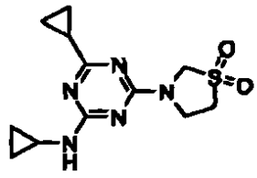
(0054)

Se ha demostrado que un potente inhibidor de PDE4 que pertenece a la clase de compuestos de pteridina tiene un valor de $CI_{50}$ de 16 nM frente a PDE4 derivada de células tumorales, y que inhibe el crecimiento de células tumorales a concentraciones micromolares, 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 tumour cell growth", *J. Med. Chem.* **41**(24), 4733-4743, 1998. El inhibidor pteridina de PDE4 puede representarse por la fórmula (0 0.55):

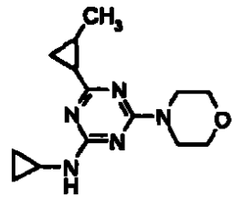


(0 0 55)

Las triazinas representan una clase más de compuestos químicos a la que pertenecen los inhibidores de PDE4 que se han descrito en la técnica hasta el momento. Se han descrito dos de dichas triazinas que presentan actividad broncodilatadora y son potentes agentes en un modelo de tráquea de conejillo de indias. Estos compuestos, que pueden representarse por las fórmulas (0.0.56) y (0.0.57) siguientes, son también inhibidores de PDE4 moderadamente potentes con valores de $CI_{50}$ de 150 y 140 nM, respectivamente:



(0 0 56)

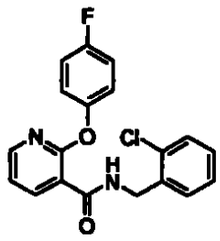


(0 0 57)

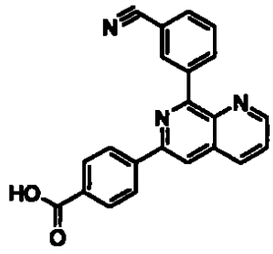
Una triazina de estructura que se supone estrechamente

relacionada con 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 de ratón de choque séptico, Danhaive et al., "UCB29936, a selective phosphodiesterase Type IV inhibitor: therapeutic potential in endotoxic shock", *Am. J. Respir. Crit. Care Med.* **159** A611, 1999.

Se han hecho esfuerzos también en la técnica por mejorar la selectividad de los inhibidores de PDE4 respecto de los subtipos A a D descritos anteriormente. Existen actualmente cuatro isoformas conocidas (subtipos) de isozima PDE4, que comprenden siete variantes de ayuste, también descritas anteriormente El ARNm de la isoforma de PDE4D se expresa en células inflamatorias tales como neutrófilos y eosinófilos, y se ha sugerido en la técnica que los inhibidores selectivos de D de PDE4 proporcionarán una buena eficacia clínica con efectos secundarios reducidos. Se ha descrito un derivado de nicotinamida que presenta selectividad por la inhibición de la isoforma PDE4D; documento WO 98/45268; así como un derivado naftiridina del que se ha informado que es un inhibidor selectivo de PDE4D; documento WO 98/18796. Estos compuestos pueden representarse por las fórmulas (0 0.58) y (0.0.59), respectivamente:

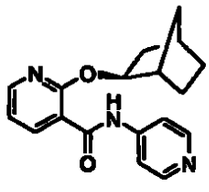


(0 0 58)

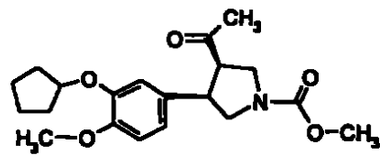


(0 0 59)

Se ha descrito otro compuesto de nicotinamida en la técnica que puede ser útil en el tratamiento de enfermedades del SNC, tales como esclerosis múltiple; GB-2327675; y se ha descrito un derivado de rolipram en la técnica que es un inhibidor de PDE4 que se une con igual afinidad tanto a los sitios catalítico como HARB en PDE4B2B humana; 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. El derivado de nicotinamida y el derivado de rolipram pueden representarse por las fórmulas (0.0.60) y (0.0.61), respectivamente:



(0.0 60)



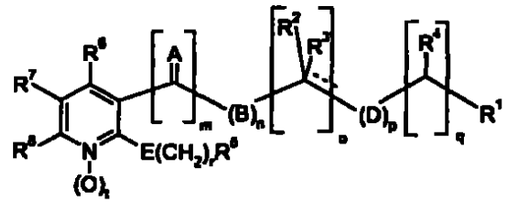
(0 0 61)

Puede encontrarse información de fondo adicional respecto de isozimas PDE4 selectivas 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 potential of PDE4 inhibitors", *Exp. Opin. Invest. Drugs* 8(9), 1301-1325, 1999 (Ashley Publications Ltd.).

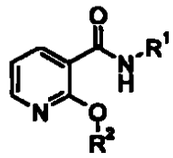
## 3.0 DESCRIPCION DEL ESTADO DE LA TECNICA

El documento WO 98/45268 (Marfat et al.), publicado el 15 de octubre de 1998, describe derivados de nicotinamida con actividad como inhibidores selectivos de la isozima PDE4D. Estos inhibidores selectivos se representan por la fórmula (0.1.1)



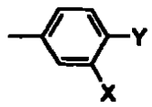
(011)

El documento US 4.861.891 (Saccomano et al.), expedido el 29 de agosto de 1989, describe compuestos de nicotinamida cuya función como inhibidores de fosfodiesterasa de AMPc independientes de calcio les hace útiles como antidepresivos, de fórmula (0.1.2)·



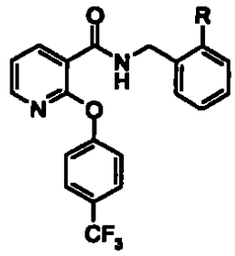
(012)

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 mono-sustituido con metilo, metoxi, cloro ó fluoro. El sustituyente $R^2$ es biciclo[2.2.1]hept-2-ilo ó



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

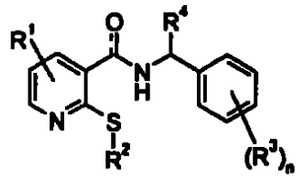
El documento US 4.692.185 (Michaely et al.) describe herbicidas tales como aquellos de fórmula (0.1.3):



(0 1.3)

en la que R es alquilo ($C_1$-$C_4$), haloalquilo ($C_1$-$C_4$) ó halo.

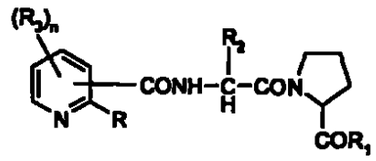
El documento EP 550900 (Jeschke et al.) describe herbicidas y nematicidas de plantas de fórmula (0.1 4):



(0 1 4)

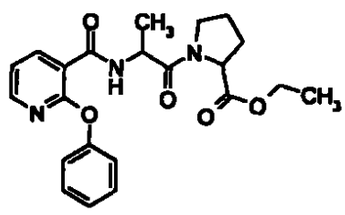
en la que n es 0-3; $R^1$ se selecciona de numerosos grupos, pero es habitualmente H, 6-$CH_3$ ó 5-Cl, $R^2$ es alquilo, alquenilo, alquinilo, cicloalquilo, arilo o aralquilo; $R^1$ y $R^2$ son halo, CN, $NO_2$, alquilo, haloalquilo, alcoxi, haloalcoxi, alquiltio, haloalquiltio, alquilsulfonilo, haloalquilsulfonilo,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

El documento EP 500989 (Mollner et al.) describe inhibidores de ACE de fórmula (0.1.5):



(015)

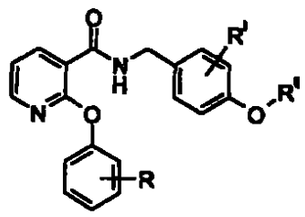
en la que n es 0-3; R es OH, SH, COOH, $NH_2$, halo, $OR_4$, $SR_4$, $COOR_4$, $NHR_4$ ó $N(R_4)_2$, siendo $R_4$ alquilo inferior, arilo opcionalmente sustituido o acilo; $R_1$ es OH, alcoxi inferior, arilalcoxi inferior opcionalmente sustituido, ariloxi o amino disustituido, $R_2$ es alquilo inferior o aminoalquilo inferior, y $R_1$ y $R_2$ son halo, $NO_2$, alquilo inferior, haloalquilo inferior, arilalquilo inferior o arilo. Las realizaciones específicas descritas incluyen compuestos tales como el de fórmula (0 1.16):



(016)

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

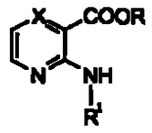
171
00135



(0 1 7)

en la que R es 1 ó 2 sustituyentes seleccionados de alquilo inferior, trihalometilo, alcoxi y halo; R' es H ó alquilo; y R'' es hidrógeno ó alquilo.

El documento JP 07304775 (Otsuka et al.) 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):



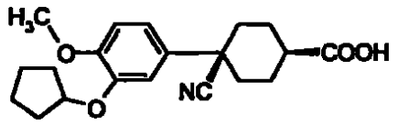
(0 1.8)

en la que 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 anteriormente identificadas, se observará que sólo la descripción del documento WO 98/45268

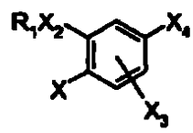
(Marfat et al.) se refiere a la inhibición de isozimas PDE4. El estado de la técnica contiene también información respecto a compuestos completamente distintos en su estructura química a aquellos de fórmula (1.0.0) de la presente invención, pero que, por otro lado, poseen una actividad biológica similar a la de los compuestos de fórmula (1.0.0). Las patentes y solicitudes de patente publicadas representativas que describen dicha información se ilustrarán más adelante.

Los documentos US 5.552.438, US 5.602.157 y US 5.614.540 (todos de Christensen), que comparten todos la misma fecha de prioridad, 2 de abril de 1992, se refieren a un agente terapéutico identificado como ARIFLO(R), que es un compuesto de fórmula (0.1.9) y se nombra como se indica a continuación:



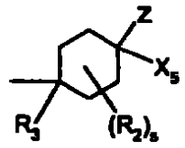

ARIFLO®
ácido cis-[4-ciano-4-(3-ciclopentiloxi-4-metoxifenil)ciclohexano-1-carboxílico (0.1.9)

El compuesto de fórmula (0.1.9) se encuentra dentro del alcance del documento US 5.552.438, que describe un género de compuestos de fórmula (0.1.10):



(0 1 10)

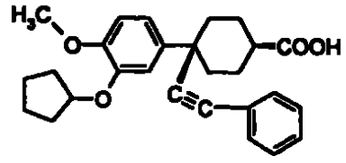
en la que $R_1$= -($CR_4R_5$), siendo r=0 y $R_6$= cicloalquilo $C_{3-6}$; X= $YR_2$, siendo Y= O y $R_2$= $-CH_3$; $X_2$= O; $X_3$= H; y $X_4$= un resto de fórmula parcial (0.1.10.1)



(0 1 10 1)

en la que $X_5$= H, s= 0, $R_1$ y $R_2$= CN, y E= $C(O)OR_{14}$, siendo $R_{14}$= H. Las descripciones de los documentos US 5.602.157 y US 5.614.540 se diferencian de la del documento US 5.552.438 y entre sí en la definición del grupo $R_3$, que en el caso del compuesto ARIFLO(R) es CN. Se describe que una forma de sal preferida del compuesto ARIFLO(R) es la sal de tris(hidroximetil)amoniometano.

El documento US 5.863.926 (Christensen et al.) describe análogos del compuesto ARIFLO(R), por ejemplo, el de fórmula (0.1.11):

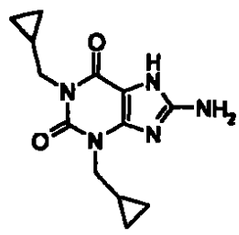



(0 1 11)

El documento WO 99/18793 (Webb et al.) describe un procedimiento de preparación de ARIFLO(R) y compuestos relacionados. El documento WO 95/00139 (Barnette et al.) reivindica un compuesto que tiene una relación de $CI_{50}$ de aproximadamente 0,1 o superior respecto de la $CI_{50}$ de la forma catalítica de PDE IV que se une a rolipram con una alta afinidad, dividida entre la $CI_{50}$ para la forma que se une a rolipram con baja afinidad, pero en una reivindicación dependiente limita el alcance de ésta a un compuesto que no se conocía que fuera un inhibidor de PDE4 antes del 21 de junio de 1993.

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

45

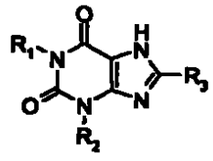


cipamfilina

(0 1 12)

10

El documento WO 99/20280 (Griswold et al.) describe un procedimiento de tratamiento de prurito mediante la 15 administración de una cantidad eficaz de un inhibidor de PDE4, por ejemplo, un compuesto de fórmula (0.1.13):



20

(0 1 13)

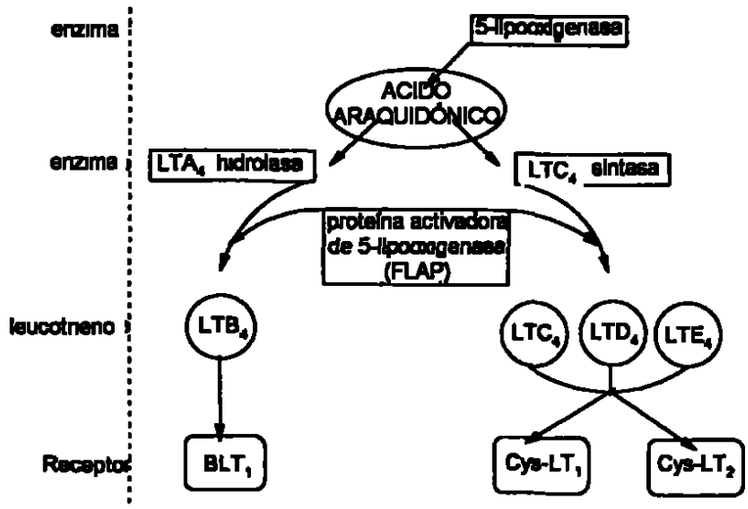
El documento US 5.922.557 (Pon) describe una línea celular CHO-K1 que expresa establemente altos niveles de enzima PDE4A específica de AMPc de baja Km de longitud completa, que se ha 25 utilizado a su vez para examinar potentes inhibidores

enzimáticos de PDE4 y para comparar el orden de clasificación de sus potencias en la elevación del nivel de AMPc en una preparación de célula entera con su capacidad de inhibir la actividad de fosfodiesterasa en una preparación de célula rota. 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. Se describe entonces un ensayo mejorado de enzima soluble con célula entera, que se dice que refleja el comportamiento de los inhibidores que actúan in vivo. Se describe también que existen al menos cuatro isoformas o subtipos de PDE4 distintos, y que cada subtipo se ha mostrado que puede dar lugar una serie de variantes de ayuste, que pueden exhibir ellas mismas diferentes localizaciones celulares y afinidades por los inhibidores.

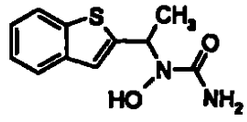
Con respecto a las descripciones de las patentes y solicitudes de patente publicadas identificadas anteriormente, se observará que los compuestos implicados poseen la misma actividad biológica que los compuestos de fórmula (1.0.0). Sin embargo, al mismo tiempo, el experto observará que las estructuras químicas de los citados compuestos descritos en la técnica anterior no son sólo distintos entre sí, sino también diferentes a las de los nuevos compuestos de la presente invención. El estado de la técnica contiene aún más información respecto de compuestos que son de estructura química distinta de

aquellos de fórmula (1.0.0), y que, además, no poseen actividad inhibitoria de PDE4 similar a la de los compuestos de fórmula (1.0.0). Sin embargo, dichos compuestos descritos en la técnica anterior tienen a menudo una utilidad terapéutica similar a la poseída por 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 de la denominada ruta del leucotrieno. Este es especialmente el caso con respecto a los leucotrienos $LTB_4$ y $LTD_4$. Consiguientemente, las patentes y solicitudes de patente publicadas representativas que describen información adicional de este tipo se describen a continuación.

El ácido araquidónico se metaboliza por la ciclooxigenasa-1 y la 5-lipooxigenasa. La ruta de la 5-lipooxigenasa conduce a la producción de leucotrienos (LT), que contribuyen a la respuesta inflamatoria mediante su efecto sobre la agregación, desgranulación y quimotaxia de neutrófilos, la permeabilidad vascular; la contractilidad del músculo liso; y sobre los linfocitos. Los cisteinil-leucotrienos, $LTC_4$, $LTD_4$ y $LTE_4$, desempeñan un importante papel en la patogénesis del asma. Los componentes de la ruta del leucotrieno que proporcionan dianas para intervención terapéutica se ilustran en el siguiente diagrama.



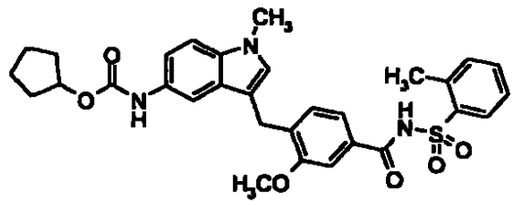

Consiguientemente, los agentes que son capaces de intervenir en cualquiera de las etapas de la ruta de la 5-lipooxigenasa proporcionan una oportunidad de tratamiento terapéutico. Un ejemplo de uno de dichos agentes es el inhibidor de 5-lipooxigenasa, zileutón, un agente terapéutico identificado como ZYFLO(R), que puede representarse por la fórmula (0.1.14)




ZYFLO®

zileutón (0 1 14)

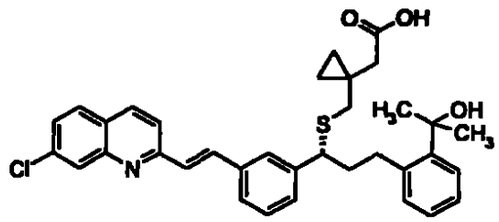
Otro de dichos agentes es el antagonista de receptor de $LTD_4$, zafirlukast, un agente terapéutico identificado como ACCOLATE(R), que puede representarse por la fórmula (0.1.15):



ACCOLATE®

Zafirlukast (0.1.15)

Otro antagonista de receptor de $LTD_4$ es el montelukast, un agente terapéutico identificado como SINGULAIR(R), que puede representarse por la fórmula (0.1.16):

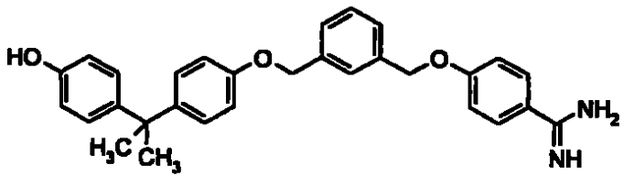


SINGULAIR®

Montelukast (0.1.16)

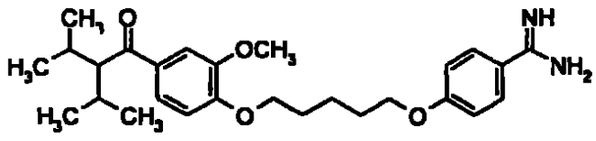
Otro tipo de las dianas terapéuticas anteriormente citadas es el receptor de $LTB_4$, y un ejemplo de antagonista para el citado receptor es BIIL-260, un agente terapéutico que puede

representarse por la fórmula (0.1.17):



BIIL-260 (0 1 17)

Otro ejemplo de un agente terapéutico que es un antagonista de receptor de $LTB_4$ es el CGS-25019c, que puede representarse por la fórmula (0.1.18):



CGS-25019c (0 1 18)

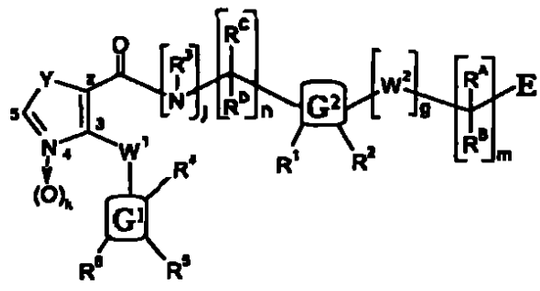
Nada en el estado de la técnica anteriormente descrito describe o sugeriría al experto los nuevos compuestos de la presente invención o su actividad inhibidora de PDE4 y la significativa mejora resultante de la utilidad terapéutica y del índice terapéutico en el tratamiento de enfermedades y afecciones inflamatorias, respiratorias y alérgicas.

## 4.0 SUMARIO DE LA INVENCION

La presente invención se refiere a nuevos compuestos que tienen actividad biológica como inhibidores de la

fosfodiesterasa denominada isoenzima "de tipo IV" ("isozima PDE4"). Las realizaciones de los nuevos compuestos de la presente invención son activAs como inhibidores no selectivos de la isozima PDE4. Otras realizaciones de los citados nuevos compuestos tienen especificidad de sustrato de isozima PDE4, especialmente por el subtipo D. Los citados nuevos compuestos con actividad inhibitoria de PDE4 no selectiva o selectiva de D son generalmente útiles en el tratamiento terapeutico de diversas enfermedades y afecciones inflamatorias, alérgicas y respiratorias, y proporcionan en particular una mejora significativa en el tratamiento terapéutico de enfermedades respiratorias obstructivas, especialmente asma y enfermedad pulmonar obstructiva crónica (EPOC).

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



(100)

en la 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, 2 ó 3;

-n es 1 ó 2,

$-W^1$ es -O-; ó $-S(=O)_t-$, siendo t 0, 1 ó 2; ó $-N(R^3)-$, teniendo $R^3$ el mismo significado que se define a continuación;

$-W^2$ es -O-, $-S(=O)_t$, siendo t 0, 1 ó 2, $-N(R^3)-$, teniendo $R^3$ el mismo significado que se define a continuación; ó $-CR^{29}R^{39}-$ ,en la que

$-R^{29}$ 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 piridinilo; estando cada uno de los citados restos alquilo, cicloalquilo, fenilo, bencilo y piridilo sustituidos independientemente cada uno con 0 a 3 sustituyentes $R^{10}$, teniendo $R^{10}$ el mismo significado que se define a continuación;

-Y es $-S(=O)_t-$, siendo t 0, 1 ó 2; -O-; $-[N->(O)_k]-$ ó $-N(R^3)-$, siendo k 0 ó 1, y teniendo $R^3$ el mismo significado que se define a continuación; ó $-CH(R^1_a)-$, teniendo $R^1_a$ el mismo significado que se define a continuación;

en la que

$-R^1_a$ es un miembro seleccionado del grupo constituido por -H; -F; -Cl; -CN; $-NO_2$; -alquilo ($C_1$-$C_4$); -alquinilo ($C_2$-$C_4$); alquil ($C_1$-$C_3$) fluorado, alcoxi ($C_1$-$C_3$) fluorado; $-OR^{16}$; y $-C(=O)NR^{22}_aR^{22}_b$;

en la que

$-R^{22}_a$ 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; ó 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; estando los citados restos cicloalquilo, fenilo y bencilo sustituidos cada uno independientemente con 0 a 3 sustituyentes $R^{10}$;

siendo

$-R^{10}$ un miembro seleccionado del grupo constituido por fenilo; piridilo; -F; -Cl; $-CF_3$; oxo (=O); $-OR^{16}$; $-NO_2$; -CN; $-C(=O)R^{16}$; $-O-C(=O)R^{16}$; $-C(=O)NR^{16}R^{17}$; $-O-C(=O)NR^{16}R^{17}$; $-NR^{16}R^{17}$;

$-NR^{16}C(=O)R^{17}$; $-NR^{16}C(=O)OR^{17}$; $-NR^{16}S(=O)_2R^{17}$; y $-S(=O)_2NR^{16}R^{17}$; estando el citado fenilo o piridilo sustituido con 0 a 3 $R^{11}$;

siendo

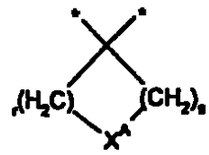
$-R^{11}$ -F; -Cl; $-CF_3$; -CN; $-NO_2$; -OH; -alcoxi ($C_1$-$C_3$); -alquilo ($C_1$-$C_3$); ó $-NR^{16}R^{17}$,

y

$-R^{16}$ y $R^{17}$ son cada uno 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; estando sustituidos los citados alquilo, alquenilo, cicloalquilo, fenilo, bencilo, o piridilo con 0 a 3 sustituyentes seleccionados del grupo constituido por -F, -Cl, -$CF_3$, -CN y -alquilo ($C_1$-$C_3$);

ó

$-R^A$ y $R^B$ se toman conjuntamente, pero sólo en el caso en que m sea 1, para formar un resto espiro de fórmula (1.2.0):



(120)

en la que

-r y s son independientemente 0 a 4, con la condición de que la suma de r + s sea al menos 1, pero no superior a 5;

y

-$X^A$ se selecciona de $-CH_2-$, $-CH(R^{11})-$ ó $C(R^{11})_2-$, seleccionándose cada $R^{11}$ independientemente del otro, y teniendo cada uno el mismo significado que se definió anteriormente; $-NR^{15}-$, teniendo $R^{15}$ el mismo significado que se define a continuación, -O-, y $-S(=O)_t-$, siendo t 0, 1 ó 2;

y

el citado resto espiro de fórmula parcial (1.2.0) está sustituido en uno o más de los átomos de carbono de éste, distintos del que define $X^A$, con 0 a 3 sustituyentes $R^{14}$, teniendo $R^{14}$ el mismo significado que se define a continuación, en un átomo de nitrógeno de éste con 0 ó 1 sustituyentes $R^{15}$;

teniendo $R^{15}$ el mismo significado que se define a continuación; y en un átomo de azufre de éste con 0 ó 2 átomos de oxígeno;

$-R^C$ y $R^D$ tienen el mismo significado que se definió anteriormente para $R^A$ y $R^B$, excepto que uno de ellos debe ser -H, y se seleccionan independientemente entre sí y de $R^A$ y $R^B$;

$-R^1$ y $R^2$ pueden aparecer individual o conjuntamente sobre cualquier anillo o anillos que comprenda un significado del resto $G^2$ como se define a continuación, 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 $-C(=O)NR^{22}{}_aR^{22}{}_b$, teniendo $R^{16}$, $R^{22}{}_a$ y $R^{22}{}_b$ los mismos significados que se definieron anteriormente;

$-R^3$ es -H; -alquilo ($C_1$-$C_3$); fenilo, bencilo ó $-OR^{16}$; teniendo $R^{16}$ el mismo significado que se definió anteriormente;

$-R^4$, $-R^5$ y $-R^6$ pueden aparecer individual o conjuntamente en cualquier anillo o anillos que comprenda un significado del resto $G^1$ como se define a continuación; 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 $-CH_2C(=NR^{22}{}_a)NR^{16}R^{17}$;

en las que

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

-(b) -alquilo ($C_1$-$C_4$); y -alcoxi ($C_1$-$C_4$) en el caso en que uno o más de $R^4$, $R^5$ ó $R^6$ tenga el significado de $-OR^{16}$ en (a) anterior, y $R^{16}$ se defina como -alquilo ($C_1$-$C_6$); estando el citado alquilo y alcoxi sustituido independientemente cada uno con 0 a 3 sustituyentes -F ó -Cl; ó 0 ó 1 sustituyentes alcoxi ($C_1$-$C_2$)carbonilo-; alquil ($C_1$-$C_2$)carbonilo-; ó 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; imidazolinilo, 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: quinazolilinilo; quinoxalinilo y purinilo, estando cada uno de los citados restos arilo y heterociclilo independientemente sustituidos con 0 a 2 sustituyentes $R^{14}$ siendo

$-R^{14}$ un miembro seleccionado del grupo constituido por -alquilo ($C_1$-$C_4$), -cicloalquilo ($C_3$-$C_7$), fenilo; bencilo; piridilo y quinolinilo; estando sustituidos los citados alquilo, cicloalquilo, fenilo, bencilo, piridilo o quinolinilo con 0, 1 ó 2 sustituyentes -F, -Cl, $-CH_3$, $-OR^{16}$, $-NO_2$, -CN ó $-NR^{16}R^{17}$; estando constituido el citado grupo $R^{14}$ adicionalmente por -F; -Cl, $-CF_3$; oxo (=O); $-OR^{16}$; $-NO_2$, -CN; $-C(=O)OR^{16}$; $-O-C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$; $-O-C(=O)NR^{16}R^{17}$; $-NR^{16}R^{17}$; $-NR^{16}C(=O)R^{17}$; $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$; ó $-S(=O)_2NR^{16}R^{17}$; teniendo $R^{16}$ y $R^{17}$ los mismos significados que se definieron anteriormente; y siendo además

199
80203

$-R^{15}$ un miembro seleccionado independientemente del grupo constituido por -H, $-C(=O)R^{16}$; $-OR^{16}$; -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 $(C_3-C_7)$, siendo u 0, 1 ó 2; fenilo; bencilo; piridilo; y quinolinilo; estando los citados alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, bencilo, piridilo o quinolinilo sustituidos con 0 a 3 sustituyentes $R^{12}$, teniendo $R^{16}$ y $R^{17}$ los mismos significados que se definieron anteriormente; y siendo

$-R^{12}$ un miembro seleccionado independientemente del grupo constituido por -F; -Cl, $-CO_2R^{18}$, $-OR^{16}$; -CN; $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$; $-NR^{18}C(=O)OR^{19}$, $-NR^{18}S(=O)_pR^{19}$, $-S(=O)_pNR^{18}R^{19}$, siendo p 1 ó 2; -alquilo $(C_1-C_4)$, y -alcoxi $(C_1-C_4)$ en el caso en que $R^{12}$ tenga el significado de $-OR^{16}$ anterior y $R^{16}$ se defina como alquilo $(C_1-C_4)$; estando el citado alquilo y alcoxi sustituidos independientemente 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; teniendo $R^{16}$ el mismo significado que se definió anteriormente; y en las que

$-R^{18}$ y $R^{19}$ se seleccionan independientemente del grupo constituido por -H; -alquilo $(C_1-C_4)$; y fenilo; estando el

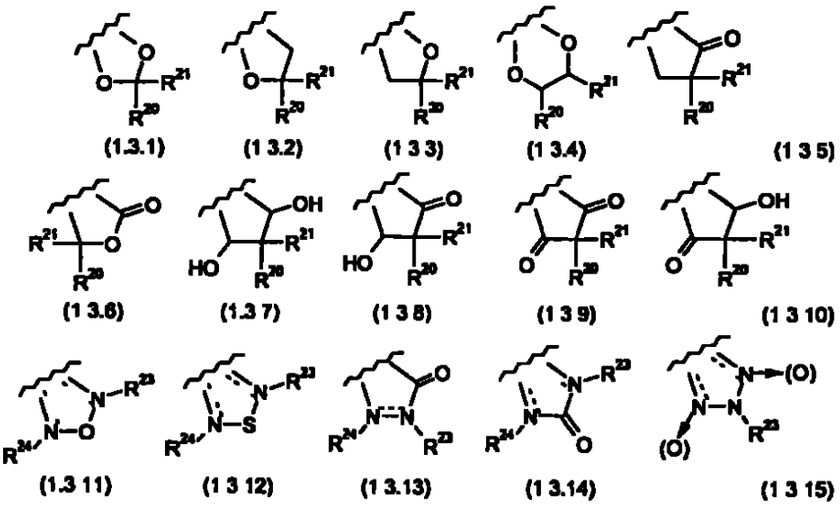
200
CB204



citado alquilo o fenilo sustituido con 0-3 de -F; ó -Cl,

o en el caso en que $G^1$ sea 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)




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 $-OCF_3$;

$-R^{23}$ 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 de trazos ---- representa un doble enlace;

$-G^1$ es un resto que comprende un sistema carbocíclico saturado o insaturado que es monocíclico de 3 a 7 miembros, o policíclico condensado de 7 a 12 miembros; con la condición de que $G^1$ no es un resto biarilo discontinuo o limitado como se define en $G^2$ a continuación; y en el que opcionalmente un carbono del citado sistema carbocíclico puede estar reemplazado por un heteroátomo seleccionado de N, O y S; pudiendo estar reemplazado opcionalmente un segundo carbono de éste, y además opcionalmente un tercer carbono de éste, por un N; estando

el citado resto que se define como $G^1$ sustituido en cualquier anillo o anillos de éste con $R^4$, $R^5$ y $R^6$, que tienen el mismo significado que se definió anteriormente;

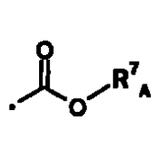
$-G^2$ es un sistema carbocíclico saturado o insaturado que es monocíciclo de 3 a 7 miembros; o que es policíclico condensado de 7 a 12 miembros; o que es un resto biarilo discontinuo o limitado de 7 a 18 miembros; pudiendo estar reemplazado opcionalmente, para cada uno de los sistemas carbocíclicos citados, un átomo de carbono del citado sistema carbocíclico por un heteroátomo seleccionado de N, O y S; pudiendo estar opcionalmente reemplazado un segundo átomo de

carbono de éste, y además opcionalmente un tercer átomo de carbono de éste, por un N; estando

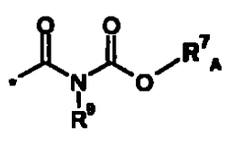
el citado resto definido como $G^2$ sustituido en cualquier anillo o anillos de éste con $R^1$ y $R^2$, que tienen los mismos significados que se definieron anteriormente;

-E es un miembro seleccionado independientemente del grupo constituido por los siguientes

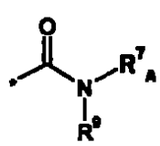
-(a) el grupo constituido por las fórmulas parciales (1.1.1) a (1.1.15):



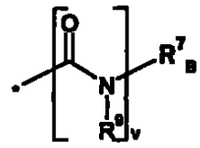
(1 1 1)



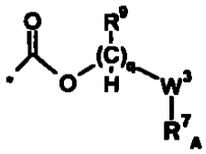
(1 1 2)



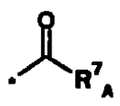
(1 1 3)



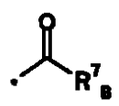
(1 1.4)



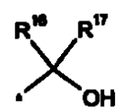
(1 1 5)



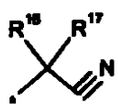
(1 1 6)



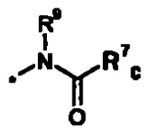
(1 1 7)



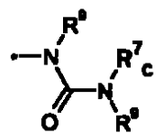
(1 1 8)



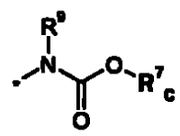
(1 1 9)



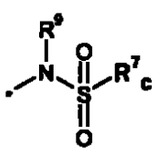
(1 1 10)



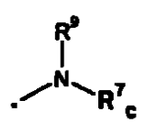
(1 1 11)



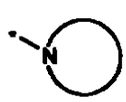
(1 1 12)



(1 1 13)



(1 1 14)



(1 1 15)

en las que

cuando $R^{16}$ y $R^{17}$ tienen el mismo significado que se definió anteriormente; y $R^{9}$ tiene el mismo significado que se define a continuación;

-"*" indica el punto de unión de cada fórmula parcial (1.1.1) a (1.1.15) a la parte restante de fórmula (1.0.0);

-q es 1, 2, ó 3, con la condición de que cuando q es 2 ó

3, entonces $R^9$ tiene el significado de -H en al menos un caso, o dos casos, respectivamente;

-v 0 ó 1;

$-W^3$ es -O-; $-N(R^9)-$, teniendo $R^9$ el mismo significado que se definió anteriormente, ó -CO(=O)-;

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

los siguientes·

-(1) -H;

-(2) -alquilo ($C_1$-$C_6$); -alquenilo ($C_2$-$C_6$); ó -alquinilo ($C_2$-$C_6$); estando sustituido el citado alquilo, alquenilo o alquinilo con 0 a 3 sustituyentes, teniendo $R^{10}$ el mismo significado que se definió anteriormente,

-(3) $-(CH_2)_u$-cicloalquilo ($C_3$-$C_7$), siendo u 0, 1 ó 2; y estando sustituido además el citado cicloalquilo ($C_3$-$C_7$) con 0 a 3 sustituyentes $R^{10}$, teniendo $R^{10}$ el mismo significado que se definió anteriormente; y

-(4) fenilo, bencilo o piridilo, estando opcionalmente

sustituidos los citados fenilo, bencilo o piridilo con 0 a 3 sustituyentes $R^{10}$, teniendo $R^{10}$ el mismo significado que se definió anteriormente;

$-R^7_s$ 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; 2H-1-benzopiranilo; 2-H-cromenilo; cromanilo; benzotienilo; 1H-indazolilo; bencimidazolilo; benzoxazolilo; benzoisoxazolilo, benzotiazolilo; benzotriazolilo, benzotriazinilo; ftalazinilo; 1,8-

naftiridinilo; quinolinilo; isoquinolinilo; quinazolinilo; quinoxalinilo; pirazolo[3,4-d]pirimidinilo, pirimido[4,5-d]pirimidinilo; imidazo[1,2-a]piridinilo, piridopiridinilo, pteradinilo; y 1H-purinilo, estando

cualquier resto enumerado anteriormente en (1) ó (2) opcionalmente sustituido con respecto a (i) uno cualquiera o más de los átomos de carbono de éste, opcionalmente con un sustituyente $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió anteriormente, (ii) uno cualquiera o más átomos de nitrógeno de éste que no sean un punto de unión del citado resto, opcionalmente con un sustituyente $R^{15}$, teniendo $R^{15}$ el mismo significado que se definió anteriormente, y todas las formas tautoméricas de éste; y (iii) cualquier átomo de azufre de éste que no sea un punto de unión del citado resto, con 0, 1, ó 2 átomos de oxígeno,

$-R^9$ es un miembro seleccionao 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 ($C_1$-$C_2$)-$C(=O)OR^{16}$; teniendo $R^{16}$ el mismo significado que se definió anteriormente;

$-R^7{}_a$ es un miembro seleccionado independientemente del grupo constituido por los significados de $R^7{}_A$ y los significados

de $R^7_a$ definidos anteriormente; y además en las que



(1 1 15)

comprende un sistema de anillo carbocíclico monocíclico saturado o insaturado 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); pudiendo estar opcionalmente reemplazados de 1 a 3 átomos de carbono individualmente del citado sistema de anillo carbocíclico por un heteroátomo de nitrógeno, o pudiendo estar opcionalmente reemplazado 1 átomo de carbono de éste por un heteroátomo de oxígeno o por un heteroátomo de azufre; o pudiendo estar opcionalmente reemplazados 2 átomos de carbono individualmente por un heteroátomo de nitrógeno y un heteroátomo de oxigeno, o por un heteroátomo de nitrógeno y un heteroátomo de azufre; estando

cualquier resto de fórmula parcial (1 1 15) citado anteriormente opcionalmente sustituido con respecto a (1) uno cualquiera o más átomos de carbono de éste, con un sustituyente $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió anteriormente; (2) uno cualquiera o más átomos de nitrógeno de éste, con un sustituyente $R^{15}$, teniendo $R^{15}$ el mismo significado que se

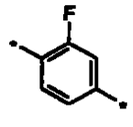
definió anteriormente, y todas las formas tautoméricas, y opcionalmente formas N-óxido de éste; ó (3) cualquier átomo de azufre de éste con 0, 1 ó 2 átomos de oxígeno, y E se selecciona adicionalmente de:

-(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); $-O-S(=O)_2OH$ (sulfúrico), $-S(=O)_2OH$ (sulfónico), $-S(=O)_2NHR^{26}$ ó $-NHS(=O_2)R^{26}$ (sulfonamido), siendo $R^{26}$ $-CH_3$, $-CF_3$ ó 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 $(C_1-C_4)$, $-C(=O)NHS(=O)_2NH$alquilo $(C_1-C_4)$; $-C(=O)NHS(=O)_2N[$alquilo $(C_1-C_4)]_2$; $-S(=O)_2NHC(=O)$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=O)NH_2$; $-S(=O)_2NHC(=O)NH$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=O)N[$alquilo $(C_1-C_4)]_2$, $-S(=O)_2NHC(=O)R^{25}$; $-S(=O)_2NHCN$, $-S(=O)_2NHC(=S)NH_2$; $-S(=O)_2NHC(=S)NH$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=S)N[$alquilo $(C_1-C_4)]_2$; y $-S(=O)_2NHS(=O)_2R^{25}$; en las que

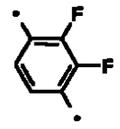
$-R^{25}$ es -H; -alquilo $(C_1-C_4)$; fenilo; ó $-OR^{18}$, teniendo $R^{18}$ el mismo significado que se definió anteriormente; ó

una sal farmacéuticamente aceptable de éste.

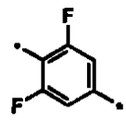
La presente invención se refiere en particular a un compuesto de fórmula (1.0.0) como se indicó anteriormente, en el que el grupo $G^2$ y los sustituyentes $R^1$ y $R^2$ unidos a éste se seleccionan de tal manera que la parte resultante de un compuesto de fórmula (1.0.0) está representada por las fórmulas parciales (2.5.1) a (2.5.50):



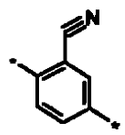

(2.5.1)



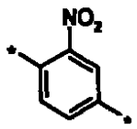

(2.5.2)



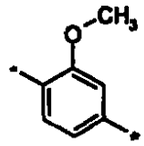

(2.5.3)



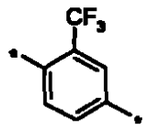

(2.5.4)



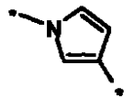
(2 5 5)



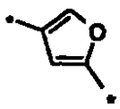
(2 5 6)



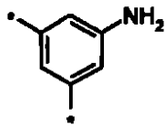
(2 5 7)



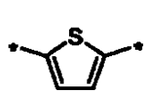
(2 5 8)



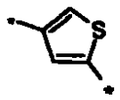
(2 5 9)



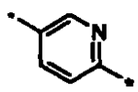
(2 5 10)



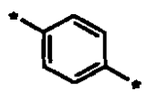
(2 5 11)



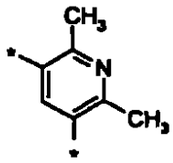
(2 5 12)



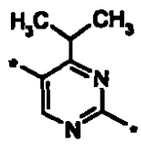
(2 5 13)



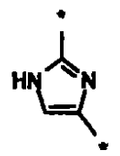
(2 5 14)



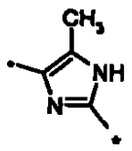
(2 5 15)



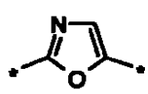
(2 5 16)



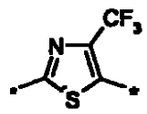
(2 5 17)



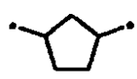
(2 5 18)



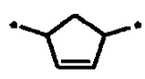
(2 5 19)



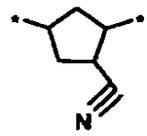
(2 5 20)



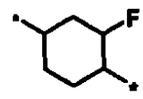
(2 5 21)



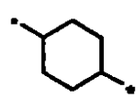
(2 5 22)



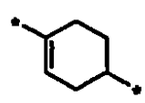
(2 5 23)



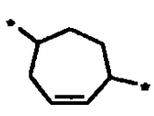
(2 5.24)



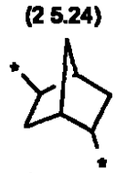
(2 5 25)



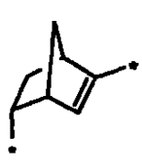
(2 5 26)



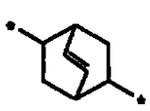
(2 5 27)



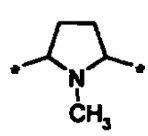
(2 5 28)



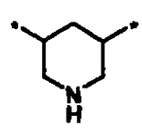
(2 5.29)



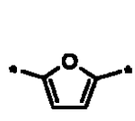
(2 5 30)

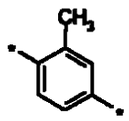


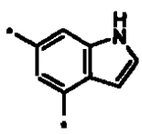
(2 5 31)

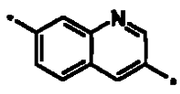


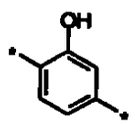
(2 5.32)

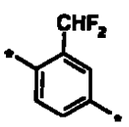

(2 5.33)

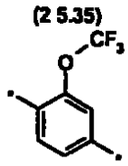

(2 5.34)

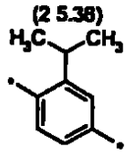

(2 5.35)

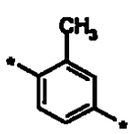

(2 5.36)

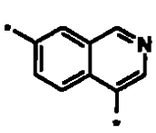

(2.5 37)

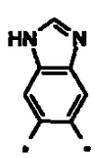

(2 5.38)

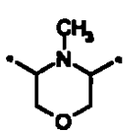

(2 5.39)

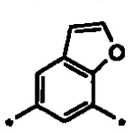

(2 5.40)

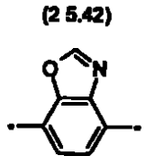

(2 5.41)

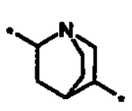

(2 5.42)

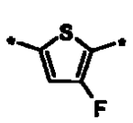

(2 5.43)

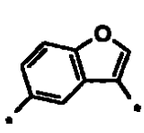

(2 5.44)

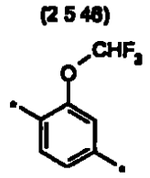

(2 5.45)


(2 5.46)


(2 5.47)


(2 5.48)


(2 5.49)


(2.5 50)

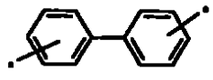
5

La presente invención se refiere también a un compuesto de fórmula (1.0.0) como se indicó anteriormente, en el que el grupo

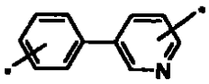
$G^2$ es un resto biarilo discontinuo o limitado de 7 a 18 miembros que comprende un miembro seleccionado del grupo constituido por

5

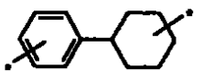
los siguientes restos, representados por las fórmulas parciales (1.2.1) a (1.2.32):



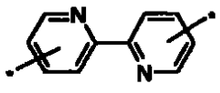
(1 2 1)



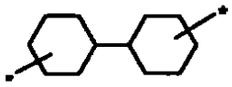
(1 2.2)



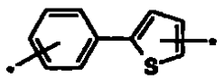
(1 2.3)



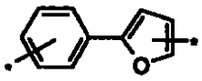
(1 2.4)



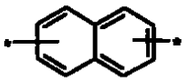
(1 2 5)



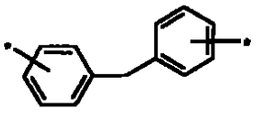
(1 2 6)



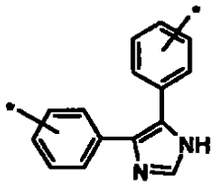
(1.2 7)



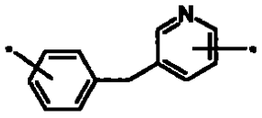
(1.2.8)



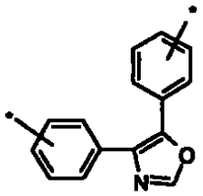
(1 2 9)



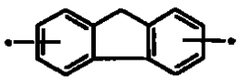
(1 2 10)



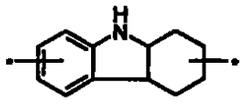
(1 2 11)



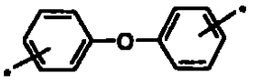
(1.2 12)



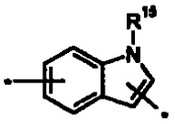
(1 2 13)



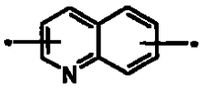
(1 2 14)



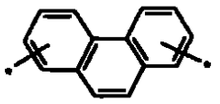
(1.2 15)



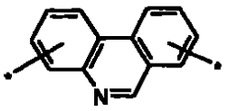
(1 2 16)



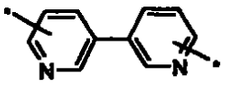
(1 2 17)



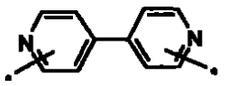
(1.2 18)



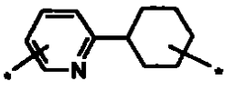
(1 2 19)



(1.2.20)



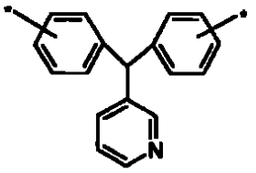
(1 2 21)



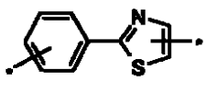
(1 2.22)



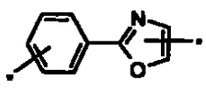
(1.2 23)



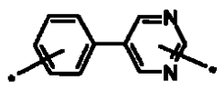
(1 2.24)



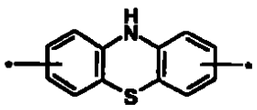
(1 2 25)



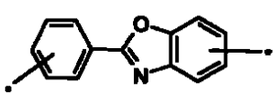
(1.2.26)



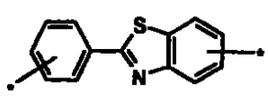
(1.2.27)



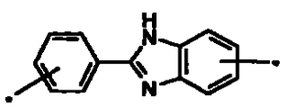
(1 2.28)



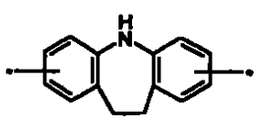
(1 2 29)



(1 2 30)



(1 2 31)

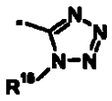


(1 2 32)

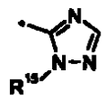
en los que "*" es un símbolo que indica los dos puntos de unión del citado grupo $G^2$ a los componentes restantes de fórmula (1.0.0).

La presente invención se refiere en particular a un compuesto de fórmula (1.0.0) como se indicó anteriormente, en el que el grupo E terminal 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 las que el significado preferido de $R^7_A$ ó $R^7_C$ es el significado de hidrógeno, metilo, trifluorometilo, isopropilo, fenilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

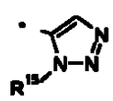
La presente invención se refiere también a un compuesto de fórmula (1.0.0) en la que E comprende las fórmulas parciales (1.1.4) y (1.1.10) a (1.1.14). Un significado preferido de $R^7_B$ de la fórmula parcial (1.1.4) en la que v es 0 ó 1, o de $R^7_C$ de las fórmulas parciales (1.1.10) a (1.1.14) es el significado de un miembro seleccionado del grupo constituido por las fórmulas parciales (1.4.1) a (1.4.32) ilustrado a continuación:



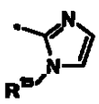
tetrazol-5-ilo
(1.4 1)



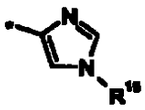
1,2,4-triazol-3-ilo
(1.4 2)



1 2 3-triazol-5-ilo
(1.4.3)

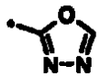


imidazol-2-ilo
(1.4 4)



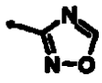
imidazol-4-ilo

(1.4.5)



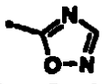
1,3,4-oxadiazolilo

(1.4.6)



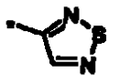
1,2,4-oxadiazol-3-ilo

(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)



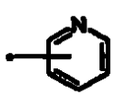
pirrolilo

(1.4.15)



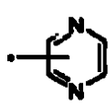
pirazolilo

(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)



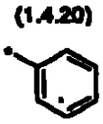
tetrahidrofuranilo

(1.4.22)



tienilo

(1.4.23)



fenilo

(1.4.24)



ciclopropilo

(1.4.25)



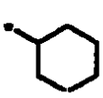
ciclobutilo

(1.4.26)



ciclopentilo

(1.4.27)



ciclohexilo

(1.4.28)



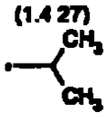
metilo

(1.4.29)



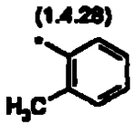
trifluorometilo

(1.4.30)



isopropilo

(1.4.31)

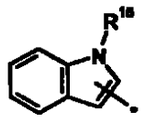


o-tolilo

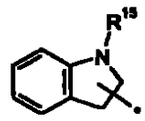
(1.4.32)

en las que "*" indica el punto de unión a la parte restante de fórmula (1.0.0), y en las que cada átomo de carbono está opcionalmente sustituido con un sustituyente $R^{14}$; teniendo $R^{14}$ y $R^{15}$ el mismo significado que se definió anteriormente; y todas las formas tautoméricas, y opcionalmente formas N-óxido, de estas.

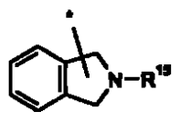
La presente invención se refiere también en particular a un compuesto de fórmula (1.0.0) como se indicó anteriormente, en la que el grupo E terminal comprende las fórmulas parciales (1.1.4) y (1.1.10) a (1 1.14) y en la que los significados preferidos de $R^7_A$ y $R^7_C$ en las citadas fórmulas parciales (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):



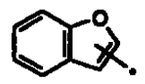
indolilo
(1 5 1)



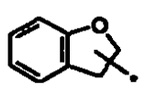
indolinilo
(1 5 2)



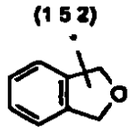
isoindolinilo
(1 5.3)



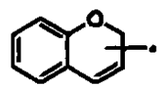
benzo[b]furanilo
(1.5.4)



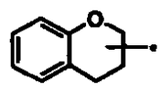
2,3-dihidro-
benzofuranilo
(1 5 5)



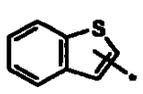
1 3-dihidroisobenzo-
furanilo, ftalanilo
(1 5.6)



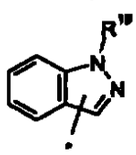
2H-1-benzopiranilo
(1 5 7)



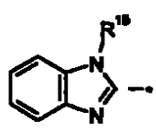
cromanilo
(1.5.8)



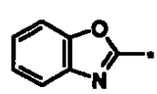
benzotienilo
(1 5 9)



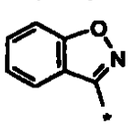
1H-indazolilo
(1 5.10)



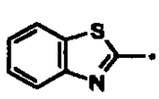
bencimidazolilo
(1.5 11)



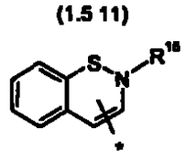
benzoxazolilo
(1 5 12)



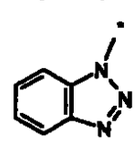
benzoisoxazolilo
(1 5 13)



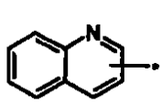
benzotiazolilo
(1 5 14)



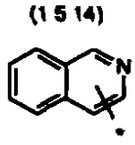
2H-1,2-benzotiazinilo
(1 5 15)



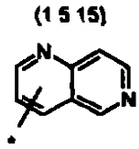
benzotriazolilo
(1 5 16)



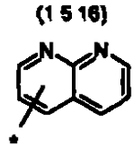
quinolinilo
(1 5 17)



isoquinolinilo
(1 5 18)

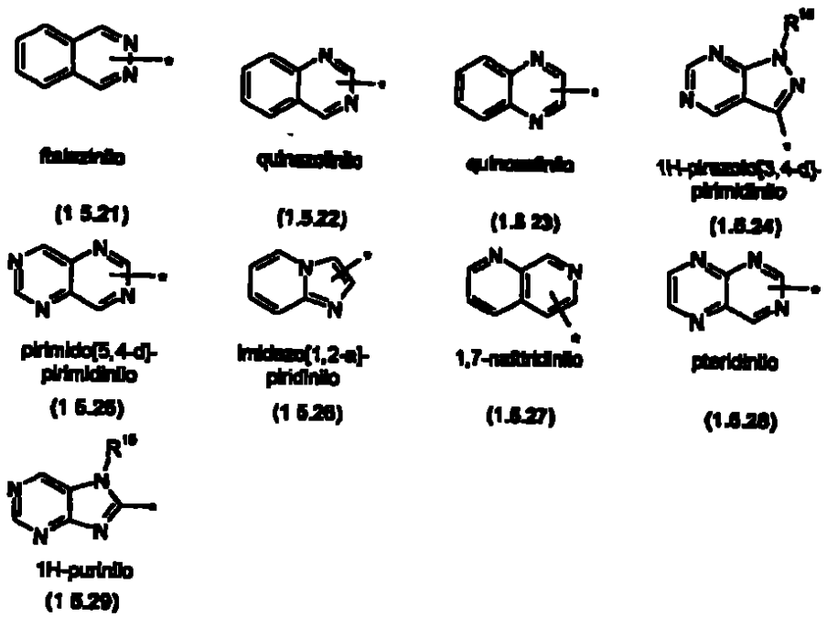


1,6-naftiridinilo
(1 5 19)



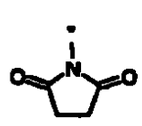
1,8-naftindinilo
(1 5 20)

5

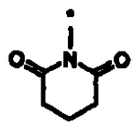



en las que "*" indica el punto de unión a la parte restante de fórmula (1.0.0); y en las que cada átomo de carbono está opcionalmente sustituido con un sustituyente $R^{14}$, teniendo $R^{14}$ y $R^{15}$ los mismos significados que se definieron anteriormente, y todas las formas tautoméricas, y opcionalmente formas N-óxido, de este.

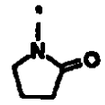
La presente invención se refiere también a un compuesto de fórmula (1.0.0) en la que el grupo terminal E tiene el significado de un resto de fórmula parcial (1.1.15), en el que el número y la posición de los átomos de carbono y los reemplazos de estos por uno o más heteroátomos, así como la sustitución de uno o más de los citados átomos de carbono con $R^{14}$, siendo $R^{14}$ oxo (=O), están seleccionados de tal manera que E comprende un miembro seleccionado del grupo constituido por las fórmulas parciales (1.7.1) a (1.7.46)



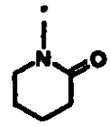
succinimid-1-ilo
(1 7 1)



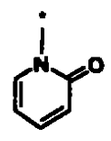
glutarimid-1-ilo
(1 7.2)



pirrolidin-2-on-1-ilo
(1 7 3)



piperid-2-on-1-ilo
(1 7.4)



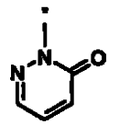
pirid-2-on-1-ilo

(1 7 5)



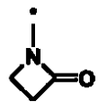
pirid-4-on-1ilo

(1 7 6)



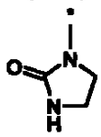
piridazin-3-on-2-ilo

(1 7 7)



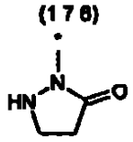
azetidin-2-on-1-ilo

(1 7 8)



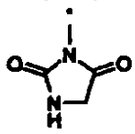
imidazolidin-2-on-1-ilo

(1 7 9)



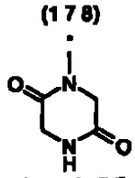
pirazol-5-on-1-ilo

(1 7 10)



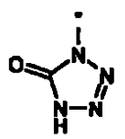
imidazolidin-2 4-dion-1-ilo

(1 7 11)



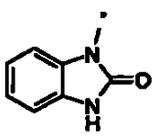
piperazin-2,5-dion-1-ilo

(1 7 12)



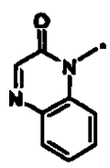
4 5-dihidro-5-oxo-1H-tetrazol-1-ilo

(1 7 13)



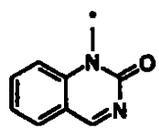
bencimidazolin-2-on-1-ilo

(1 7 14)



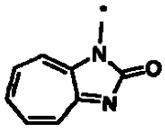
1H-quinoxalin-2-on-1-ilo

(1 7 15)



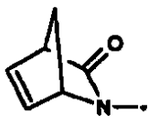
1H-quinozalin-2-on-1-ilo

(1 7 16)



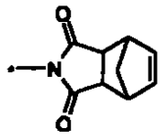
1H-ciclohepimidazol-2-on-1-ilo

(1 7 17)



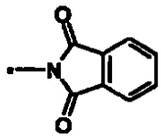
2-azabiciclo[2 2 1]-hept-5-en-3-on-1-ilo

(1 7 18)



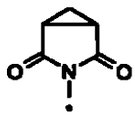
norborn-5-en-2,3-dicarboximid-1-ilo

(1 7 19)



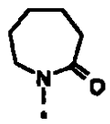
ftalimid-1-ilo, 1H-isoindol-1,3(2H)-dion-1-ilo

(1 7 20)



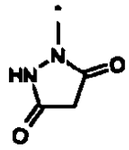
3-azabiciclo[3 1 0]-hexano-2,4-dion-3-ilo

(1 7.21)



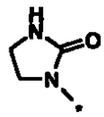
2H-azepin-2-on-1-ilo

(1 7.22)



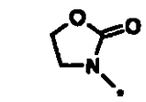
pirazolidin-3,5-dion-1-ilo

(1 7.23)



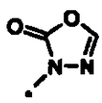
imidazolidin-2-on-1-ilo

(1 7.24)



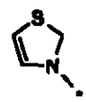
oxazolidin-2-on-1-ilo

(1 7.25)



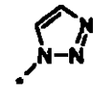
1,3,4-oxadiazol-2(3H)-on-3-ilo

(1 7 26)



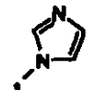
tiazol-3-ilo

(1 7.27)



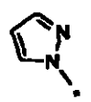
1H-1,2 3-triazol-1-ilo

(1 7 28)



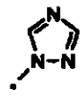
imidazol-1-ilo

(1 7.29)



pirazol-1-ilo

(1 7.30)



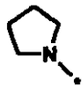
1H-1,2,4-triazol-1-ilo

(1 7 31)



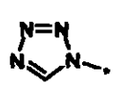
azetidin-1-ilo

(1 7.32)



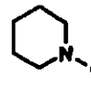
pirrolidin-1-ilo

(1 7.33)



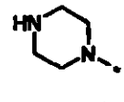
tetrazol-1-ilo

(1 7 34)



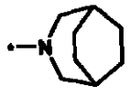
piperidin-1-ilo

(1 7 35)



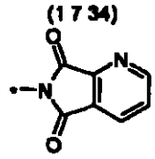
piperazin-1-ilo

(1 7.36)



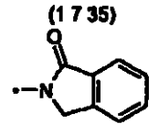
3-azabiciclo[3.2.2]-non-3-ilo

(1 7.37)



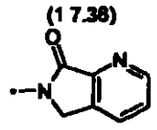
pirrolo[3 4-b]piridin -5,7-dion-6-ilo

(1 7.38)



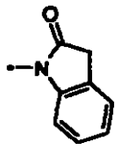
2,3-dihidroisoindol-1-on-2-ilo

(1 7 39)



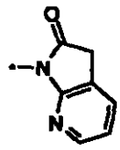
pirrolo[3,4-b]piridin -7-on-6-ilo

(1 7.40)



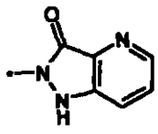
1,3-dihidroindol-2-on-1-ilo

(1 7 41)



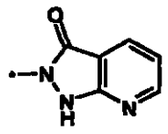
pirrolo[4,5-b]-piridin-3-on-2-ilo

(1 7 42)



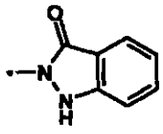
1H-pirazolo[4,5-e] piridin-7-on-2-ilo

(1 7 43)



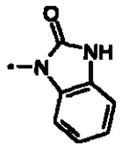
1H-pirazolo[4,5-b] piridin-4-on-2-ilo

(1 7.44)



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

(1 7 45)



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

(1 7 46)

Cualquier resto que sea un miembro seleccionado del grupo constituido por las fórmulas parciales (1.7.1) a (1.7.46) descritas anteriormente incluye la sustitución opcional de éste respecto de (1) uno cualquiera o más átomos de carbono de éste con un sustituyente $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió aneriormente; (2) uno cualquiera o más átomos de nitrógeno de éste con un sustituyente $R^{15}$, teniendo $R^{15}$ el mismo significado que se definió anteriormente, y todas las formas tautoméricas, y opcionalmente las formas N-óxido de éste; ó (3) cualquier átomo de azufre de éste con 0, 1 ó 2 átomos de oxígeno.

La presente invención se refiere también a un procedimiento de tratamiento de un sujeto que sufre una enfermedad o afección mediada por la isozima PDE4, especialmente el subtipo D de ésta, en su papel de regular la activación y desgranulación de eosinófilos humanos, que comprende administrar al citado sujeto necesitado de dicho tratamiento una cantidad terapéuticamente eficaz de un compuesto de fórmula (1.0.0) como se describió anteriormente. De forma similar, la presente invención se refiere también a una composición farmacéutica para uso en dicho tratamiento terapéutico, que comprende un compuesto de fórmula (1.0.0) como se describió anteriormente, junto con un vehículo farmacéuticamente aceptable.

La presente invención se refiere a inhibidores de la isozima PDE4, especialmente del subtipo D, que comprenden un compuesto de fórmula (1.0.0) como se describe anteriormente, que es útil en el tratamiento o la prevención de uno o varios 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 selecionado del grupo constituido por asma atópica, asma no atópica, asma alérgica; asma mediada por IgE bronquial atópica; asma bronquial; asma esencial; asma verdadera, asma intrínseca causada por perturbaciones patofisiológicas, asma extrínseca causada por factores medioambientales; asma esencial de causa desconocida o no evidente; asma no atópica, asma bronquítica; asma enfisematosa; asma inducida por ejercicio, asma ocupacional; asma infecciosa causada por infección bacteriana, fúngica, protozooaria o viral; asma no alérgica; asma incipiente; síndrome de jadeos en infantes;

- broncoconstricción crónica o aguda, bronquitis crónica; obstrucción de las vías aéreas pequeñas, y enfisema;

- enfermedades obstructivas o inflamatorias de las vías

aéreas de cualquier tipo, etiología o patogénesis; o una enfermedad inflamatoria u obstructiva de las vías aéreas que es un miembro seleccionao del grupo constituido por asma; neumoconiosis; neumonía eosinófila crónica; enfermedad pulmonar obstructiva crónica (EPOC); EPOC que incluye bronquitis crónica, enfisema pulmonar o dispnea asociadas con ésta; EPOC que se caracteriza por una obstrucción irreversible progresiva de las vías aéreas; síndrome del distrés respiratorio en adultos (SDRA) y exacerbación de la hiperreactividad de las vías aéreas posterior a otra terapia de fármacos;

- neumoconiosis de cualquier tipo, etiología o patogénesis, o neumoconiosis que es un miembro seleccionado del grupo constituido por aluminosis o enfermedad de los trabajadores con bauxita; antracosis o asma de los mineros; asbestosis o asma de los montadores de calderas; calicosis o enfermedad del sílex; ptilosis causada por la inhalación de polvo de plumas de avestruz; siderosis causada por la inhalación de partículas de hierro; silicosis o enfermedad de los molineros, bisinosis o asma de polvo de algodón y neumoconiosis de 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 de crup; bronquitis seca; bronquitis asmática infecciosa; bronquitis productiva; bronquitis por estafilococo o estreptococo; y bronquitis vesicular;

- bronquiectasis de cualquier tipo, etiología o patogénesis, o bronquiectasis que es un miembro seleccionado del grupo constituido por bronquiectasis cilíndrica; bronquiectasis de sáculos, bronquiectasis fusiforme; bronquiectasis capilar; bronquiectasis quística; bronquiectasis seca, y bronquiectasis 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 esfenoide;

- 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 psoriática y artritis vertebral:

- gota, y fiebre y dolor asociados con inflamación;

- un trastorno relacionado con eosinófilos de cualquier tipo, etiología o patogénesis; o un trastorno relacionado con eosinófilos que es un miembro seleccionado del grupo constituido por eosinofilia; eosinofilia de 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 nodular (PAN); y vasculitis necrotizante sistémica;

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

- urticaria de cualquier tipo, etiología o patogénesis; o urticaria que es un miembro seleccionado del grupo constituido por urticaria mediada por sistema inmune; urticaria mediada por complemento; urticaria inducida por material urticariogénico; urticaria inducida por un agente físico; urticaria inducida por el estrés, urticaria idiopática, urticaria aguda, urticaria crónica, angioedema; urticaria colinérgica; urticaria por el frío en la forma autosómica dominante o en la forma adquirida; urticaria de contacto; urticaria gigante; 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; conjuntitivitis contagiosa aguda; conjuntivitis alérgica; conjuntivitis atópica; conjuntivitis catarral crónica, conjuntivitis purulenta; y conjuntitivitis primaveral:

- uveitis de cualquier tipo, etiología o patogénesis; o uveitis que es un miembro seleccionao del grupo constituido por inflamación de toda o parte de la úvea, uveitis anterior; iritis, ciclitis, iridociclitis; uveitis granulomatosa; uveitis no granulomatosa; uveitis facoantigénica; uveitis posterior; coroiditis, y coriorretinitis,

- psoriasis;

- 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 de remisión recurrente;

- enfermedades autoinmunes/inflamatorias de cualquier tipo, etiología o patogénesis; o una enfermedad

autoinmune/inflamatoria que es un miembro seleccionado del grupo constituido por trastornos hematológicos autoinmunes; anemia hemolítica; anemia aplásica; anemia pura de glóbulos rojos; púrpura trombocitopénica idiopática; lupus sistémico eritematoso; policondritis; escleroderma, granulomatosis de Wegner; dermatomiositis; hepatitis activa crónica, miastenia grave; síndrome de Stevens-Johnson, esprúe idiopático; enfermedades inflamatorias intestinales autoinmunes; colitis ulcerosa; enfermedad de Crohn; oftamopatía endocrina, enfermedad de Grave; sarcoidosis; alveolitis; neumonitis de hipersensibilidad crónica; cirrosis biliar primaria; diabetes juvenil o diabetes mellitus tipo I; uveitis anterior; uveitis granulomatosa o posterior; queratoconjuntivitis seca, queratoconjuntivitis epidérmica, fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial, fibrosis pulmonar idiopática, fibrosis quística; artritis psoriática; glomerulonefritis con y sin síndrome nefrótico; glomerulonefritis aguda, síndrome nefrótico idiopático; nefropatía con cambios mínimos; enfermedades dérmicas inflamatorias/ hiperproliferativas, psoriasis; dermatitis atópica; dermatitis de contacto; dermatitis de contacto alérgico; pénfigo familiar benigno, pénfigo eritematoso; pénfigo foliáceo y pénfigo vulgar;

- prevención de rechazo de injertos alogénicos después de

un trasplante de órganos;

- enfermedad inflamatoria del intestino (EII) de cualquier tipo, etiología o patogénesis; o enfermedad inflamatoria del intestino que es un miembro del grupo constituido por colitis ulcerosa (CU); colitis colágena; colitis poliposa; colitis transmural, y enfermedad de Crohn (EC);

- 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 de 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 la inmunodeficiencia humana (VIH):

- daño hepático,

- 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 de aprendizaje y memoria; discinesia tardía; dependencia de drogas; demencia arterioscleróticа y demencias que acompañan a la corea de Huntigton, enfermedad de Wilson, parálisis agitante y atrofias talámicas;

- infección, especialmente infección por virus en la que dichos virus aumentan la producción de TNF-α en su huésped, o en la que dichos virus son sensibles a la sobrerregulación de TNF-α en su huésped de modo que su replicación u otras actividades vitales se ven afectadas adversamente, incluyendo un virus que es un miembro seleccionado del grupo constituido por VIH-1, VIH-2 y VIH-3, citomegalovirus, CMV; gripe, adenovirus; y herpesuirus, incluyendo *Herpes zoster* y *Herpes simplex*,

- infecciones por levaduras y hongos en las que las citadas levaduras y hongos son sensibles a la sobrerregulación por TNF-α o desencadenan la producción de TNF-α en su huésped, por ejemplo, meningitis fúngica, particularmente cuando se administra en combinación con otros fármacos de elección para el tratamiento de infecciones sistémicas por 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, anfotericina B y anfotericina B liposómica,

- daños de reperfusión por isquemia; diabetes autoinmune; autoinmunidad retinal; leucemia linfocítica crónica; infecciones por VIH; lupus eritematoso; enfermedades renales y de uréter; trastornos urogenitales y gastrointestinales; y enfermedades de próstata.

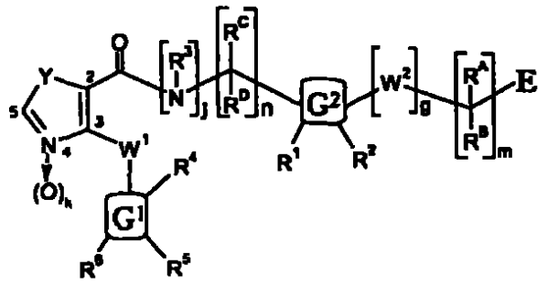
Particularmente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento de (1) enfermedades y afecciones inflamatorias que comprenden: inflamación de articulaciones, artritis reumatoide, espondilitis reumatoide, osteoartritis, enfermedades intestinales inflamatorias, colitis ulcerosa, glomerulonefritis crónica, dermatitis y enfermedad de Crohn; (2) enfermedades y afecciones respiratorias que comprenden: asma, síndrome de distrés respiratorio agudo, enfermedad inflamatoria pulmonar crónica, bronquitis, enfermedad obstructiva crónica de las vías aéreas y silicosis; (3) enfermedades y afecciones infecciosas que comprenden: sepsis, choque séptico, choque endotóxico, sepsis gram negativa, síndrome del choque tóxico, fiebre y mialgias debidas a infección bacteriana, viral o

fúngica, y gripe; (4) enfermedades y afecciones inmunes que comprenden: diabetes autoimune, lupus sistémico eritematoso; reacción de injerto frente al huésped, rechazos de aloinjertos, esclerosis múltiple, psoriasis y rinitis alérgica; y (5) otras enfermedades y afecciones que comprenden: enfermedades de resorción ósea, daños de reperfusión; caquexia secundaria a infección o malignidad, caquexia secundaria al síndrome de la inmunodeficiencia adquirida (SIDA) humana, infección por el virus de la inmunodeficiencia humana (VIH) o complejo relacionado con el SIDA (ARC), formación de queloides, formación de tejido cicatricial; diabetes mellitus de tipo 1 y leucemia.

## DESCRIPCION DETALLADA DE LA INVENCION

### 5.0 Compuestos

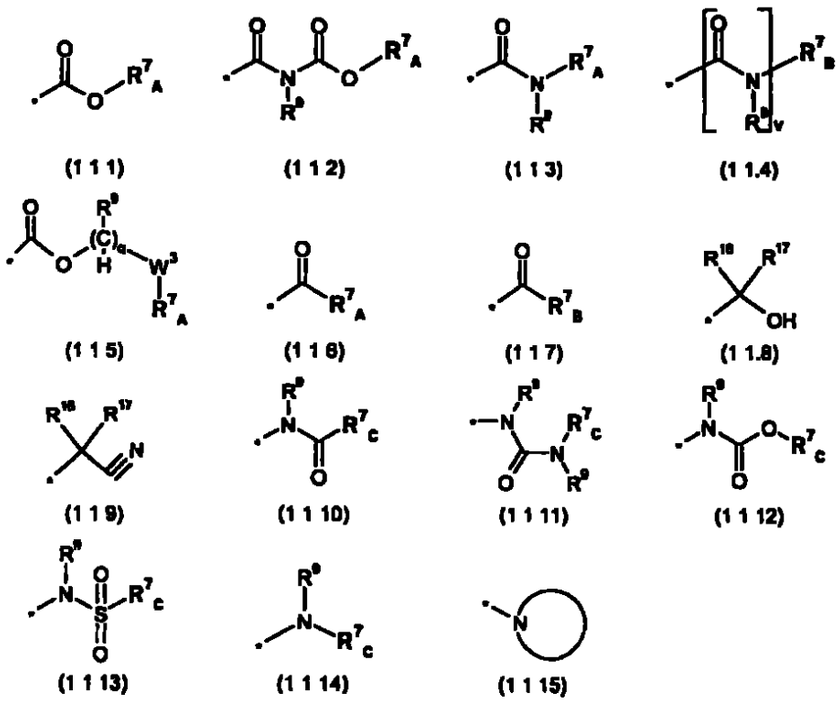
La presente invención se refiere a nuevos compuestos que pueden representarse por la fórmula (1.0.0) siguiente:



(100)

El alcance más amplio de los compuestos de la presente invención está limitado por la sección 4.0 anterior referente al sumario de la invención. Se proporciona a continuación una descripción adicional de los citados compuestos en términos de una serie de tipos y grupos de realizaciones diferentes, así como realizaciones específicas que caracterizan e ilustran los compuestos de fórmula (1.0.0). Se indican también realizaciones preferidas y más preferidas de los citados compuestos, pero se comprenderá que la enumeración de dichas preferencias no supone en modo alguno limitar, y no lo hace, el alcance de la presente invención con respecto de los citados compuestos.

El significado del resto terminal E indicado anteriormente con detalle es el de un miembro seleccionado independientemente del grupo constituido por las fórmulas parciales (1.1.1) a (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 anteriormente enumeradas, así como sus sub-sustituyentes $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$, $R^{18}$ y $R^{19}$ se han definido anteriormente, y proporcionan una clara delimitación

del alcance pretendido de los compuestos de la presente invención. Las realizaciones particulares dentro del citado alcance comprenden los significados particulares de los sustituyentes $R^{7}_{A}$, $R^{7}_{B}$, $R^{7}_{C}$ y $R^{9}$, así como de los demás sustituyentes que forman parte de la fórmula (1.0.0). Las citadas realizaciones incluyen, pero sin limitación, las citadas en los párrafos (i) a (vi) a continuación.

Para ayudar a la persona de conocimiento medio de la técnica a considerar el alcance y la extensión de la descripción de la presente invención indicada a continuación, se definen ciertos términos y expresiones utilizados en la presente descripción en los párrafos inmediatamente posteriores

Como se utilizan en la presente descripción, 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 ramificada así como lineal de estos grupos alifáticos. Así, las expresiones anteriormente indicadas incluyen, además de las entidades de cadena lineal metilo, etilo, n-propilo, n-butilo, n-pentilo y n-hexilo, las entidades de cadena ramificada isopropilo, isobutilo, sec-butilo, terc-butilo, isopentano (2-metilbutano), 2-metilpentano, 3-metilpentano, 1-etilpropano y 1-etilbutano. Los significados de las expresiones anteriormente indicadas se pretende también que se apliquen a las citadas

expresiones tanto si están sustituidas como si no. Así, la expresión "-alquilo ($C_1$-$C_3$) flurorado" se pretende que comprenda las diversas especies fluoradas de los grupos alifáticos n-propilo e isopropilo.

Como se utiliza en la presente descripción respecto de los compuestos de fórmula (1.0.0), así como de otras fórmulas parciales referentes a estos, cuando se representa uno o más componentes de átomos de nitrógeno de éstos como [N->(O)], puede(n) comprender un óxido de nitrógeno opcional del (de los) citado(s) átomo(s) de nitrógeno. Cuando hay más de una de dichas formas de óxido de nitrógeno, se seleccionan independientemente entre sí. Además, se observará que las citadas formas de óxido de nitrógeno pueden representarse también como "[N->$(O)_u$]", en la que u es 0 ó 1.

Tanto $G^1$ como $G^2$ se definen en la presente descripción como comprendiendo un sistema carbocíclico saturado o insaturado que es monocíclico de 3 a 7 miembros, o que es policíclico condensado de 7 a 12 miembros; pudiendo estar opcionalmente reemplazado un átomo de carbono del citado sistema carbocíclico por un heteroátomo seleccionado de N, O y S; pudiendo estar opcionalmente reemplazado un segundo átomo de carbono de éste, y opcionalmente un tercer átomo de carbono de éste, por N. Estas

definiciones se pretende que signifiquen, en primer lugar, un sistema carbocíclico con dos o más anillos, especialmente, biciclico y triciclico, más especialmente bicíclico, en el que los anillos estén condensados, es decir, que esté presente al menos un par de átomos de carbono de puente. Estos sistemas de anillo policíclicos pueden ser saturados o insaturados. En segundo lugar, la definición anteriormente indicada se pretende que signifique también un sistema carbocíclico con dos o más anillos, en el que los citados anillos sean discontinuos, es decir, estén unidos entre sí mediante un enlace covalente sencillo o doble, y no estén presentes átomos de carbono de puente. Estos sistemas de anillo policíclicos pueden ser también saturados o insaturados.

Respecto de la situación en la que se ha seleccionado un sistema carbocíclico que es discontinuo, en contraposición con el que es condensado, debe observarse que no se permite que el resto $G^1$ sea uno de dichos sistemas carbocíclicos discontinuos. Por otra parte, el resto $G^2$, es necesario que sea discontinuo en esta situación. Se proporciona además en la presente descripción que el resto $G^2$ puede tener el significado de un sistema carbocíclico que sea discontinuo, o puede tener el significado de un sistema carbocíclico "biarílico limitado". Estos dos aspectos se han reunido bajo la expresión "biarilo discontinuo o limitado" que, como se utiliza en la presente descripción,

significa un sistema de anillo discontinuo o un sistema de anillo policíclico condensado como se definió inmediatamente antes, en el que (1) los átomos de carbono de puente están unidos por un enlace, es decir, no hay átomos de carbono adicionales presentes entre los citados átomos de carbono de puente; y (2) los heteroátomos, si están presentes, están contenidos sólo en un sistema de anillo tricíclico o policíclico superior condensado.

Sin embargo, además debe observarse que el resto $G^2$ puede tener el significado de un sistema carbocíclico como se definió anteriormente que no es un biarilo discontinuo ni limitado. Así, $G^2$ puede ser monocíclico o policíclico saturado o insaturado que contiene opcionalmente heteroátomos, como se describió anteriormente. Consiguientemente, el resto $G^2$ tiene el significado, por ejemplo, de fenilo, ciclohexilo o piridinilo. El resto $G_1$ tiene también este significado.

Los tipos de sistemas de anillo discontinuos y biarílico limitados que pueden comprender un significado de $G^2$, pero que no pueden comprender un significado de $G^1$, incluyen, entre otros, los siguientes, en los que los números detrás de los nombres representan las fórmulas parciales para estos enumeradas en otro sitio en la presente descripción: bifenilo (1.2.1); 3-fenilpiridina (1.2.2), ciclohexil-benceno (1.2.3); [2,2']-

bipiridinilo (1.2.4); bicyclohexilo (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); 9H-carbazol (1.2.14); feniléter (1.2.15), 1H-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); 10H-fenotiazina (1.2.28); 2-fenilbenzoxazol (1.2.29); 2-fenilbenzotiazol (1.2.30), 2-fenil-1H-bencimidazol (1.2.31) y 10,11-dihidro-5H-dibenzo[b,f]azepina (1.2.32).

Como ilustración adicional, se comprenderá que, por ejemplo, un resto naftilo es un resto biarilo limitado como se define en la presente descripción, puesto que es un bicyclo condensado con un enlace entre los átomos puente de carbono, y no hay heteroátomos presentes. Un resto quinolinilo, por otro lado, aunque es también un bicyclo condensado con un enlace entre los átomos puente de carbono, no es un resto biarilo limitado como se define en la presente descripción, puesto que está presente también un heteroátomo de nitrógeno, y la definición de biarilo limitado como se utiliza en la presente descripción requiere que el sistema de anillo condensado sea

tricíclico o policíclico superior cuando está presente un heteroátomo. El resto bifenilo es un ejemplo de sistema de anillo discontinuo que, consiguientemente, puede ser un significado de $G^2$ pero no puede ser un significado de $G^1$.

Como se utiliza en la presente descripción, la expresión "sistema carbocíclico saturado o insaturado que es policíclico condensado o discontinuo de 7 a 12 miembros" se pretende que incluya sistemas carbocíclicos bi y tricíclicos saturados tales como norbornano, biciclo[2.2.2]octanilo, biciclo[3.2.1]octanilo, biciclo[3.3.0]octanilo, biciclo[3.3.1]nonanilo, ciclodecanilo y adamantanilo. La expresión indicada anteriormente se pretende también que incluya sistemas carbocíclicos monoinsaturados bi y tricíclicos tales como norbornenilo, biciclo[2.2.2]oct-5-enilo y biciclo[2.2.2]oct-7-enilo; así como sistemas carbocíclicos aromáticos bi y tricíclicos tales como naftileno y bifenileno. La expresión anteriormente indicada se pretende también que incluya sistemas carbocíclicos bicíclicos discontinuos aromáticos tales como bifenileno.

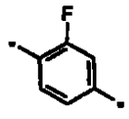
Los sistemas carbocíclicos incluidos dentro del alcance de la expresión anteriormente indicada y anteriormente descrita incluyen también restos en los que puede estar reemplazado opcionalmente un átomo de carbono de estos por un heteroátomo seleccionado de N, O ó S, y cuando es N el seleccionado, puede

estar reemplazado opcionalmente un segundo átomo de carbono de estos por un heteroátomo seleccionado de N, O y S. Los restos resultantes incluyen pirrolilo, pirrolidinilo; furanilo; tienilo; piridilo; pirimidinilo, piperidinilo; piperazinilo; imidazolilo; imidazolinilo; oxazolilo; isoxazolilo; tiazolilo; indolilo; quinolinilo; isoquinolinilo; bencimidazolilo; benzoxazolilo; morfolinilo, quinuclidinilo; y azabiciclo[3.3.0]octanilo. Ambos restos $G^1$ y $G^2$ pueden tener estos significados.

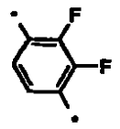
Los compuestos preferidos de fórmula (1.0.0) incluyen aquellos en los que $G^2$ comprende especialmente un miembro seleccionado del grupo constituido por fenilo; pirrolilo; pirrolidinilo; furanilo; tienilo; piridilo, pirimidinilo; piperidinilo; piperazinilo, imidazolilo, imidazolinilo; oxazolilo; isoxazolilo, tiazolilo, indolilo, quinolinilo, isoquinolinilo; bencimidazolilo; benzoxazolilo; morfolinilo, quinuclidinilo y azabiciclo[3.3.0]octanilo; un resto -cicloalquilo ($C_3$-$C_7$) monocíclico, un resto -cicloalquenilo ($C_5$-$C_7$) monocíclico que es un miembro seleccionado del grupo constituido por ciclopentenilo, ciclohexenilo y cicloheptenilo; y un resto -cicloalquilo ($C_7$-$C_{10}$) ó -cicloalquenilo ($C_7$-$C_{10}$) bicíclico que es un miembro seleccionado del grupo constituido por norbornanilo, norbornenilo, biciclo[2.2.2]octanilo, biciclo[3.2.1]octanilo,

biciclo[3.3.0]octanilo, biciclo[2.2.2]oct-5-enilo, biciclo[2.2.2]oct-7-enilo, biciclo[3.3.1]nonanilo, ciclodecanilo y adamantanilo.

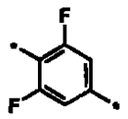
Las realizaciones preferidas adicionales de los compuestos de fórmula (1.0.0) incluyen aquellos en que particularmente $G^2$ y los sustituyentes $R^1$ y $R^2$ se seleccionan de tal manera que la parte del extremo derecho del citado compuesto de fórmula (1.0.0) está representada por las siguientes fórmulas parciales (2.5.1) a (2.5.50) indicadas a continuación.



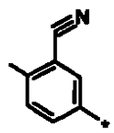

(2.5.1)



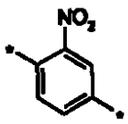

(2.5.2)



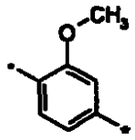

(2.5.3)



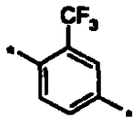

(2.5.4)



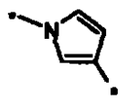
(2 5 5)



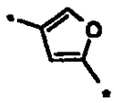
(2 5.6)



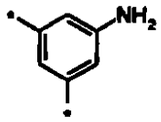
(2 5 7)



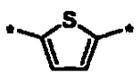
(2 5.8)



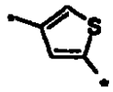
(2 5 9)



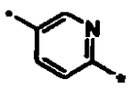
(2 5 10)



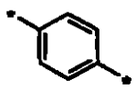
(2 5 11)



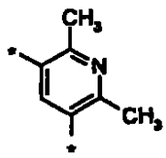
(2 5 12)



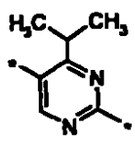
(2 5 13)



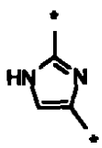
(2 5 14)



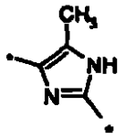
(2 5 15)



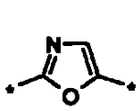
(2 5 16)



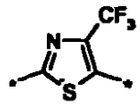
(2 5 17)



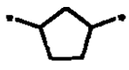
(2 5 18)



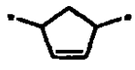
(2 5 19)



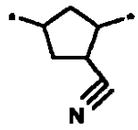
(2 5.20)



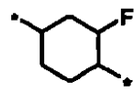
(2 5.21)



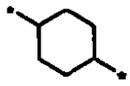
(2 5 22)



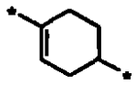
(2 5 23)



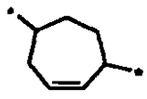
(2 5.24)



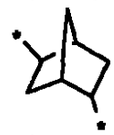
(2 5.25)



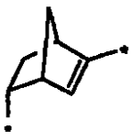
(2 5 26)



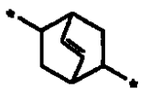
(2 5 27)



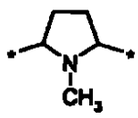
(2 5 28)



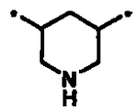
(2 5 29)



(2 5 30)

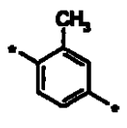


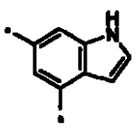
(2 5 31)

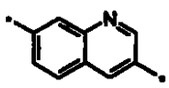


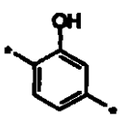
(2 5 32)

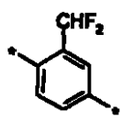

(2.5.33)

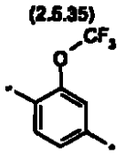

(2.5.34)

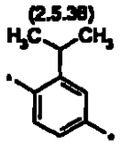

(2.5.35)

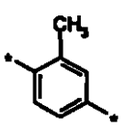

(2.5.36)

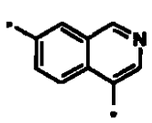

(2 5 37)

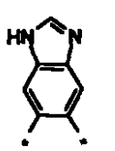

(2 5.38)

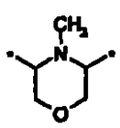

(2 5 39)

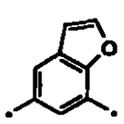

(2 5.40)

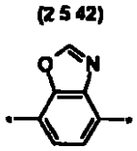

(2 5.41)

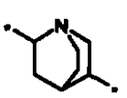

(2 5 42)

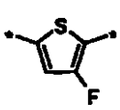

(2.5.43)

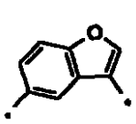

(2 5.44)

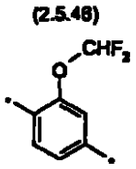

(2 5.45)


(2.5.46)


(2 5.47)


(2 5.48)


(2 5.49)


(2.5 50)

5

Otras realizaciones preferidas de los compuestos de fórmula (1.0.0) se ilustran en los párrafos siguientes, que enumeran los significados preferidos de diversos sustituyentes y componentes de fórmula (1.0.0).

(i) Las realizaciones de la presente invención incluyen aquellas que son un compuesto de fórmula (1.0.0), en la que Y es -S-, -O-, -NH- ó $-CH_2-$; $-G^1$ es fenilo o piridilo; $-G^2$ es fenilo, ciclopentilo, ciclohexilo, piridilo, oxadiazolilo, tiadiazolilo, bifenilo, 3-fenilpiridina, ciclohexilbenceno, [2,2']bipiridinilo o bicyclohexilo; -j es 1; -m es 0 ó 1, -n es 1; -E 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), en las que $R^7_a$ es (a) -H, (b) $-CH_3$ sustituido con 0-3 $R^{10}$, siendo $R^{10}$ -F; (c) $-CH_3$ sustituido con 0 ó 1 $R^{10}$, siendo $R^{10}$ -CN, $-OR^{16}$, siendo $R^{16}$ $-CH_3$ ó $-CH_2CH_3$, ó siendo $R^{10}$ $-NR^{16}R^{17}$ ó $-NR^{16}C(=O)R^{17}$, siendo $R^{16}$ y $R^{17}$ -H ó $-CH_3$; (d) ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, ó (e) fenilo, bencilo, o piridilo sustituido con 0-2 $R^{10}$, siendo $R^{10}$ -F, -Cl, $-CF_3$, $-CH_3$, $-CH_2OH$, $-SCH_3$, -CN, $-NO_2$, $-OR^{16}$ ó $-NR^{16}R^{17}$, siendo $R^{16}$ y $R^{17}$ -H, $-CH_2$, ó $-CH_2CH_3$; $-R^9$ es -H ó $-CH_3$, $-W^1$ es -O-; -g es 1 y $W^2$ es -O- ó $-CR^{29}R^{30}-$, siendo $R^{29}$ y $R^{30}$ ambos -H, ó g es 0 y $W^2$ está entonces ausente $-R^A$ y $R^B$ son independientemente -H ó $-CH_3$; ó $R^A$

y $R^B$ se toman conjuntamente para formar un resto -cicloalquilespiro ($C_3$-$C_7$); -uno de $R^C$ y $R^D$ es -H y el otro es -H ó $-CH_3$; $-R^1$ y $R^2$ son -H, -F ó $-OCH_3$; $-R^3$ es -H ó $-CH_3$; y $-R^4$, $R^5$ y $R^6$ son -H, -F, -Cl, $-OCH_3$, -CN; $-NO_2$, ó $-C(=O)R^3$ ó $-C(=O)OR^3$, siendo $R^3$ $-CH_3$; ó $R^5$ 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) ó (1.3.15).

(ii) Las realizaciones preferidas del tipo descrito en el párrafo inmediatamente anterior son aquellas en que Y es -S- ó $-CH_2-$, E es un resto de fórmulas parciales (1 1.1), (1.1.3), (1.1 6) ó (1.1.10); $R^9$ es -H, g es 0 y $W^2$ está ausente, $R^A$ 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, -CH, $-OCH_3$, $-C(=O)CH_3$ ó $-NO_2$; $R^6$ es -H, con la condición de que $R^5$ y $R^6$ no sean ambos -H al mismo tiempo, ó -F; ó $R^5$ y $R^6$ se toman conjuntamente para formar un resto de fórmula parcial (1.3.1), en la que $R^{20}$ y $R^{21}$ son -H ó $-CH_3$, ó un resto de fórmula parcial (1.3 11), (1.3.12) ó (1.3 15), estando $R^{23}$ y $R^{24}$ ausentes o siendo -H ó $-CH_3$.

(iii) Realizaciones adicionales de la presente invención comprenden un compuesto de fórmula (1.0.0) en la que Y es -S-, -O-, -NH- ó $-CH_2-$; $-G^1$ es fenilo o piridilo; $-G^2$ es fenilo, ciclopentilo, ciclohexilo, piridilo, oxadiazolilo, tiadiazolilo, bifenilo, 3-fenilpiridina, ciclohexilbenceno, [2,2']-

bipiridinilo ó bicıclohexılo; -ȷ es 1; -m es 0 ó 1; -n es 1; -E es un resto seleccıonado de fórmula parcıal (1.1.4), en la que $R^{7}_{a}$ es tetrazol-5-ılo, 1,2,4-triazol-3-ılo, 1,2,4-trıazol-3-on-5-ılo, imidazol-2-ilo, ımidazol-4-ılo, 1,3,4-oxadiazolılo, 1,2,4-oxadıazol-3-ılo, 1,2,4-oxadiazol-5-ılo, oxazolılo, isoxazolilo, pırrolılo, pırazolılo, succınımidılo, pırrolidinilo, tiazolılo, ısotıazolılo, 1,2,3-tıadıazolılo, 1,3,4-tıadıazolılo, pırıdılo, pirazinilo, furanılo, tetrahıdrofuranılo, tıenılo, ındolılo, 2,3-dıhıdrobenzofuranılo, benzotıenılo, 1H-ındazolılo, bencımıdazolılo, benzoxazolilo, benzotrıazolılo, quınolınılo, ısoquınolınılo, quınazolınılo, quınoxalınılo, 1,6-naftırıdınılo ó 1,8-naftırıdınılo, todos los cuales están sustıtuıdos ındependıentemente con 0 ó 1 $R^{14}$, sıendo $R^{14}$ $-CH_3$; $-OR^{16}$, sıendo $R^{16}$ -H ó $-CH_3$, oxo (=O), $-C(=O)OR^{16}$, sıendo $R^{16}$ -H ó $-CH_3$; $-R^9$ es -H ó $-CH_3$, $-W^1$ es -O-; -g es 1 y $W^2$ es -O- ó

$-CR^{29}R^{30}-$, sıendo $R^{29}$ y $R^{30}$ ambos -H, o g es 0 y $W^2$ está entonces ausente; $-R^A$ y $R^B$ son ındependıentemente -H ó $-CH_3$; ó $R^A$ y $R^B$ se toman conjuntamente para formar un resto

-cıcloalquılespıro ($C_3$-$C_7$); -uno de $R^C$ y $R^D$ es -H y el otro es -H ó $-CH_3$; $-R^1$ y $R^2$ son -H, -F ó $-OCH_3$; $-R^3$ es -H ó $-CH_3$; y $-R^4$, $R^5$ y $R^6$ son -H, -F, -Cl, $-OCH_3$, -CN; $-NO_2$ ó $-C(=O)R^3$ ó $-C(=O)OR^3$, sıendo $R^3$ $-CH_3$; ó $R^5$ y $R^6$ se toman conjuntamente para formar un resto de fórmula parcıal (1.3.1), (1.3.2), (1.3.3), (1.3.4), (1.3.11), (1 3.12) ó (1.3.15).

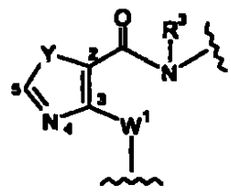
(iv) Las realizaciones preferidas del tipo descrito en el párrafo inmediatamente anterior son aquellas en que Y es -S- ó -$CH_2$-; $R^9$ es -H; g es 0 y $W^2$ está ausente; $R^A$ y $R^B$ son ambos -H; $R^C$ y $R^D$ son ambos -H; $R^3$ es -H; $R^4$ es -H; $R^5$ es -H, -F, -Cl, -CN, -$OCH_3$, -C(=O)$CH_3$ ó -$NO_2$; $R^6$ es -H, con la condición de que $R^5$ y $R^6$ no sean ambos -H al mismo tiempo, ó -F; ó $R^5$ y $R^6$ se toman conjuntamente para formar un resto de fórmula parcial (1.3.1), en la que $R^{20}$ y $R^{21}$ son -H ó -$CH_3$, o un resto de fórmula parcial (1.3.11), (1.3.12) ó (1.3.15) en las que $R^{23}$ y $R^{24}$ están ausentes o son -H ó -$CH_3$.

(v) Realizaciones adicionales de la presente invención incluyen un compuesto de fórmula (1 0 0) en la que Y es -S-, -O-, -NH- ó -$CH_2$-, $-G^1$ es fenilo o piridilo; $-G^2$ es fenilo, ciclopentilo, ciclohexilo, piridilo, oxadiazolilo, tiadiazolilo, bifenilo, 3-fenilpiridina, ciclohexilbenceno, [2,2']-bipiridinilo o biciclohexilo; -j es 1; -m es 0 ó 1; -n es 1; -E 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-1H-tetrazol-1-ilo, bencimidazolin-2-on-1-ilo, norborn-5-en-2,3-dicarboximid-1-ilo, imidazolidin-2-on-1-ilo, tiazolidin-3-ilo, 1H-1,2,3-triazol-1-ilo, 1H-1,2,4-triazol-

1-ilo, pirrolidin-1-ilo, tetrazol-1-ilo, piperidin-1-ilo, piperazin-1-ilo, 1H-pirazolo[4,5-e]piridin-7-on-2-ilo, 1H-indazol-3-on-2-ilo, 1H-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- ó -$CR^{29}R^{30}$, siendo $R^{29}$ y $R^{30}$ ambos -H, ó g es 0 y $W^2$ está así ausente, $-R^A$ y $R^B$ son independientemente -H ó $-CH_3$, ó $R^A$ y $R^B$ se toman conjuntamente para formar un resto -cicloalquilespiro ($C_3$-$C_7$); -uno de $R^C$ y $R^D$ es -H y el otro es -H ó $-CH_3$, $-R^1$ y $R^2$ son -H, -F ó $-OCH_3$, $-R^3$ es -H ó $-CH_3$; y $-R^4$, $R^5$ y $R^6$ son -H, -F, -Cl, $-OCH_3$, -CN, $NO_2$ ó $-C(=O)R^3$ ó $-C(=O)OR^3$, siendo $R^3$ $-CH_3$; ó $R^5$ 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) ó (1.3.15), estando ambos $R^{23}$ y $R^{24}$ ausentes en las fórmulas parciales (1.3.11) y (1.3.12).

(vi) Las realizaciones preferidas del tipo descrito en el párrafo inmediatamente anterior son aquellas en que Y es -S- ó -$CH_2$-; $R^9$ es -H; g es 0 y $W^2$ está ausente, $R^A$ y $R^B$ son ambos -H, $R^C$ y $R^D$ son ambos -H; $R^3$ es -H, $R^4$ y $R^5$ son ambos -H, y $R^6$ es -F; ó $R^5$ y $R_6$ se toman conjuntamente para formar un resto de fórmula parcial (1.3.1) ó (1 3.11).

Una parte del núcleo central de los compuestos de fórmula (1.0.0) es aquella de una tiazolil-, oxazolil-, pirrolil- o imidazolilamida de fórmula (1.0.1):



(101)

Esta parte del núcleo central está elaborada definiendo el resto Y como $-S(=O)_t-$, siendo t 0, 1 ó 2; -O-; $-[N->(O)_k]-$, ó $-N(R^3)-$, siendo k 0 ó 1 y teniendo $R^3$ el mismo significado que se define en la presente descripción; ó $-CH(R^1_a)-$, teniendo $R^1_a$ el mismo significadc que se define en la presente descripción; e indicando además el símbolo ->(O) un heteroátomo de nitrógeno en forma de su N-óxido, cuando k es 1 Consiguientemente, la citada parte del núcleo central se convierte, respectivamente, en un resto tiazolilo, oxazolilo, pirrolilo o imidazolilo.

Se ha destacado ya anteriormente que en el caso de 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 los citados restos heterociclilo puede estar en forma del N-óxido de los citados N-heteroátomos. Consiguientemente, las consideraciones referentes a los N-óxidos recién descritos se aplican también a dichos restos que contienen N-óxidos que definen $R^7_B$ y $R^7_C$.

Cuando Y tiene el significado de $-S(=O)_t-$, siendo t 0, 1 ó 2, los compuestos de la presente invención son tiazolilamidas que pueden estar presentes en forma de sus derivados sulfinilo o sulfonilo. Sin embargo, se prefiere que t sea 0, y los derivados de tiazolilamida son el significado preferido de Y en los compuestos de fórmula (1.0.0).

Cuando Y tiene el significado de -O-, los compuestos de la presente invención son oxazolilamidas, que son los siguientes compuestos más preferidos de fórmula (1.0.0) después de las tiazolilamidas.

Cuando Y tiene el significado de $-CH(R^1_a)-$, los compuestos de la presente invención son pirrolilamidas, que después de las tiazolilamidas y las oxazolilamidas, son los compuestos más preferidos de fórmula (1.0.0). El sustituyente $R^1_a$ se selecciona independientemente de los demás sustituyentes que forman los compuestos de fórmula (1.0.0), pero es preferiblemente -H, -F, $-CH_3$ ó $-OCH_3$.

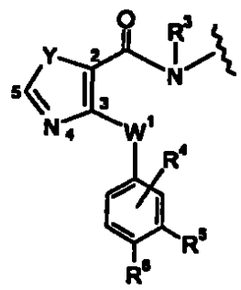
Finalmente, cuando Y tiene el significado de $-[N->(O)_k]-$, los compuestos de la presente invención son imidazolilamidas. Se prefiere que k sea 0. Las imidazolilamidas no son tan preferidas como las tiazolilamidas, oxazolilamidas y pirrolilamidas de fórmula (1.0.0) descritas anteriormente.

Además de -H, $R^1_a$ del resto $-CH(R^1_a)-$ 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; $-OR^{18}$; y $-C(=O)NR^{12}_aR^{12}_b$; siendo $R^{12}_a$ y $R^{12}_b$ 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 $-CH(R^1_a)-$ tenga el significado de -H, -F; -Cl, $-CH_3$; $-OCH_3$; ó -alquinilo ($C_2$-$C_4$); más preferiblemente $R^1_a$ es -F ó -H.

**5 1 Engarce de ($W^1$) y el resto $G^1$ sustituido con $R^4$, $R^5$ y $R^6$**

Los núcleos de tiazolilamida y análogos de los compuestos de fórmula (1.0.0) en los que Y es -S-, etc., se caracterizan por la formación, en el átomo de carbono de la posición 3 del anillo de tiazolilo o análogos, de un engarce con un sistema de anillo que comprende el resto $G^1$. En las realizaciones preferidas, el resto $G^1$ 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 cualquiera de las posiciones restantes con un resto $R^4$, dando como resultado un resto de fórmula parcial (1.0.3):



(103)

en la que $W^1$ tiene el significado de -O-; $-S(=O)_t-$, siendo t 0, 1 ó 2; ó $-N(R^3)-$, siendo $R^3$ -H; -alquilo ($C_1$-$C_3$); fenilo; bencilo; ó $-OR^{16}$, teniendo $R^{16}$ el mismo significado que se definió anteriormente.

En otras realizaciones de la presente invención, $W^1$ tiene el significado de $-S(=O)_t-$, siendo t 0, 1 ó 2; y preferiblemente tiene el significado de -S-, con el que se forma un engarce tioéter. Cuando el átomo de azufre del engarce tioéter está oxigenado, da lugar a un engarce sulfinilo o sulfonilo. En aún más realizaciones, cuando $W^1$ tiene el significado de $-N(R^3)-$, se forma un engarce amino, que será preferiblemente -NH-. Sin embargo, el átomo de nitrógeno puede estar sustituido y cuando éste es el caso, se prefiere que el citado sustituyente sea $-CH_3$.

Los significados de los sustituyentes $R^4$, $R^5$ y $R^6$ se seleccionan del mismo conjunto de definiciones, pero se

comprenderá que los citados significados se seleccionan sobre una base independiente entre sí. $R^5$ y $R^6$ pueden ser también -H. Consiguientemente, cuando el resto $G^1$ tiene el significado de un anillo fenilo, la posición para ($R^6$), meta ($R^5$) u orto ($R^4$) del anillo fenilo puede estar sustituida, o las tres posiciones pueden estar sustituidas, o cualquier combinación de las citadas posiciones puede estar sustituida. Sin embargo, se prefiere en los compuestos de fórmula (1.0.0) que estén sustituidas las posiciones para y/o meta en vez de la posición orto.

Cuando el resto $G^1$ tiene el significado preferido de un anillo fenilo, $R^5$ y $R^6$ pueden tomarse también conjuntamente para formar un miembro seleccionado de un grupo de fórmulas parciales descritas con 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, consiguientemente, estará presente siempre un sustituyente en una o ambas de las posiciones ocupadas por $R^5$ y $R^6$. Además de -H, $R^5$ y $R^6$ pueden ser, entre otros, -F; -Cl; -CN, $-NO_2$, $-C(=O)R^{16}$; $-OR^{16}$; $-C(=O)OR^{16}$; ó $-NR^{16}R^{17}$. Cuando $R^5$ es -H y $R^6$ es -F, dan como resultado realizaciones preferidas de la presente invención. En una realización preferida adicional de la presente invención, $R^5$

y $R^6$ pueden ser también $-OR^{16}$, en la que $R^{16}$ es hidrógeno; alquilo ($C_1$-$C_4$); ó cicloalquilo ($C_3$-$C_6$); estando sustituido el citado alquilo y cicloalquilo con 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 observara que la selección de los sustituyentes de entre los descritos anteriormente estará influenciada por el efecto que dichos sustituyentes tengan a su vez sobre las propiedades físico-químicas de las moléculas totales que resulten. El presente estado de la técnica proporciona la capacidad de sintetizar rápida y fácilmente un gran número de compuestos químicamente muy similares basados en las selecciones de sustituyentes descritas anteriormente, y del ensayo posterior de la eficacia relativa de las moléculas resultantes con procedimientos rápidos de ensayo in vitro. La síntesis química combinatoria y los procedimientos de ensayo disponibles actualmente en la técnica han aumentado incluso más considerablemente el número de combinaciones de sustituyentes posibles que pueden evaluarse rápidamente. La información que se produce de esta manera mediante el uso de estas técnicas permite una predicción razonable en éstas de ciertas preferencias que existen en diversas realizaciones de la presente invención. Dichas realizaciones preferidas se describen en detalle en la

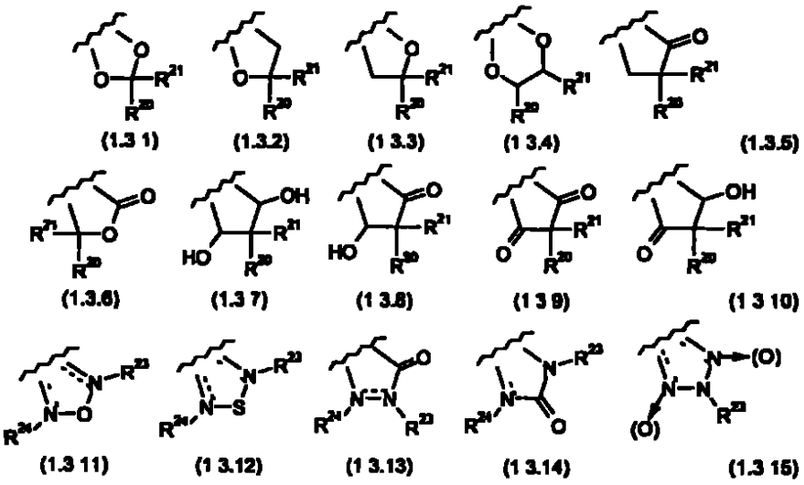
presente descripción.

Las realizaciones preferidas de la presente invención incluyen además aquellas en las que tanto $R^5$ como $R^6$ son ambos -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 $-OCH_3$, $-OCH_2F$, $-OCHF_2$ ó $-OCF_3$; -CN, -COOH; $-COOCH_3$; $-CONH_2$; $-OCOCH_3$, ó $NH_2$. 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, $-OCH_3$, ó $-C(=O)CH_3$ y $R^6$ es -H.

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

**5.2.0 $G^1$ es fenilo y $R^5$ y $R^6$ se toman conjuntamente**

Cuando el resto $G^1$ 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):

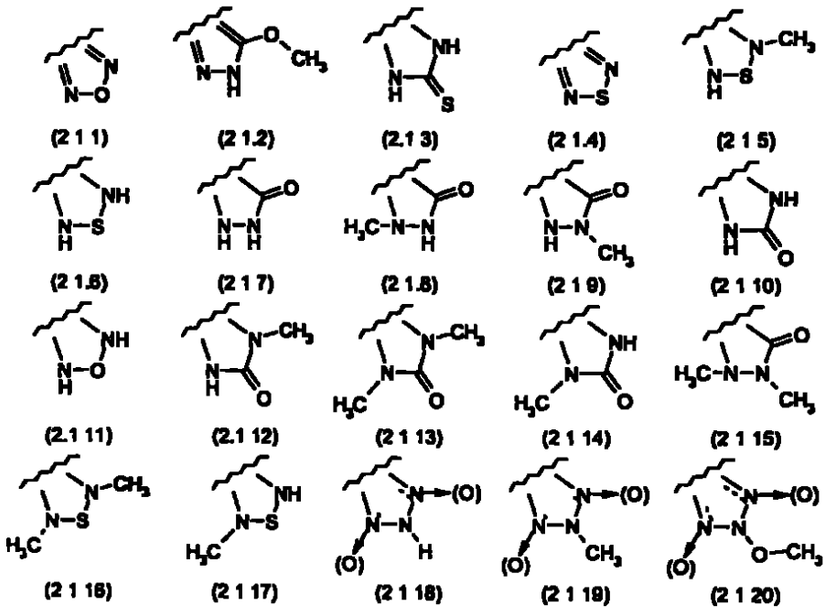



en las que $R^{20}$ y $R^{21}$ son cada uno un miembro seleccionado independientemente del grupo constituido por -H; -F; -Cl; $-CH_3$; $-CH_2F$; $-CHF_2$; $-CF_3$; $-OCH_3$; y $-OCF_3$; y $R^{23}$ y $R^{24}$ son cada uno independientemente -H; $-CH_3$; $-OCH_3$; $-CH_2CH_3$, $-OCH_2CH_3$, $-CH_2CH_2CH_3$; $-CH_2(CH_3)_2$; $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$; $-C(CH_3)_3$ o ausente, en cuyo caso la línea de trazos --- representa un doble enlace. Para el resto de fórmula parcial (1.3.13), los componentes de átomc de nitrógeno de estos se representan como -[N(->O)]-, y comprenden así formas de óxido de nitrógeno opcionales de los citados átomos de nitrógeno,

seleccionadas independientemente entre sí. Se observará que la citada forma de óxido de nitrógeno puede representarse también como -N[(->O)$_j$]-, siendo j 0 ó 1, como en la fórmula (1.0.0).

Cuando el resto $G^1$ 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, se forma junto con el grupo fenilo al que está unido, 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 $G^1$ 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 definieron, se forman benzofurazano, benzotiofurazano, triazol y otros grupos análogos, así como derivados sustituidos de estos incluyendo, entre otros, los siguientes restos de fórmulas parciales (2.1.1) a (2.1.20).

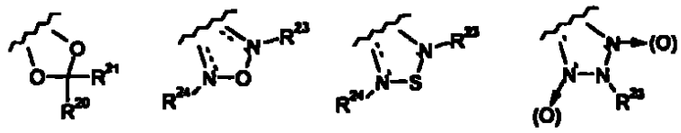



en las que la línea de trazos --- en las fórmulas parciales (2.1.18), (2.1.19) y (2.1.20) representa un doble enlace cuando no está unido ningún átomo de oxígeno al correspondiente átomo de nitrógeno, y representa un enlace sencillo cuando está unido un átomo de oxígeno al citado átomo de nitrógeno correspondiente.

El experto conocedor medio de la técnica de la preparación de moléculas orgánicas observará que los compuestos de fórmula (1.0.0) en la que $R^5$ y $R^6$ se toman conjuntamente para formar restos de las fórmulas parciales anteriormente ilustradas

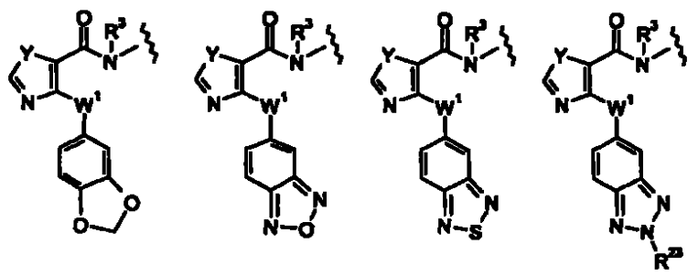
(2.1.2), (2.1.3), (2.1.7), (2.1.8), (2.1.10), (2.1.12) y (2.1.14) existen en forma tautomérica, y cada resto de las citadas fórmulas parciales (2.1.2), (2.1.3), (2.1.7), (2.1.8), (2.1.10), (2.1.12) y (2.1.14) tiene una contraparte tautomérica. Estos tautómeros están relacionados con el desplazamiento de un hidrógeno y uno o más enlaces π, y cuando sea necesario, el experto será capaz de discernir o determinar fácilmente cuál forma tautomérica está presente o es la más estable.

Las realizaciones preferidas de la presente invención son el resultado directo de la definición de $R^5$ y $R^6$ tomados 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) y (1.3.15)



(1.3.1) (1.3.11) (1.3.12) (1.3.15)

Consiguientemente, de estos resultan adicionalmente restos de fórmulas parciales (1.0.15) a (1.0.18).



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

en las que $R^{23}$ es -H ó $-CH_3$; y $W^1$ tiene el significado de -O-; $-S(=O)_t-$, siendo t 0, 1 ó 2; o $-N(R^3)-$, siendo $R^3$ como se define en la presente descripción, y siendo preferiblemente -H ó $-CH_3$. En los compuestos preferidos de fórmula (1.0.0), $W^1$ tiene el significado de -O-, con el que se crea un engarce éter para unir el heterociclo bicíclico benzocondensado al núcleo central descrito anteriormente.

En realizaciones preferidas de los compuestos de fórmula (1.0.0), $R^{23}$ y $R^{24}$ están ambos ausentes, excepto en compuestos del tipo ilustrado por la fórmula parcial (1.3.11), en la que sólo puede estar ausente uno de $R^{23}$ ó $R^{24}$. Se reconocerá que cuando $R^{23}$ y $R^{24}$ están ambos ausentes, y las líneas de trazos --- representen consiguientemente dobles enlaces, que la parte fenilo de los heterociclos bicíclicos benzocondensados resultantes descritos no puede tener todos los dobles enlaces descritos en las citadas fórmulas parciales, puesto que el

resultado sería átomos de carbono pentavalente prohibidos en la citada parte fenilo.

Consiguientemente, cuando $R^{23}$ y $R^{24}$ están ambos ausentes, los compuestos resultantes se caracterizan por estructuras tales como las mostradas en las fórmulas parciales (1.0.16) y (1.0.17) anteriores.

En otras realizaciones de los compuestos de fórmula (1 0.0), los sustituyentes $R^{20}$ y $R^{21}$ de los heterociclos bicíclicos benzocondensados representados por la fórmula parcial (1 3.1) son -H, -F, -Cl, $-CH_3$, $-CH_2F$, $-CHF_2$ ó $-CF_3$. Preferiblemente, $R^{20}$ y $R^{21}$ son ambos -H ó -F, en cuyo caso los compuestos resultantes se caracterizan por la estructura mostrada en la fórmula parcial (1.0.15) anterior, o su correspondiente análogo difluoro (no mostrado). 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 ausentes, en cuyo caso la línea de trazos --- representa un doble enlace. Se comprenderá, por supuesto, que cuando $R^{23}$ y $R^{24}$ están ausentes, no hay átomos de carbono pentavalentes en la parte fenilo de los citados heterociclos bicíclicos benzocondensados. Las estructuras heterocíclicas bicíclicas benzocondensadas se muestran en las fórmulas

parciales (1.0.15) a (1.0.18) anteriores.

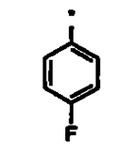
**5.2.1 $G^1$ es distinto de fenilo**

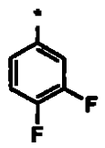
Además de aquellas realizaciones de la presente invención en las que $G^1$ tiene el significado preferido de fenilo, la presente invención se ha definido también anteriormente como referida a un compuesto de fórmula (1.0.0), en la que $G^1$ tiene el significado definido anteriormente como un resto que comprende un sistema carbocíclico saturado o insaturado monocíclico de 3 a 7 miembros, o policíclico condensado de 7 a 12 miembros, pudiendo estar opcionalmente reemplazado un átomo de carbono del citado sistema carbocíclico por un heteroátomo seleccionado de N, O y S; y pudiendo estar opcionalmente reemplazado un segundo átomo de carbono de éste, y opcionalmente además un tercer átomo de carbono de éste, por N. La presente invención se refiere además a un compuesto de fórmula (1.0.0) en la que $G^1$ comprende especialmente un miembro seleccionado del grupo constituido por pirrolilo; pirrolidinilo; furanilo; tienilo; piridilo; pirimidinilo; piperidinilo; piperazinilo, imidazolilo; imidazolidinilo, oxazolilo; isoxazolilo; morfolinilo; tiazolilo; indolilo; quinolinilo; isoquinolinilo; bencimidazolilo; benzoxazolilo; quinuclidinilo y azabiciclo[3.3.0]octanilo, un resto -cicloalquilo ($C_3$-$C_7$) monocíclico; un resto -cicloalquenilo ($C_5$-$C_7$) monocíclico, que

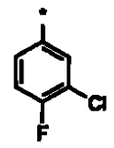
es un miembro seleccionado del grupo constituido por ciclopentenilo, ciclohexenilo y cicloheptenilo; y un resto -cicloalquilo ($C_7$-$C_{10}$) o -cicloalquenilo ($C_7$-$C_{10}$) bicíclico que es un miembro seleccionado del grupo constituido por norbornanilo, norbornenilo, biciclo[2.2.2]octanilo, biciclo[3.2.1]octanilo, biciclo[3.3.0]octanilo, biciclo[2.2.2]oct-5-enilo, biciclo[2.2.2]oct-7-enilo, biciclo[3.3 1]nonanilo, ciclodecanilo y adamantanilo.

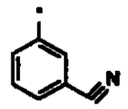
**5.2.2Restos $G^1$ subgenéricos representativos**

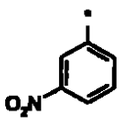
La presente invención se refiere además especialmente a un compuesto de fórmula (1.0.0) en la que se seleccionan particularmente $G^1$ y los sustituyentes $R^4$, $R^5$ y $R^6$ de tal manera que el término de la izquierda del citado compuesto de fórmula (1.0.0) está representado por las siguientes fórmulas parciales (2.0.1) a (2.0.72):

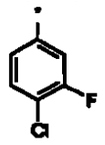

(2.0 1)

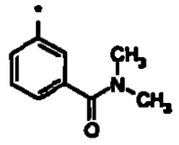

(2.0 2)

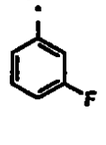

(2.0 3)

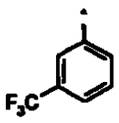

(2.0 4)

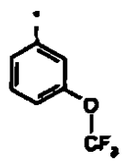

(2.0 5)

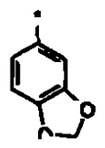

(2.0 6)

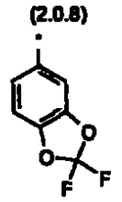

(2.0 7)

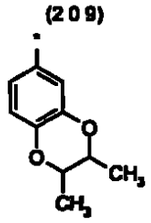

(2.0.8)

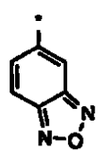

(2.0 9)

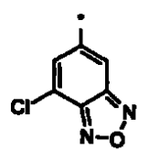

(2.0 10)

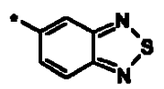

(2.0 11)

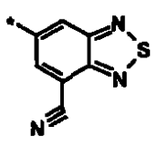

(2.0 12)

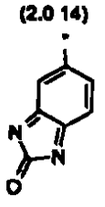

(2.0 13)

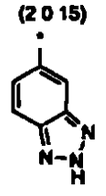

(2.0 14)

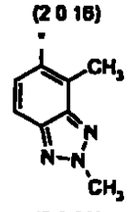

(2.0 15)

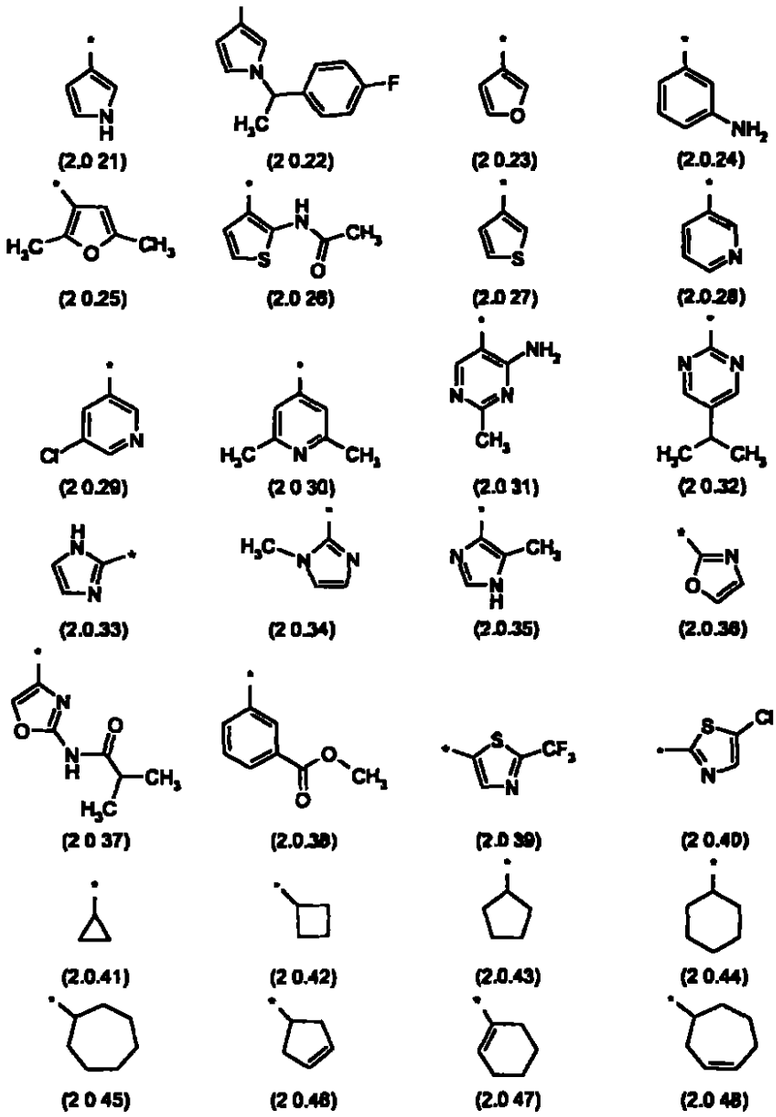

(2.0 16)

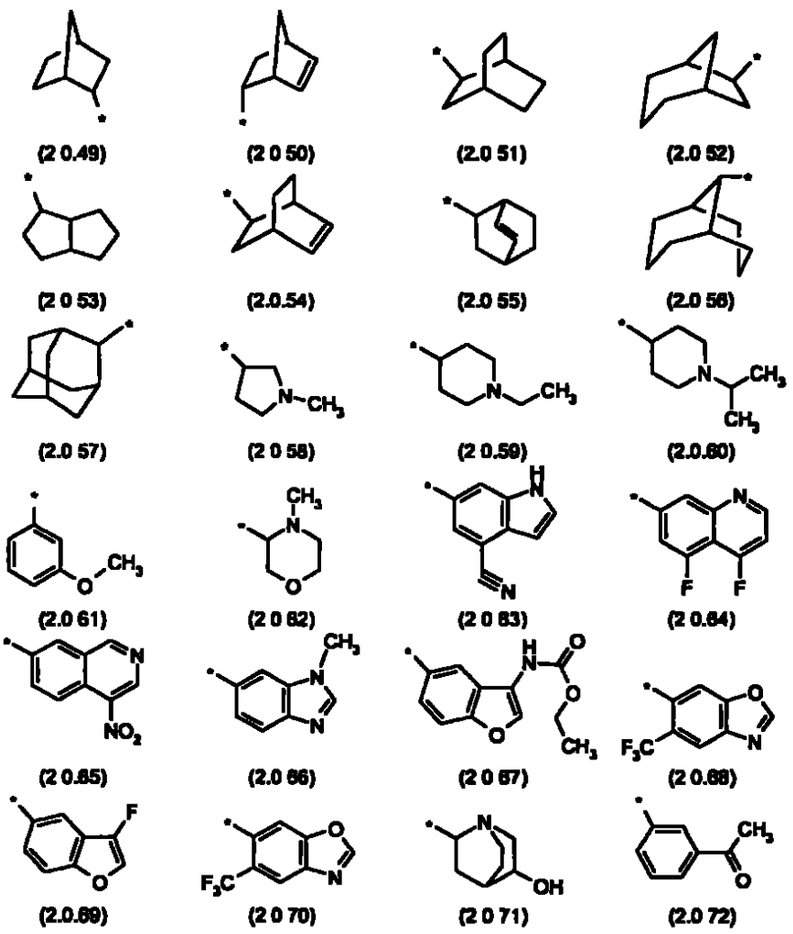

(2.0 17)


(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)

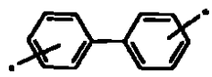

(2.0.49)
(2.0.50)
(2.0.51)
(2.0.52)
(2.0.53)
(2.0.54)
(2.0.55)
(2.0.56)
(2.0.57)
(2.0.58)
(2.0.59)
(2.0.60)
(2.0.61)
(2.0.62)
(2.0.63)
(2.0.64)
(2.0.65)
(2.0.66)
(2.0.67)
(2.0.68)
(2.0.69)
(2.0.70)
(2.0.71)
(2.0.72)

5

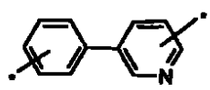
**5.3.0El resto $G^2$**

El resto $G^2$ es una de las características clave de los compuestos de fórmula (1.0.0), y es preferiblemente fenilo, pero puede sr también un resto biarilo. Como se utiliza en la presente descripción, el término "biarilo" incluye no sólo los grupos biarilo tradicionales como bifenilo, sino las variantes condensadas de éste, las variantes que contienen naftilo y contienen heteroátomos de éste, y las variantes benzhidrilo de éste. Los grupos biarilo que definen el resto $G^2$ comprenden así bifenilo (1.2.1); 3-fenilpiridina (1.2.2), ciclohexilbenceno (1.2.3); [2,2']-bipiridinilo (1.2.4); bicicloheхilo (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), 9H-carbazol (1.2.14); feniléter (1.2 15); 1H-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); 10H-fenotiazina (1.2.28), 2-fenilbenzoxazol (1.2.29); 2-

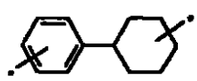
fenilbenzotiazol (1.2.30); 2-fenil-1H-bencimidazol (1.2.31) y 10,11-dihidro-5H-dibenzo[b,f]azepina (1.2.32), en los que los números entre paréntesis representan las fórmulas parciales correspondientes. Debe observarse que los puntos de unión en cada lado del resto biarilo se han ilustrado como no específicos, de modo que las fórmulas parciales pueden comprender variaciones dentro de cada resto que se consideran que están dentro del alcance de la presente invención:



(1.2.1)



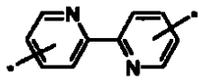

(1.2.2)



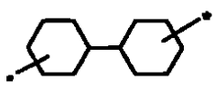
(1.2.3)

00275 271

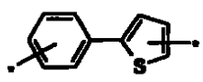




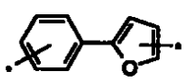
(1 2 4)



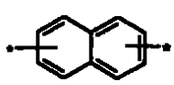
(1 2 5)



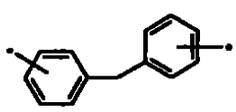
(1 2 6)



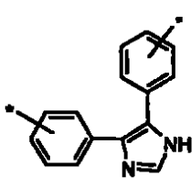
(1.2 7)



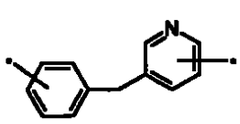
(1 2.8)



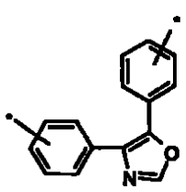
(1.2 9)



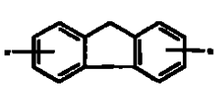
(1 2 10)



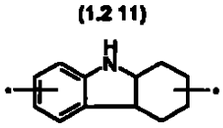
(1.2 11)



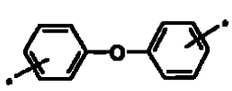
(1.2 12)



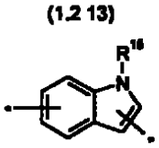
(1.2 13)



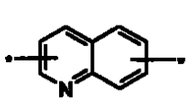
(1.2 14)



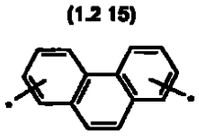
(1.2 15)



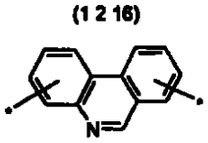
(1 2 16)



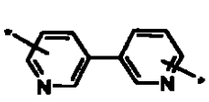
(1 2 17)



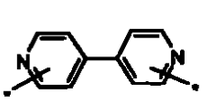
(1 2 18)



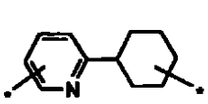
(1 2 19)



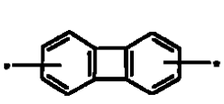
(1.2 20)



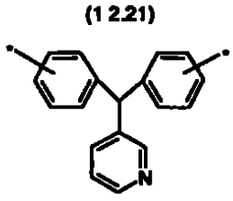
(1 2.21)



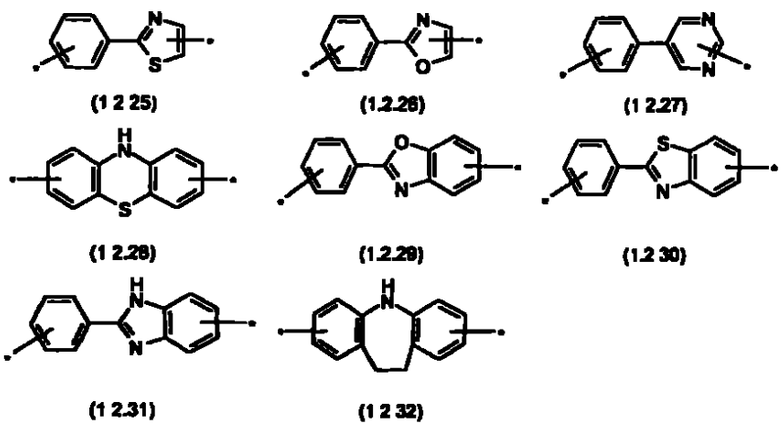
(1 2.22)



(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)

Los grupos anteriormente ilustrados de fórmulas parciales (1.2.1) a (1.2.39) que definen el resto $G^2$ están opcionalmente sustituidas con $R^1$ y $R^2$, pudiendo aparecer $R^1$ y $R^2$ individual o conjuntamente en cualquier anillo o anillos que comprenda un resto o parte componente de las fórmulas parciales (1.2.1) a (1.2.39) que definen $G^2$. $R^1$ y $R^2$ son cada uno un miembro seleccionado independientemente 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; $-NO_2$,

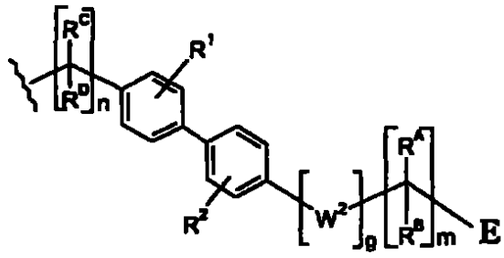
$-C(=O)NR^{12}R^{13}$; $-OC(=O)NR^{15}R^{12}$, $-NR^{14}C(=O)NR^{15}R^{12}$;

$-NR^{14}C(=NR^{14})NR^{15}R^{12}$; $-NR^{14}C(=NCN)NR^{15}R^{12}$; $-NR^{14}C(=N-NO_2)NR^{15}R_{12}$;

$-C(=NR^{14})NR^{15}R^{12}$; $-OC(=NR^{14})NR^{15}R^{12}$; $-OC(=N-NO_2)NR^{15}R^{12}$; $-NR^{15}R^{12}$; $-CH_2NR^{15}R^{12}$; $-NR^{14}C(=O)R^{12}$; $-NR^{14}C(=O)OR^{12}$; $=NOR^{12}$; $-NR^{14}S(=O)_pR^{13}$; y $-S(=O)_pNR^{12}R^{13}$; teniendo $R^{12}$, $R^{13}$, $R^{14}$ y $R^{15}$ los mismos significados definidos anteriormente.

**5.3.1 $G^2$ es bifenilo sustituido con $R^1$ y $R^2$**

El lado izquierdo de un compuesto de fórmula (1.0.0) tiene núcleos tiazolilamida y análogos con un engarce éter, tioéter o sulfonilo a un grupo fenilo sustituido; mientras que el lado derecho de un compuesto de fórmula (1.0.0) comprende realizaciones en las que $G^2$ tiene el significado de bifenilo que está sustituido con los sustituyentes $R^1$ y $R^2$. Preferiblemente, está presente un solo sustituyente, $R^1$ ó $R^2$, y el grupo bifenilo está sustituido en la posición 4 con el resto que contiene los sustituyentes $R^A$, $R^B$ y E. Este lado derecho preferido del compuesto de fórmula (1.0.0) puede representarse por la fórmula (1.0.4).



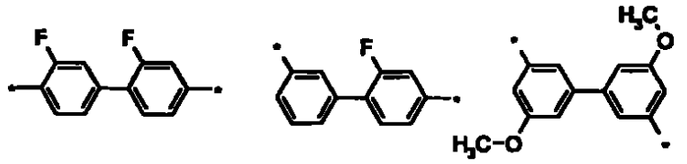
(1.0.4)

Cuando $R^1$ y/o $R^2$ son -H, no habrá ningún sustituyente en

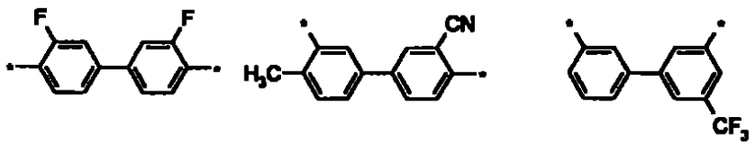
ninguna posición unido al resto del lado izquierdo de la molécula de fórmula (1.0.0). Dichas realizaciones no son tan preferidas como aquellos compuestos de la invención que tienen un sustituyente, especialmente un sustituyente en la posición 2 de cualquiera o ambos grupos fenilo que comprenden el resto 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; ó alquinilo ($C_2$-$C_4$).

Se prefiere tener un grupo halógeno en el punto de la molécula ocupado por el sustituyente $R^1$ ó $R^2$, puesto que habitualmente da como resultado una actividad inhibitoria mejorada. Se contempla como dentro del alcance de la presente invención que $R^1$ ó $R^2$ sea un grupo lipófilo pequeño que comprenda -Cl ó -F; -alquilo ($C_1$-$C_3$) clorado y/o fluorado, -alcoxi ($C_1$-$C_3$) clorado y/o fluorado.

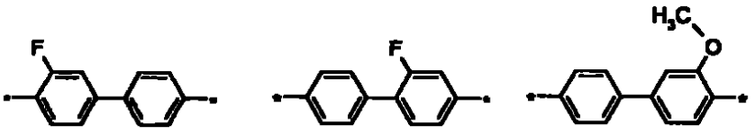
Consiguientemente, las realizaciones de la presente invención en las que el resto $G^2$ es bifenilo sustituido con $R^1$, y opcionalmente $R^2$, incluyen aquellas representadas por las fórmulas parciales (2.6.1) a (2.6.12):



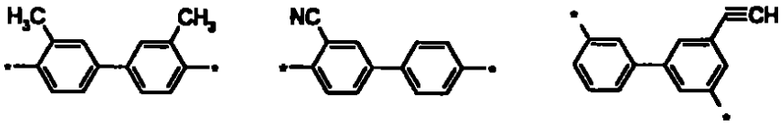
(2.6.1) (2.6.2) (2.6.3)



(2.6.4) (2.6.5) (2.6.6)



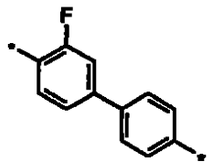
(2.6.7) (2.6.8) (2.6.9)



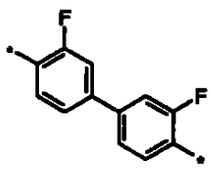
(2.6.10) (2.6.11) (2.6.12)

## 5.3.2$G^2$ en realizaciones específicas

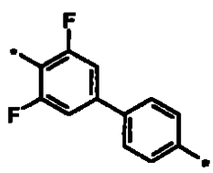
Las realizaciones de la presente invención pueden ilustrarse adicionalmente con respecto del resto $G^2$ y los sustituyentes $R^1$ y $R^2$, en las que $G^2$ tiene los significados preferidos de fenilo, ciclohexilo y piridilo, así como otros significados tales como bifenilo, por el término derecho de un compuesto de fórmula (1.0.0) representado por las siguientes fórmulas parciales (3.0.1) a (3.0.74):



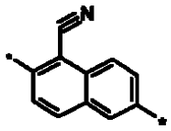

(301)



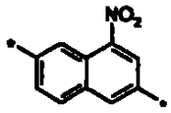

(3.0.2)



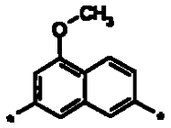

(303)



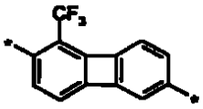
(3.0.4)



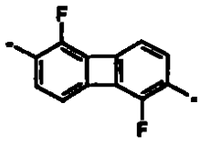
(3.0.5)



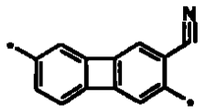
(3.0.6)



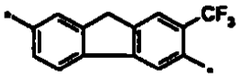
(3.0.7)



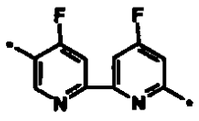
(3.0.8)



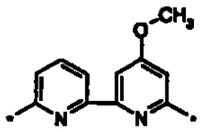
(3.0.9)



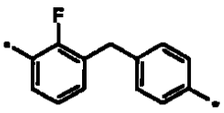
(3.0.10)



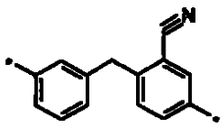
(3.0.11)



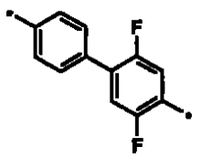
(3.0.12)



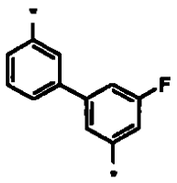
(3.0.13)



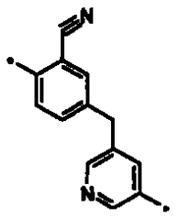
(3.0.14)



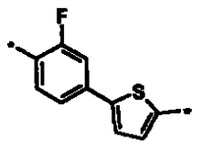
(3.0.15)



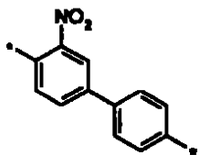
(3.0.16)



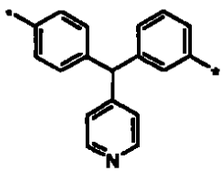
(3.0.17)



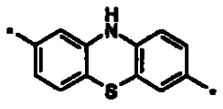
(3.0.18)



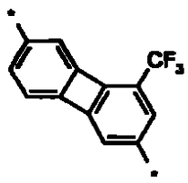
(3.0.19)



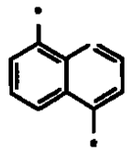
(3.0.20)



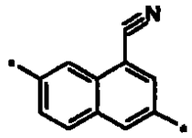
(3.0.21)



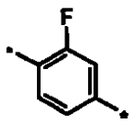
(3.0.22)



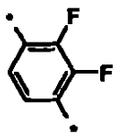
(3.0.23)



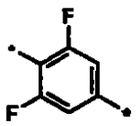
(3.0.24)



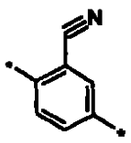
(3.0.25)



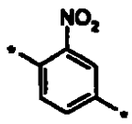
(3.0.26)



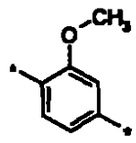
(3.0.27)



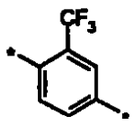
(3.0.28)



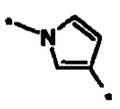
(3.0.29)



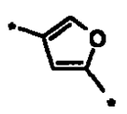
(3.0.30)



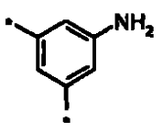
(3.0.31)



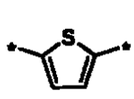
(3.0.32)



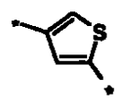
(3.0.33)



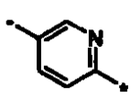
(3.0.34)



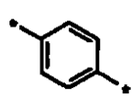
(3.0.35)



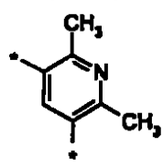
(3.0.36)



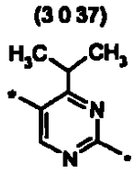
(3.0.37)



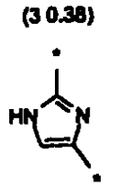
(3.0.38)



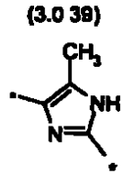
(3.0.39)



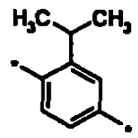
(3.0.40)



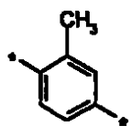
(3.0.41)



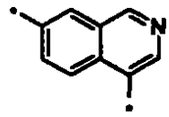
(3.0.42)



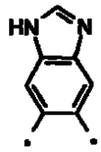
(3 0 64)



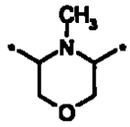
(3 0 65)



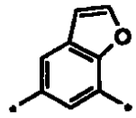
(3.0.66)



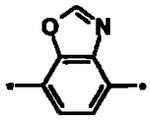
(3.0 67)



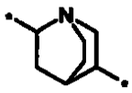
(3.0 68)



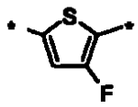
(3 0 69)



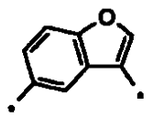
(3 0 70)



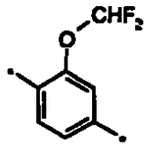
(3 0 71)



(3 0 72)



(3 0 73)



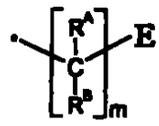
(3 0 74)

5

**5.4.0Los sustituyentes $R^A$ y $R^B$**

El grupo de fórmula parcial (1.0.4) anterior está sustituido en la posición 4 con un resto que contiene los sustituyentes E, $R^A$ y $R^B$, que puede estar representado por

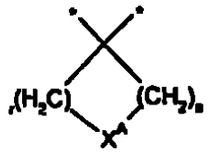
la fórmula parcial (1.1.15):



(1 1 15)

en la que m es 0, 1, 2 ó 3. 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 -$[R^A\text{-}C\text{-}R^B]_m$- y $R^A$ y $R^B$ son preferiblemente cada uno un miembro seleccionado independientemente del grupo constituido por -H; y alquilo ($C_1$-$C_4$).

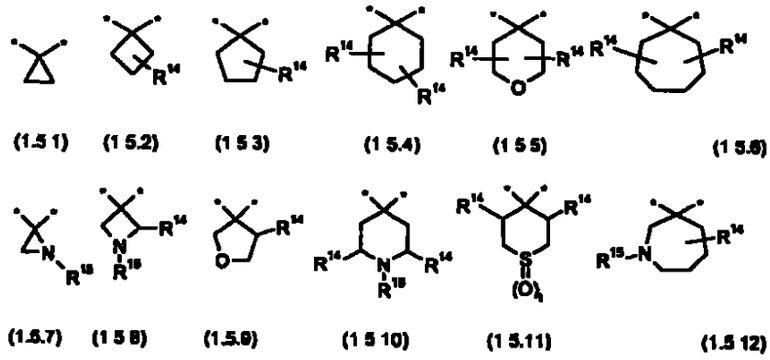
En otras realizaciones preferidas de la presente invención, $R^A$ y $R^B$ pueden tomarse conjuntamente, pero sólo en el caso en que m sea 1, para formar un resto espiro de fórmula (1.2.0):



(1 2 0)

en la que r y s son independientemente de 0 a 4, con la condición de que la suma de r+s sea al menos 1, pero no superior a 5; $X^A$ es $-CH_2$, $-CHR^{11}$ ó $-C(R^{11})_2$-, estando seleccionado cada $R^{11}$

independientemente de los demás y teniendo cada $R^{12}$ el mismo significado que se define en la presente descripción; $-NR^{15}-$, teniendo $R^{15}$ el mismo significado que se define en la presente descripción; -O-, ó $-S(=O)_t$, siendo t 0, 1 ó 2; y estando sustituido el citado resto espiro en uno cualquiera o más átomos de carbono de éste con 0 a 3 sustituyentes $R^{14}$, en un átomo de nitrógeno de éste con 0 ó 1 sustituyentes $R^{15}$, y en un átomo de azufre de éste con 0 ó 2 átomos de oxígeno. Consiguientemente, estos dan como resultado, entre otros, los restos ilustrados por las fórmulas parciales (1.5.1) a (1.5.12):




en las que t es 0, 1 ó 2; y $R^{14}$ y $R^{15}$ tienen el mismo significado que se define en la presente descripción.

Los significados preferidos del sustituyente $R^{14}$ incluyen -F; -Cl; =O; -OH; $-CH_3$; $-CH_2OH$; $-CH(CH_3)OH$; $-C(CH_3)_2OH$; $-OCH_3$, $-C(=O)OH$; $-C(=O)NH_2$; $-NH_2$; $-NHCH(CH_3)_2$;

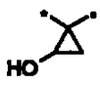
282



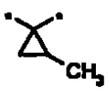
$-NHC(=O)CH_2$; $-NHC(=O)OCH_2CH_3$; $-NHS(=O)_2CH_3$ y $-S(=O)_2NH_2$, dando como resultado restos tales como los de fórmulas parciales (3.1.1) a (3.1.34):



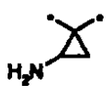

(3.1.1)




(3.1.2)



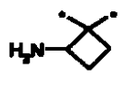

(3.1.3)




(3.1.4)



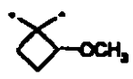

(3.1.5)



(3 1 6)



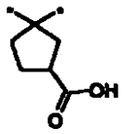
(3.1 7)



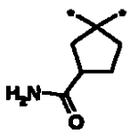
(3 1.8)



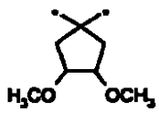
(3.1 9)



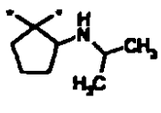
(3 1 10)



(3 1 11)



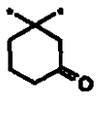
(3.1 12)



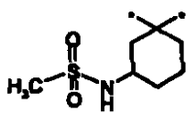
(3.1 13)



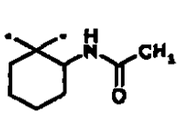
(3 1 14)



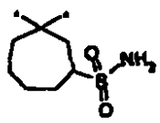
(3 1 15)



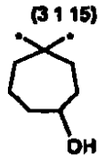
(3 1 16)



(3 1 17)



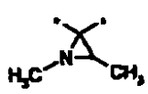
(3 1 18)



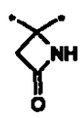
(3 1 19)



(3 1 20)



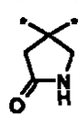
(3.1 21)



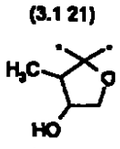
(3.1.22)



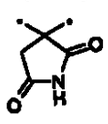
(3 1 23)



(3 1 24)



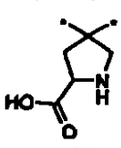
(3 1.25)



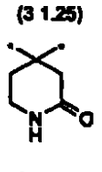
(3 1 26)



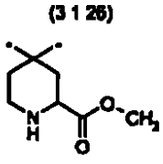
(3 1.27)



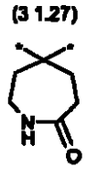
(3 1 28)



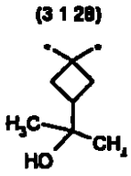
(3 1 29)



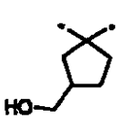
(3 1 30)



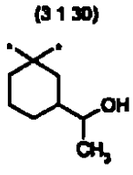
(3 1 31)



(3 1 32)



(3 1 33)



(3 1.34)

**5.4.1Los sustituyentes $R^C$ y $R^D$**

Como ya se ha descrito, $R^C$ y $R^D$ tienen el mismo significado que se definió anteriormente para $R^A$ y $R^B$, excepto que uno de ellos debe ser -H, y se seleccionan independientemente entre sí y de $R^A$ y $R^B$. Consiguientemente, todas las realizaciones particulares y preferidas de los compuestos de fórmula (1.0.0) detalladas anteriormente con respecto de los sustituyentes $R^A$ y $R^B$ son en su mayor parte también realizaciones particulares y preferidas de los compuestos de fórmula (1.0.0) con respecto de los sustituyentes $R^C$ y $R^D$

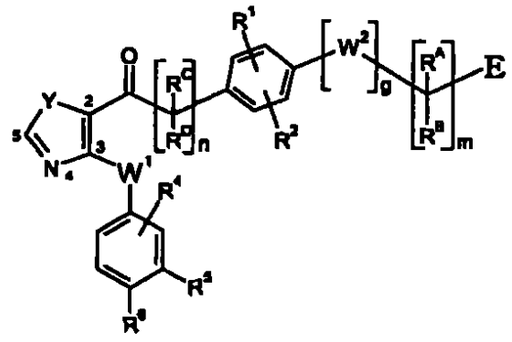
**5.5 El resto $-[N(R^3)]_j-$**

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 tiazolilamidas y amidas de estructura análoga. El sustituyente de átomo de nitrógeno $R^3$ se selecciona preferiblemente de -H; -alquilo ($C_1$-$C_3$); y -alcoxi ($C_1$-$C_3$), y más preferiblemente es -H; $-CH_3$ ó $-OCH_3$. En las realizaciones más preferidas de los compuestos de fórmula (1.0.0), $R^3$ tiene el significado de

-H.

Cuando $G^1$ tiene el significado preferido de fenilo; $G^2$

tiene el significado preferido de fenilo, ciclopentilo, ciclohexilo, piridilo, oxadiazolilo, tiadiazolilo, bifenilo, 3-fenilpiridina, ciclohexilbenceno, [2,2']-bipiridinilo o biciclohexilo, especialmente fenilo, ciclohexilo o 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 cetona. Esta estructura cetona de los compuestos de fórmula (1.0 0) se representa por la fórmula (1.0.7):



(107)

en la que todos los sustituyentes y componentes de ésta, es decir, E; $W^1$; $W^2$, 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 con detalle en la presente descripción, como cuando j es 1 y los compuestos son tiazolilamidas y amidas de estructura análoga.

**5.6.0E es un resto de fórmulas parciales (1.1.1)-(1.1.15)**

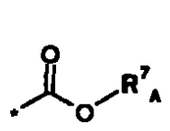
E es un miembro seleccionado del grupo de restos definidos por las fórmulas parciales (1.1.1) a (1.1.15) ilustradas anteriormente. Los restos de fórmulas parciales (1.1.1) a (1.1.5) que definen el grupo E son típicamente, pero no necesariamente, ácidos, amidas y grupos heterocíclicos que actúan como miméticos de ácido y amida, pero sin limitación a estos tipos de grupos funcionales. Los restos de fórmulas parciales (1.1.6) a (1.1.9) que definen el grupo E son típicamente, pero no necesariamente, alcoholes terciarios y sus miméticos, especialmente restos análogos acilo y nitrilo, pero sin limitación a estos tipos de grupos funcionales. Los restos de fórmulas parciales (1.1.10) a (1.1.15) que definen el grupo E son típicamente, pero no necesariamente, amidas inversas y sus miméticos, pero sin limitación a estos tipos de grupos funcionales. Pueden emplearse otros restos como los descritos en la presente descripción en el lado derecho de los compuestos de fórmula (1.0.0). Estos restos son bioisósteros en tanto que permiten alcanzar a los compuestos de fórmula (1.0.0) que los contienen una inhibición de PDE4 esencialmente equivalente a la alcanzada por otros restos, especialmente restos ácido, amida, alcohol y amida inversa.

Consiguientemente, E es un miembro seleccionado del grupo de restos definido por las fórmulas parciales (1.1.1) a

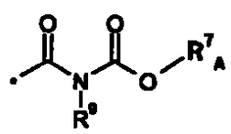
(1.1.15), y los citados restos incluyen los sustituyentes $R^7_A$, $R^7_B$ y $R^7_C$, así como $R^7_B$, $R^9$, $R^{16}$ y $R^{17}$, y en el caso de las fórmulas parciales (1.1.15), el resto está constituido por un sistema de anillo heterocíclico que contiene nitrógeno. Todos los restos de fórmulas parciales (1.1.1) a (1.1.15) están unidos a la parte restante de fórmula (1.0.0).

**5.6.1E es un resto de fórmulas parciales (1.1.1), (1.1.2) ó (1.1.3)**

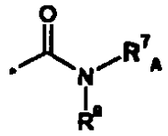
Las realizaciones de la presente invención en las que la definicion del grupo E está ilustrada por las fórmulas parciales (1.1.1), (1.1.2) y (1 1.3) son las siguientes:



(1 1 1)



(1 1 2)



(1 1 3)

Uno de una serie de restos preferidos para definir el grupo E es el de fórmula parcial (1.1.1), en la que $R^7_A$ tiene el significado de -H, que es un significado preferido de este sustituyente. Cuando $R^7_A$ es hidrógeno y m es 1, 2, ó 3 en la fórmula (1.0.0), dan como resultado un simple ácido carboxílico -COOH, y el grupo se convierte en un ácido alcanoico inferior.

$R^{10}$ es un sustituyente opcional de los restos que definen $R^7_A$, y puede haber hasta tres de dichos sustituyentes cuando

están presentes. El significado del sustituyente $R^{10}$ incluye fenilo o piridilo, estando a su vez el citado fenilo o piridilo sustituido con hasta 3 sustituyentes $R^{11}$, siendo $R^{11}$ -F, -Cl, -CN, $-NO_2$, -OH,

-alcoxi ($C_1$-$C_3$), -alquilo ($C_1$-$C_3$) ó $-NR^{16}R^{17}$. En las realizaciones preferidas que incluyen dicha sustitución $R^{11}$, habrá 1 ó 2 sustituyentes $R^{11}$ que tienen el significado de -F, -Cl, $-CH_3$, $-OCH_3$, -OH, -CN ó $-N(CH_3)_2$. Preferiblemente, existen 0 ó 1 de dichos sustituyentes $R^{11}$, y cuando está presente es -F ó -Cl. El significado del sustituyente $R^{10}$ incluye además -F, -Cl, $-CF_3$, oxo (=O),

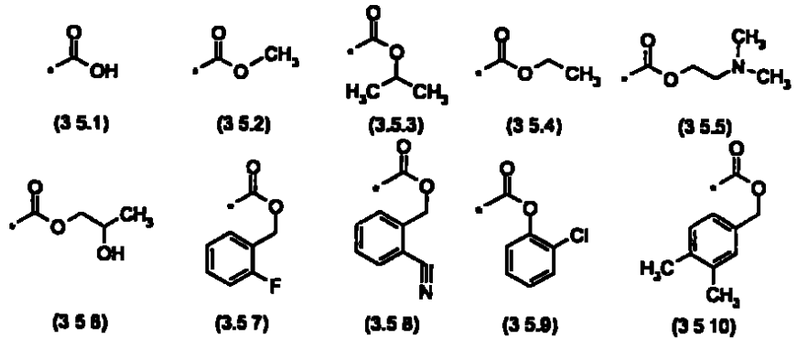
$-OR^{16}$, $-NO_2$, -CN, $-C(=O)OR^{16}$, $-O-C(=O)R^{16}$, $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$,

$-NR^{16}S(=O)_2R^{17}$ ó $-S(=O)_2NR^{16}R^{17}$.

Los subsustituyentes $R^{16}$ 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. Los citados grupos alquilo, alquenilo, cicloalquilo, fenilo, bencilo o piridilo están a su vez opcionalmente sustituidos con hasta 3 sustituyentes -F, -Cl ó -CN. Entre los significados adicionales anteriormente enumerados de $R^{10}$, se prefiere que el sustituyente $R^{10}$, cuando está presente, sea piridilo opcionalmente sustituido con -F, -Cl, $-OCH_3$, -CN, $-NO_2$ ó

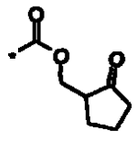
-$NR^{16}R^{17}$, siendo $R^{16}$ y $R^{17}$ independientemente -H ó $-CH_3$; o que el sustituyente $R^{10}$, cuando está presente, sea -F, -Cl, $-CF_3$, -CN, $-NO_2$, $-C(=O)OR^{16}$ ó $-NR^{16}R^{17}$, siendo $R^{16}$ y $R^{17}$ independientemente -H ó $-CH_3$.

Estas y otras realizaciones preferidas de los compuestos de fórmula (1.0.0) que comprenden los restos de fórmula parcial (1.1.1) basada en los significados preferidos de $R^7_A$ y $R^9$ como se describieron anteriormente incluyen, entre otros, los siguientes grupos ilustrados por las fórmulas parciales (3.5.1) a (3.5.15):

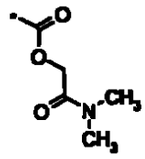


(3.5.1) (3.5.2) (3.5.3) (3.5.4) (3.5.5)

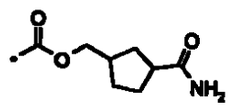
(3.5.6) (3.5.7) (3.5.8) (3.5.9) (3.5.10)



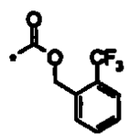
(3 5.11)



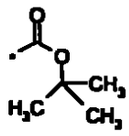
(3 5 12)



(3.5 13)



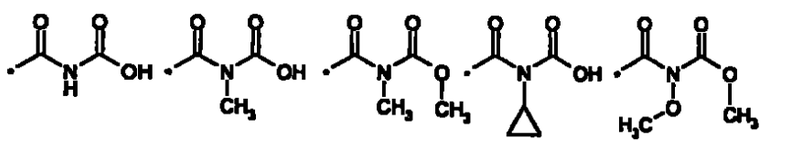
(3.5.14)



(3 5 15)

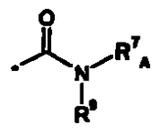
El grupo E está representado por la fórmula parcial (1.1.2), en la que el átomo de nitrógeno está sustituido con $R^9$, teniendo $R^9$ el significado de -H; -alquilo ($C_1$-$C_4$); -cicloalquilo ($C_3$-$C_7$); fenilo, bencilo, $-C(=O)OR^{16}$, $-C(=O)R^{16}$; $-OR^{16}$, -alquil ($C_1$-$C_2$)-$OR^{16}$; ó -alquil ($C_1$-$C_2$)-$C(=O)OR^{16}$, en las que $R^{16}$ es -H ó -alquilo ($C_1$-$C_4$). $R^{16}$ es preferiblemente -H ó $-CH_3$.

Consiguientemente, las realizaciones de la presente invención en las que el grupo E está representado por la fórmula parcial (1.1.2) pueden ilustrarse de la siguiente manera por las fórmulas parciales (4.1.1) a (4.1.5):



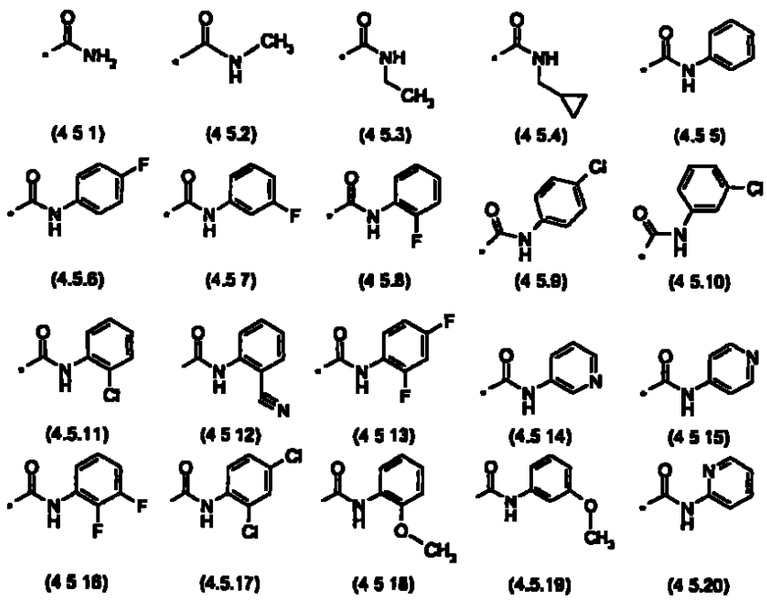
(4 1 1) (4 1 2) (4 1.3) (4 1.4) (4 1 5)

Aquellas realizaciones en las que la definición de E es la de un grupo amida están ilustradas por la fórmula parcial (1.1.3):



(1.1.3)

Estas y otras realizaciones preferidas de los compuestos de fórmula (1.0.0) que comprenden restos de fórmula parcial (1.1.3), basada 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)

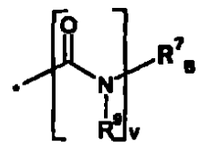
(4.5.6) (4.5.7) (4.5.8) (4.5.9) (4.5.10)

(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)

**5.6.2E 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 la que el resto E terminal entra dentro del alcance de la fórmula parcial (1.1.4), es decir, las realizaciones de este tipo están comprendidas dentro del alcance del resto E cuando tiene el significado de la fórmula parcial (1.1.4).

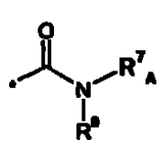


(1.1.4)

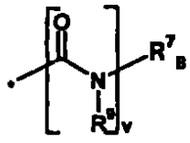
en la que $R^7_E$ es un heterociclo monocíclico o bicíclico que es un miembro seleccionado del grupo constituido por tetrazol-5-ilo; 1,2,4-triazol-3-ilo; 1,2,4-triazol-3-on-5-ilo, 1,2,3-triazol-5-ilo; imidazol-2-ilo; imidazol-4-ilo; imidazolidin-2-on-4-ilo; 1,2,4-oxadiazol-3-ilo; 1,2,4-oxadiazol-5-on-3-ilo; 1,2,4-oxadiazol-5-ilo; 1,2,4-oxadiazol-3-on-5-ilo; 1,3,4-oxadiazolilo; 1,3,4-oxadiazol-2-on-5-ilo; oxazolilo; isoxazolilo; pirrolilo; pirazolilo; succinimidilo; glutarimidilo; pirrolidonilo; 2-piperidonilo; 2-piridonilo; 4-piridonilo; piridazin-3-onilo; piridazin-3-onilo; tiazolilo; isotiazolilo; tiadiazolilo; morfolinilo; paratiazinilo;

pirıdılo; pirimidınılo; pırazınılo; pırıdazinilo; indolilo; ındolinilo; isoındolınilo; benzo[b]furanılo; 2,3-dihıdrobenzofuranılo; 1,3-dihıdroısobenzofuranılo; 2H-1-benzopıranılo; 2-H-cromenılo; cromanilo; benzotıenilo; 1H-ındozalilo, bencimidazolilo; benzoxazolılo; benzoısoxazolılo, benzotıazolılo; benzotrıazolilo; benzotriazınılo; ftalazinilo; 1,8-naftırıdınılo; quınolınılo; isoquınolınılo; quınazolınılo; quınoxalınılo; pırazolo[3,4-d]pirımıdınılo; pırımıdo[4,5-d]pırımıdınilo, ımıdazo[1,2-a]pırıdınılo; pırıdopırıdinılo, pterıdınılo, y 1H-purınılo.

Las fórmulas parcıales (1.1.3) y (1.1.4) son sımılares y debe observarse la dıferencıa entre ellas. Las fórmulas parcıales (1.1.3) y (1 1.4) son las sıguıentes:



(1 1 3)



(1 1.4)

Cuando v es 0, $R^7_B$ está enlazado de manera directa a la parte restante de un compuesto de fórmula (1.0.0) y es, consiguientemente, fácilmente diferenciable de un resto de fórmula parcıal (1.1.3) en la que $R^7_A$ está unıdo a la parte restante de un compuesto de fórmula (1.0.0) a través de un resto puente de amıda $-C(=O)NR^9-$. Cuando v es 1, por otro lado, ambos restos $R^7_B$ y $R^7_A$ están unıdos a la parte restante de un compuesto

de fórmula (1.0.0) a través del resto puente de 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 $R^7_A$ y $R^7_B$. Esta diferencia se ha descrito ya anteriormente con detalle.

Para facilitar la siguiente descripción, se tratan conjuntamente en primer lugar los restos heterocíclicos monocíclicos y los restos heterocíclicos bicíclicos y después se discuten como grupos separados.

Uno cualquiera o más de los átomos de carbono del resto fenilo, bencilo o heterociclilo está sustituido con 0 a 3 sustituyentes $R^{14}$, teniendo $R^{14}$ los significados y significados preferidos ya descritos anteriormente con respecto a las fórmulas parciales (1.1.1), (1.1.2) y (1.1.3). Uno cualquiera o más de los átomos de nitrógeno, que se observará que aparecen sólo en el caso de restos heterocíclicos, y que no sean un punto de unión del citado resto heterociclilo, están opcionalmente sustituidos con hasta 3 sustituyentes $R^{15}$. Cualquier átomo de azufre que aparezca en un resto heterociclilo que no sea un punto de unión del citado resto heterociclilo, está sustituido con 0, 1 ó 2 átomos de oxígeno.

El sustituyente heterocíclico en nitrógeno opcional $R^{15}$

comprende -H; $-C(=O)R^{16}$; $-OR^{16}$, preferiblemente $-OCH_3$; -alquil $(C_1-C_4)-OR^{16}$; $-C(=O)OR^{16}$; -alquil $(C_1-C_2)-C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$; -alquilo $(C_1-C_4)$, preferiblemente $-CH_3$; -alquenilo $(C_2-C_4)$; $-(CH_2)_u$-cicloalquilo $(C_3-C_7)$, siendo u 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 opcionalmente sustituidos con hasta 2 sustituyentes $R^{12}$.

El subsustituyente $R^{12}$ comprende -F, -Cl; $-CO_2R^{18}$; $-OR^{16}$; -CN; $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$, $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, siendo p 1 ó 2, preferiblemente 2; -alquilo $(C_1-C_4)$, preferiblemente $-CH_3$; y -alcoxi $(C_1-C_4)$, teniendo $R^{12}$ el significado de $-OR^{16}$ anterior y estando definido $R^{16}$ como -alquilo $(C_1-C_4)$, y siendo preferiblemente $R^{12}$ $-OCH_3$; estando a su vez el citado alquilo y alcoxi opcionalmente sustituidos con hasta 3 sustituyentes -F, -Cl; -alcoxi $(C_1-C_2)$carbonilo; -alquil $(C_1-C_2)$carbonilo; y -alquil $(C_1-C_2)$carboniloxi. Los sustituyentes $R^{18}$ y $R^{19}$ se seleccionan independientemente de -H; -alquilo $(C_1-C_2)$, preferiblemente $-CH_3$; ó fenilo; y están opcionalmente sustituidos con hasta 3 -F ó -Cl.

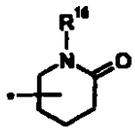
No se muestran sustituyentes $R^9$ en las fórmulas parciales

(1.4.1) a (1.4.20) anteriores, ni tampoco a continuación, debido a que el sustituyente $R^9$ está unido sólo a un átomo de nitrógeno que no forma parte componente integral 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 ha destacadodo también la distinción entre los sustituyentes $R^9$ y $R^{15}$, ambos de los cuales están unidos sólo a átomos de nitrógeno en cualquiera de los significados del resto E. El sustituyente $R^{15}$ está unido sólo a un átomo de nitrógeno que sea una parte componente integral de cualquier resto heterocíclico que pueda definirse mediante el sustituyente $R^7$, de la fórmula parcial (1.1.4), y en particular, con referencia a los restos heterocíclicos más específicos de fórmulas parciales (1 4.1) a (1.4.20), mostradas anteriormente así como a continuación. El sustituyente $R^9$, por otro lado, está unido sólo a un átomo de nitrógeno que está a su vez unido a, pero no es parte componente integral de, cualquiera de los restos heterocíclicos que están definidos por 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 los citados átomos de nitrógeno pueden estar presentes en cualquier resto que entre

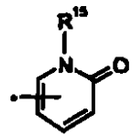
dentro del alcance de la fórmula parcial (1.1.4) que pueda caracterizarse por que contiene o comprende un resto heterocíclico que contiene nitrógeno.

Como ilustración de las realizaciones subgenéricas preferidas de la presente invención, en las que el grupo E tiene el significado de un resto que entra dentro del alcance de la fórmula parcial (1.1.4), se indican a continuación los grupos de fórmulas parciales (1 4.1) a (1.4.28):



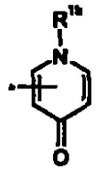
2-pipendonilo

(1 4 21)



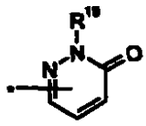
2-piridonilo

(1.4.22)



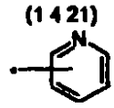
4-piridonilo

(1.4.23)



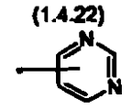
piridazin-3-onilo

(1.4.24)



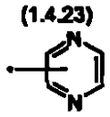
piridilo

(1.4.25)



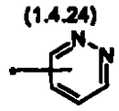
pirimidinilo

(1.4.26)



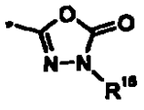
pirazinilo

(1 4.27)



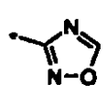
piridazinilo

(1.4 28)



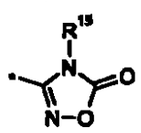
1,3,4-oxadiazol-2-on-5-ilo

(1.4 9)



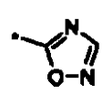
1,2,3-oxadiazol-3-ilo

(1.4 10)



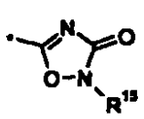
1,2,4-oxadiazol-5-on-3-ilo

(1 4 11)



1 2,4-oxadiazol-5-ilo

(1.4 12)



1 2 4-oxadiazol-3-on-5-ilo

(1.4 13)



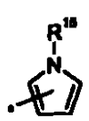
oxazolilo

(1 4 14)



isoxazolilo

(1 4 15)



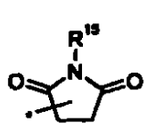
pirrolilo

(1.4 16)



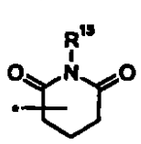
pirazolilo

(1 4 17)



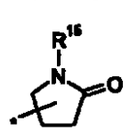
succinimidilo

(1 4 18)



glutarimidilo

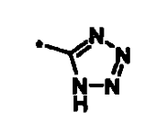
(1 4 19)

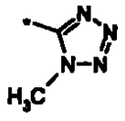


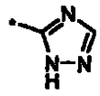
pirrolidinilo

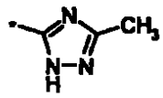
(1 4.20)

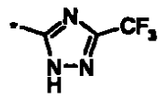
Para proporcionar otra demostración de las realizaciones preferidas de los compuestos de fórmula (1.0.0) con referencia el grupo E, cuando es un resto de fórmula parcial (1.1.4) y v es 0 ó 1, y $R^7_B$ es un grupo heterocíclico monocíclico, se indican a continuación los grupos constituyentes de fórmulas parciales (4.8.1) a (4.8.80) de los que se selecciona el resto E en dichas realizaciones preferidas:

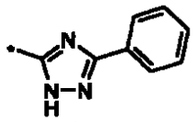

(4.8.1)

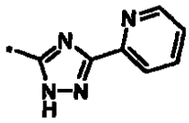

(4.8.2)

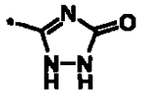

(4.8.3)

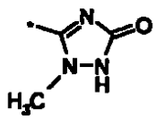

(4.8.4)

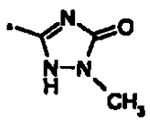

(4.8.5)

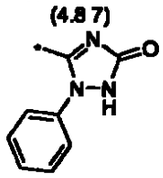

(4.8.6)

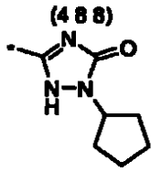

(4.8.7)

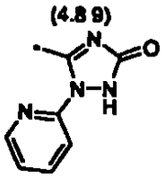

(4.8.8)

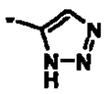

(4.8.9)


(4.8.10)

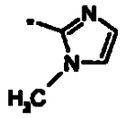

(4.8.11)


(4.8.12)


(4.8.13)

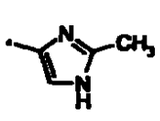

(4.8.14)


(4.8.15)

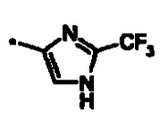

(4.8.16)



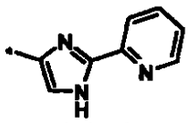
(4.8.17)



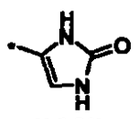
(4.8 18)



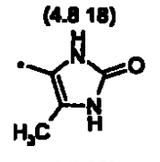
(4.8 19)



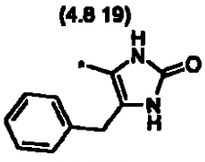
(4.8.20)



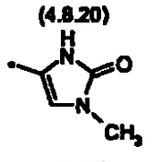
(4.8 21)



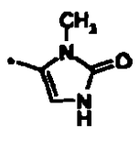
(4.8 22)



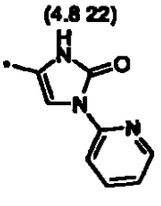
(4.8 23)



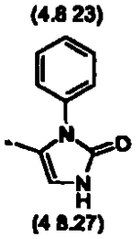
(4.8.24)



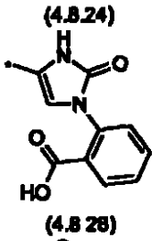
(4.8.25)



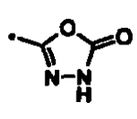
(4.8 26)



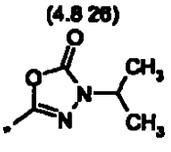
(4.8.27)



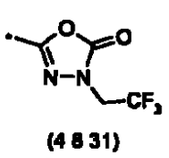
(4.8 28)



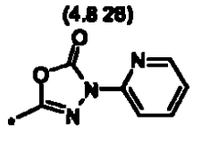
(4.8.29)



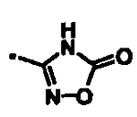
(4.8 30)



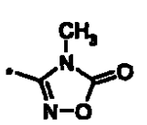
(4 8 31)



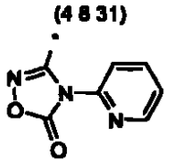
(4.8 32)



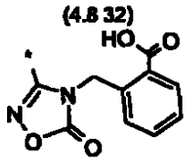
(4 8 33)



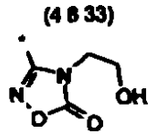
(4 8 34)



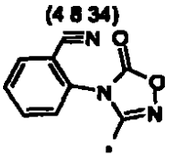
(4 8 35)



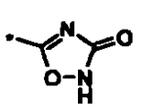
(4 8.36)



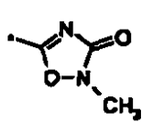
(4.8.37)



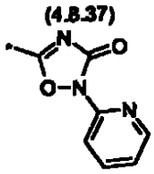
(4 8 38)



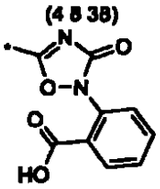
(4 8.39)



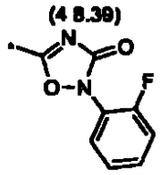
(4 8 40)



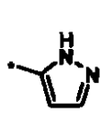
(4 8 41)



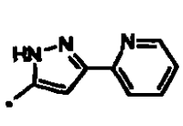
(4 8.42)



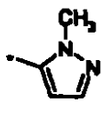
(4.8 43)



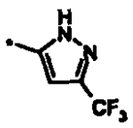
(4.8 44)



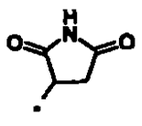
(4.8.45)



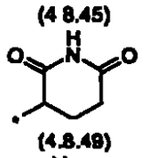
(4.8.46)



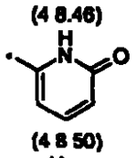
(4.8.47)



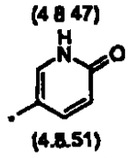
(4.8.48)



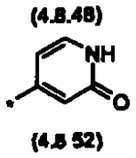
(4.8.49)



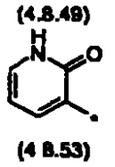
(4.8.50)



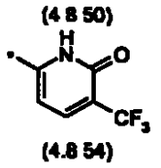
(4.8.51)



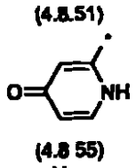
(4.8.52)



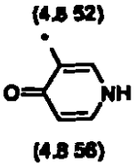
(4.8.53)



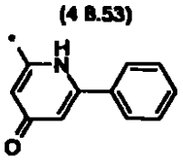
(4.8.54)



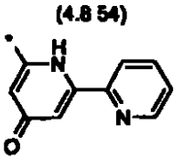
(4.8.55)



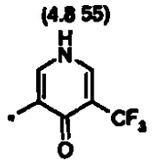
(4.8.56)



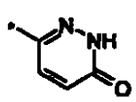
(4.8.57)



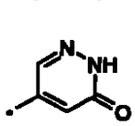
(4.8.58)



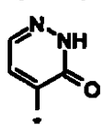
(4.8.59)



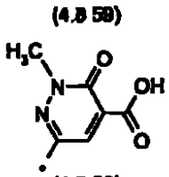
(4.8.60)



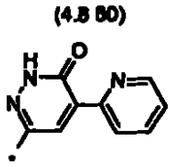
(4.8.61)



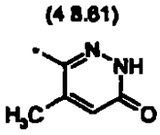
(4.8.62)



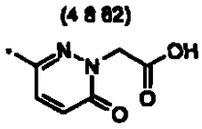
(4.8.63)



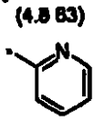
(4.8.64)



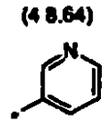
(4.8.65)



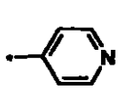
(4.8.66)



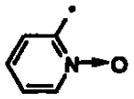
(4.8.67)



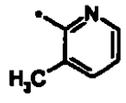
(4.8.68)



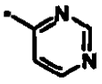
(4.8.69)



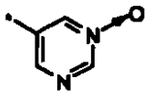
(4.8.70)



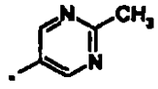
(4.8.71)



(4.8.72)



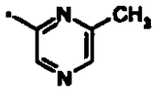
(4.8.73)



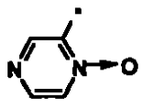
(4.8.74)

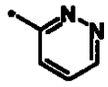


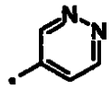
(4.8.75)

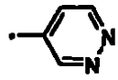


(4.8.76)


(4.8.77)


(4.8.78)

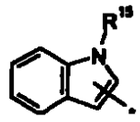

(4.8.79)


(4.8.80)

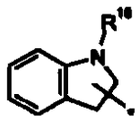
Las realizaciones preferidas de la presente invención en las que el grupo E es un resto de fórmula parcial (1.1.4) y v es 0 ó 1 incluyen también aquellas en las que el resto $R^7_s$ es un grupo heterocíclico bicíclico seleccionado del grupo constituido por indolilo; indolinilo; isoindolinilo; benzo[b]furanilo, 2,3-dihidrobenzofuranilo; 1,3-dihidroisobenzofuranilo, 2H-1-benzopiranilo; 2H-cromenilo; cromanilo, benzotienilo; 1H-indazolilo, bencimidazolilo; benzoxazolilo; benzoisoxazolilo; benzotiazolilo; benzotriazolilo; benzotriazinilo; ftalazinilo; 1,8-naftiridinilo, quinolinilo; isoquinolinilo; quinazolinilo, quinoxalinilo, pirazolo[3,4-d]pirimidinilo; pirimido[4,5-d]pirimidinilo; imidazo[1,2-a]piridinilo; piridopiridinilo; pteridinilo y 1H-purinilo.

Para proporcionar una demostración adicional más de las realizaciones preferidas de los compuestos de fórmula (1.0.0) con respecto al grupo E cuando es un resto de fórmula parcial

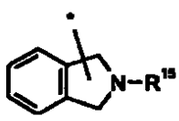
(1.1.4), v es 0 ó 1, y es un grupo heterocíclico bicíclico, se indican a continuación los grupos constituyentes de fórmulas parciales (5.0.1) a (5.0.28) de las cuales se selecciona el resto E en dichas realizaciones preferidas:



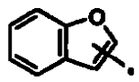
indolilo
(5.0 1)



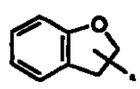
indolinilo
(5.0 2)



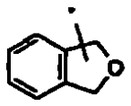
isoindolinilo
(5.0.3)



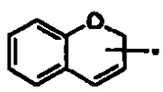
benzo[b]furanilo
(5 0.4)



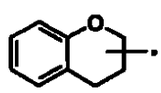
2,3-dihidro-benzofuranilo
(5 0 5)



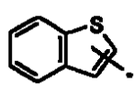
1,3-dihidroisobenzo-furanilo, ftalanilo
(5.0.6)



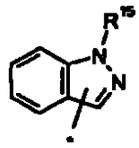
2H-1-benzopiranilo
(5 0 7)



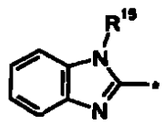
cromanilo
(5.0 8)



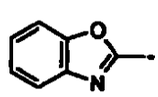
benzotienilo
(5.0 9)



1H-indazolilo
(5 0 10)

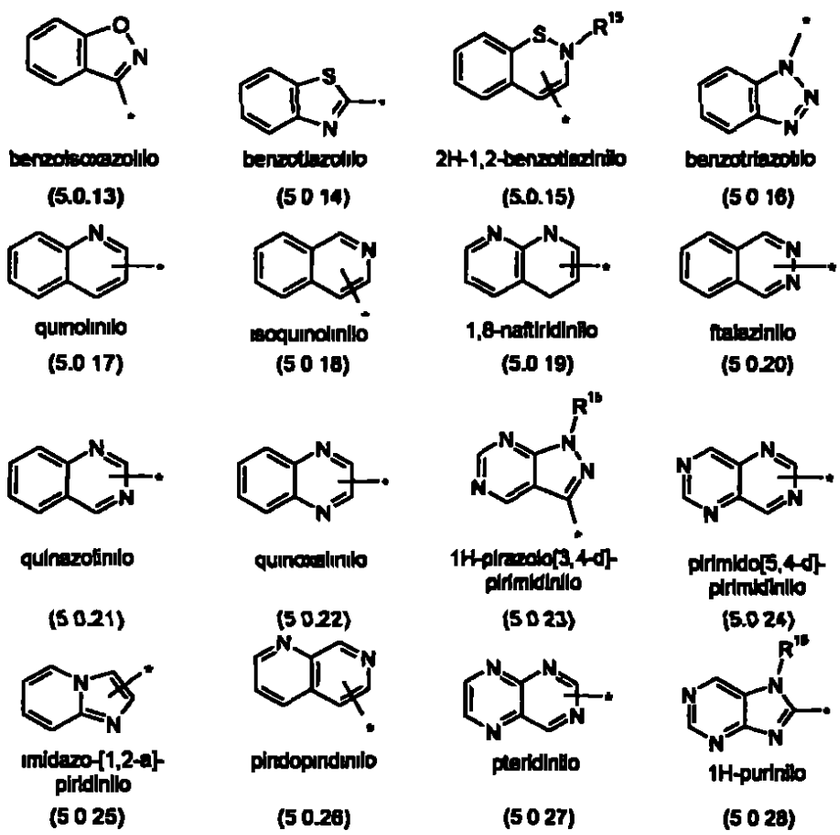


bencimidazolilo
(5 0 11)



benzoxazolilo
(5 0 12)

5

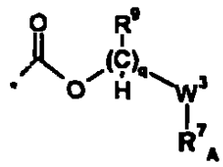



en las que "*" indica el punto de unión de la parte restante de

fórmula (1.0.0); y en las que cada átomo de carbono está opcionalmente sustituido con un sustituyente $R^{14}$; teniendo $R^{14}$ y $R^{15}$ el mismo significado que se definió anteriormente; y todas las formas tautoméricas, y opcionalmente formas N-óxido de estas.

**5.6.3E es un resto de fórmula parcial (1.1.5)**

Existen realizaciones adicionales de los compuestos de fórmula (1.0.0) en las que el resto E comprende un grupo que entra dentro del alcance de la fórmula parcial (1.1.5):



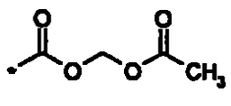
(115)

en la que q es 1, 2, ó 3, con la condición de que cuando q es 2 ó 3, $R^9$ tiene el significado de -H al menos en un caso, o en dos casos, respectivamente; $W^3$ es -O-, $-N(R^9)-$, ó $-OC(=O)-$, teniendo $R^9$ el mismo significado que se definió anteriormente; y teniendo $R^7$ el mismo significado que se definió anteriormente.

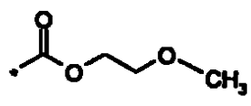
En realizaciones preferidas de los compuestos de fórmula parcial (1.1.5), q es 1 ó 2, $R^9$ es -H ó $-CH_3$, $W^3$ es -O-, $-O(C=O)-$ ó -NH-; y $R^7_A$ es uno de los restos preferidos ya descritos

anteriormente.

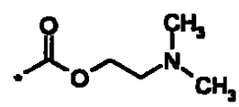
Las realizaciones representativas de los compuestos de fórmula (1.0.0) en la que el resto E entra dentro del alcance de la fórmula parcial (1.1.5) son aquellas ilustradas por las fórmulas parciales (6.0.1) a (6.0.6):



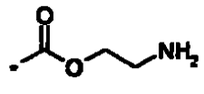
(6.0.1)



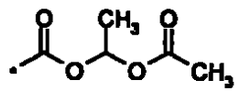
(6.0.2)



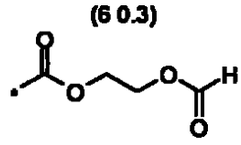
(6.0.3)



(6.0.4)



(6.0.5)



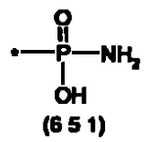
(6.0.6)

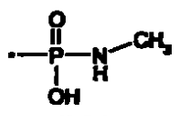
**5.6.4E es distinto de un ácido carboxílico**

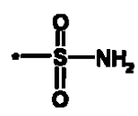
Las realizaciones de los compuestos de fórmula (1.0.0) incluyen aquellas en las que el resto E es distinto de un ácido carboxílico y es, en cambio, un ácido de fósforo o azufre o un derivado de estos. Existe un número significativo de dichos derivados de los que puede seleccionarse el resto E, e incluyen 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); $-O-S(=O)_2OH$ (sulfúrico); $-S(=O)_2OH$ (sulfónico); $-S(=O)_2NHR^{26}$ ó

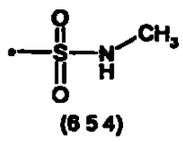
$-NHS(=O_2)R^{26}$ (sulfonamido), siendo $R^{26}$ $-CH_3$, $-CF_3$ ó o-tolulo; y acilsulfonamido seleccionado del grupo constituido por $-C(=O)NHS(=O)_2R^{25}$; $-C(=O)NHS(=O)_2NH_2$; $-C(=O)NHS(=O_2)$alquilo $(C_1-C_4)$, $-C(=O)NHS(=O)_2NH$alquilo $(C_1-C_4)$; $-C(=O)NHS(=O)_2N[$alquilo $(C_1-C_4)]_2$; $-S(=O)_2NHC(=O)$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=O)NH_2$; $-S(=O)_2NHC(=O)NH$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=O)N[$alquilo $(C_1-C_4)]_2$, $-S(=O)_2NHC(=O)R^{25}$; $-S(=O)_2NHCN$; $-S(=O)_2NHC(=S)NH_2$; $-S(=O)_2NHC(=S)NH$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=S)N[$alquilo $(C_1-C_4)_2]$; y $-S(=O)_2NHS(=O)_2R^{25}$; siendo $R^{25}$ $-H$; -alquilo $(C_1-C_4)$; fenilo ó $-OR^{16}$, teniendo $R^{16}$ el mismo significado que se definió anteriormente.

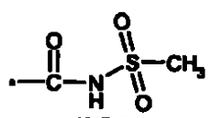
Las realizaciones preferidas de los compuestos de fórmula (1.0.0), en la que E es un ácido de fósforo o azufre o un derivado de estos, son aquellas en las que E es $-P(=O)(OH)NHR^{25}$ (fosforamido sustituido); $-S(=O)_2NHR^{26}$ ó $-NHS(=O_2)R^{26}$ (sulfonamido), ó $-C(=O)NHS(=O)_2R^{25}$ (acilsulfonamido); en los que $R^{26}$ y $R^{25}$ tienen el mismo significado que se definió anteriormente. Algunas de estas realizaciones preferidas pueden ilustrarse con las fórmulas parciales (6.5.1) a (6.5.9):

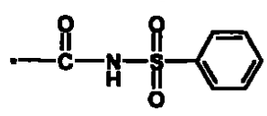

(6 5 1)

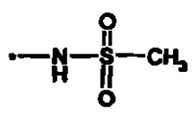

(6 5.2)

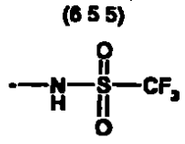

(6 5.3)

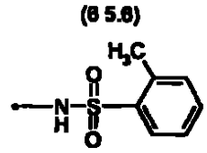

(6 5 4)


(6 5 5)


(6 5.6)

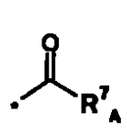

(6 5 7)

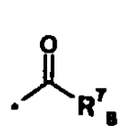

(6 5.8)

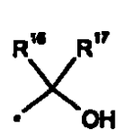

(6 5 9)

## 5.6.5 E es un resto de fórmulas parciales (1.1.6) a (1.1.9)

Existen realizaciones adicionales de los compuestos de fórmula (1.0 0) en las que el resto E comprende un grupo que entra dentro del alcance de las fórmulas parciales (1.1.6) a (1.1.9):


(1 1 6)


(1 1 7)


(1 1.8)


(1 1 9)

en las que $R^7_A$, $R^7_B$, $R^{16}$ y $R^{17}$ tienen el mismo significado que se definió anteriormente. Por ejemplo, $R^{16}$ y $R^{17}$ se seleccionan cada uno independientemente de -H; -alquilo ($C_1$-$C_4$); -alquenilo ($C_2$-$C_4$); -cicloalquilo ($C_3$-$C_6$); fenilo; bencilo; y piridilo, estando sustituidos el citado alquilo, alquenilo, cicloalquilo, fenilo,

bencilo o piridilo con 0 a 3 sustituyentes seleccionados del grupo constituido por

-F, -Cl, -$CF^3$, -CN y -alquilo ($C_1$-$C_3$).

Los grupos ceto de fórmulas parciales (1.1.6) y (1.1.7) son los mismos con respecto a la entidad enlazante carbonilo, pero se diferencian con respecto del grupo unido, $R^7_A$ ó $R^7_B$:



(116) (117)

$R^7_A$ en el resto de fórmula parcial (1.1.6) tiene el mismo significado que se definió anteriormente, pero en las realizaciones preferidas de los compuestos de fórmula (1.0.0), $R^7_A$ tiene especialmente el significado de -H; -alquilo ($C_1$-$C_6$), preferiblemente metilo, etilo, isopropilo o terc-butilo; -alquenilo ($C_2$-$C_6$), preferiblemente 2-propenilo, -alquinilo ($C_2$-$C_6$), preferiblemente etinilo. Cada uno de estos significados de $R^7$ está opcionalmente sustituido con hasta 3 sustituyentes $R^{10}$. El significado de $R^{10}$ es el mismo que se definió anteriormente, pero es preferiblemente fenilo o piridilo opcionalmente sustituido con hasta 3 $R^{11}$, siendo $R^{11}$ preferiblemente -F, -$CF_3$, -CN, -$CH_3$ ó -$OCH_3$. $R^{10}$ tiene también preferiblemente el significado de -F, -$CF_3$, -$OR^{16}$, -CN, -C(=O)$OR^{16}$,

$-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$ ó $-NR^{16}S(=O)_2R^{17}$, siendo $R^{16}$ y $R^{17}$ preferiblemente -H, metilo, etilo, ciclopropilo, fenilo, bencilo o piridilo opcionalmente sustituido con hasta 3 -F, ó 1 $-CF_3$, -CN ó $-CH_3$.

$R^7_A$ tiene también el significado de $-(CH_2)_u$-cicloalquilo ($C_3$-$C_7$), siendo u preferiblemente 0 ó 1, y siendo el cicloalquilo ($C_3$-$C_7$) preferiblemente ciclopropilo, ciclopentilo o ciclohexilo opcionalmente sustituido con hasta 3 sustituyentes $R^{10}$, teniendo $R^{10}$ los mismos significados preferidos que se definieron en el párrafo inmediatamente anterior.

$R^7_A$ tiene también el significado de fenilo, bencilo o piridilo, estando los citados fenilo, bencilo o piridilo opcionalmente sustituidos con hasta 3 sustituyentes $R^{10}$, teniendo $R^{10}$ los mismos significados preferidos que se definieron en el párrafo inmediatamente anterior.

$R^7_B$ en el resto de fórmula parcial (1 1.7) tiene el mismo significado que se definió anteriormente, pero en las realizaciones preferidas de los compuestos de fórmula (1.0.0), $R^7_B$ tiene especialmente el significado de tetrazol-5-ilo; 1,2,4-triazol-3-ilo; 1,2,3-triazol-5-ilo; imidazol-2-ilo; imidazol-4-ilo; 1,3,4-oxadiazolilo; 1,2,4-oxadiazol-3-ilo; 1,2,4-oxadiazol-5-ilo; 1,2,5-tiadiazolilo; 1,3,4-tiadiazolilo; morfolinilo, oxazolilo, isoxazolilo; tiazolilo; isotiazolilo; pirrolilo,

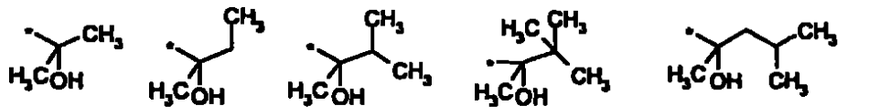
pirazolilo; piridilo; indolilo, benzo[b]furanilo; 2,3-dihidrobenzofuranilo; 1H-indazolilo; bencimidazolilo; benzoxazolilo; benzoisoxazolilo; benzotiazolilo; benzotriazolilo; quinolinilo, isoquinolinilo; quinazolinilo ó quinoxalinilo.

Cualquiera de los significados especialmente preferidos anteriormente citados de $R^7_B$ está opcionalmente sustituido en un átomo de carbono con $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió anteriormente, y en un átomo de nitrógeno con $R^{15}$, teniendo $R^{15}$ el mismo significado que se definió anteriormente. Están especialmente incluidas en el caso de dichos sutituyentes de átomo de nitrógeno todas las formas tautoméricas de los restos de fórmula parcial (1.1.9). Los átomos de azufre de los citados restos están opcionalmente sustituidos con 1 ó 2 átomos de oxígeno.

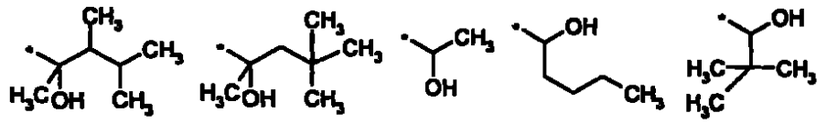
Para ilustrar los significados adicionales de E que entran dentro del alcance de las fórmulas parciales (1.1.6). (1.1.7), (1.1.8) y (1.1.9), se describen a continuación restos de fórmulas parciales (3.3.1) a (3.3.15) que representan distintos significados que entran dentro del alcance de la fórmula parcial (1.1.8)·



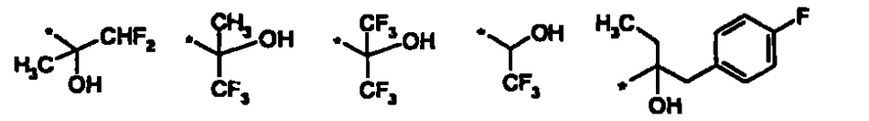
(1.1.8)



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

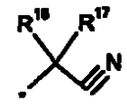


(3.3.6) (3.3.7) (3.3.8) (3.3.9) (3.3.10)

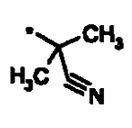


(3.3.11) (3.3.12) (3.3.13) (3.3.14) (3.3.15)

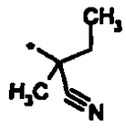
Son significados adicionales de E aquellos que entran dentro del alcance de la fórmula parcial (1.1.9) en la que un grupo nitrilo -C≡N reemplaza al grupo hidroxilo de la fórmula parcial (1.1.8). Consiguientemente, se describen a continuación restos de fórmulas parciales (3.8.1) a (3.8.10) que representan significados distintos que entran dentro del alcance de la fórmula parcial (1.1.9):



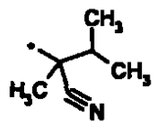
(1 1 9)



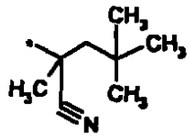
(3 8 1)



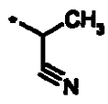
(3 8 2)



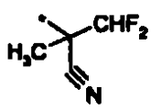
(3 8 3)



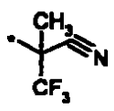
(3.8 4)



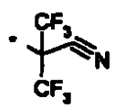
(3 8 5)



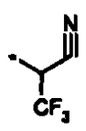
(3.8.6)



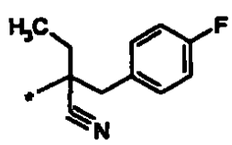
(3 8 7)



(3 8 8)



(3 8 9)

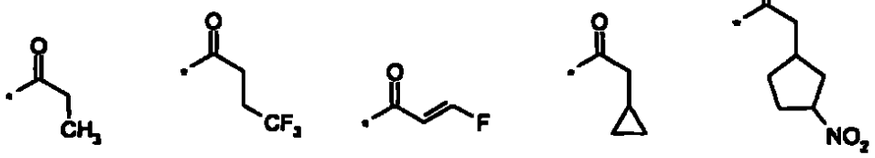


(3.8 10)

Para ilustrar los significados adicionales de E que entran dentro del alcance de las fórmulas parciales (1.1.6), (1.1.7), (1.1.8) y (1.1.9), se describen a continuación restos de fórmulas parciales (3 9.1) a (3 9.9) que representan diferentes significados que entran dentro del alcance de las fórmulas parciales (1.1.6) y (1.1.7)



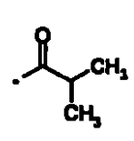
(116) (117)



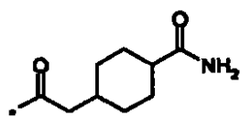
(391) (392) (393) (394) (395)

3/5

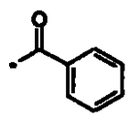
00319



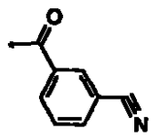
(3 9 6)



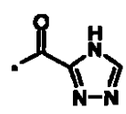
(3 9 7)



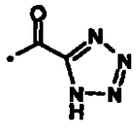
(3 9 8)



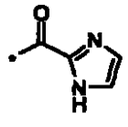
(3.9.9)



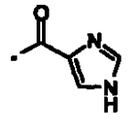
(3 9 10)



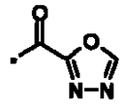
(3 9 11)



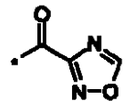
(3 9 12)



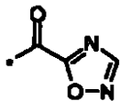
(3 9 13)



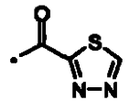
(3 9 14)



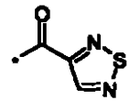
(3 9 15)



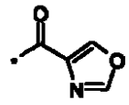
(3 9 16)



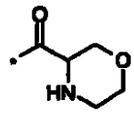
(3 9 17)



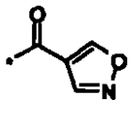
(3 9 18)



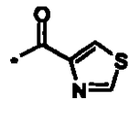
(3 9 19)



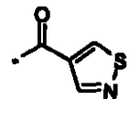
(3 9 20)



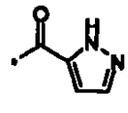
(3 9.21)



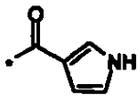
(3.9 22)



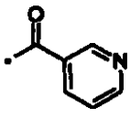
(3 9 23)



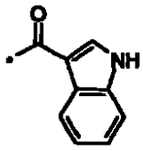
(3 9.24)



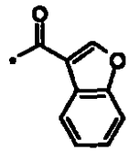
(3 9.25)



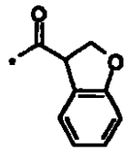
(3 9 26)



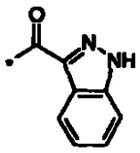
(3 9.27)



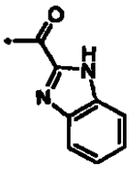
(3 9.28)



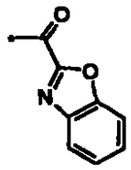
(3.9 29)



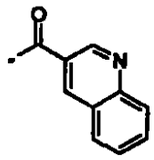
(3 9.30)



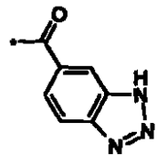
(3 9 31)



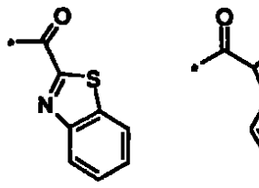
(3 9 32)



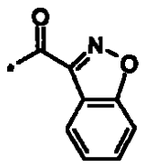
(3 9.33)



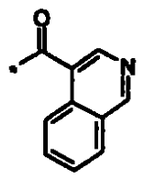
(3 9 34)



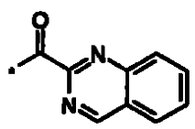
(3 9 35)



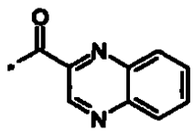
(3 9 36)



(3.9 37)



(3.9 38)



(3 9 39)

**5.6.6E es un resto de fórmulas parciales (1.1.10) a (1.1.15)**

E es también un miembro seleccionado del grupo de restos definidos por las fórmulas parciales (1.1.10) a (1.1.15) ilustradas anteriormente. En los restos de fórmulas parciales (1.1.10) a (1.1.14), el significado de E está constituido por un grupo terminal $R^7_C$ unido a la parte restante de fórmula (1.0.0) mediante lo que puede denominarse un grupo enlazante que comprende la parte restante de las citadas fórmulas parciales (1.1.10) a (1.1.14). $R^7_C$ tiene a su vez el significado de un miembro seleccionado independientemente del grupo constituido por los significados de $R^7_A$ y los significados de $R^7_B$ definidos anteriormente.

El grupo enlazante de fórmula parcial (1.1.10) comprende una estructura carbamoílo o amida inversa que puede

representarse por la fórmula: $-N(R^9)-C(=O)-$, que se lee de izquierda a derecha. El sustituyente $R^9$ tiene lo más frecuentemente el significado de -H, de modo que el citado grupo enlazante amida inversa puede representarse de la siguiente manera, leyendo de izquierda a derecha $-NHC(=O)-$. Consiguientemente, cuando E tiene el significado de la fórmula parcial (1.1.10), las realizaciones preferidas de los compuestos de fórmula (1.0.0) tendrán el siguiente término a la derecha: $-NHC(=O)-R^7_c$.

E puede seleccionarse también como el resto definido por la fórmula parcial (1.1.11). Cuando ambas presencias del sustituyente $R^9$ tienen el significado de -H, como se prefiere, entonces las realizaciones resultantes de los compuestos de fórmula (1.0.0) tendrán el siguiente término a la derecha: $-NHC(=O)NH-R^7_c$. De forma similar, cuando se selecciona E como el resto definido por la fórmula parcial (1.1.11) 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 término a la derecha: $-NHC(=O)O-R^7_c$.

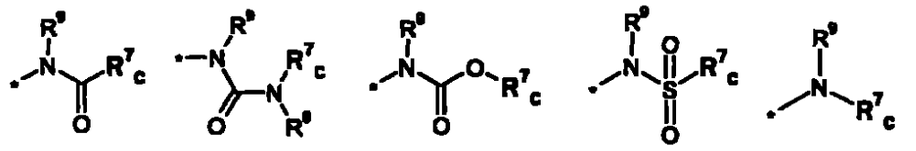
E puede seleccionarse también como un resto definido por las fórmulas parciales (1.1.13) ó (1.1.14), y en el caso de que el sustituyente $R^9$ tenga el significado preferido de -H, las realizaciones resultantes de los compuestos de fórmula (1.0.0)

tendrán los siguientes términos a la derecha: $-NHS(=O)_2-R^7_C$ y $-NH-R^7_C$. Los significados de E definidos por las fórmulas parciales (1.1.12) y (1.1.13) no son, sin embargo, tan preferidos como los significados de E definidos por las fórmulas parciales (1.1.10) y (1.1.11), y a veces (1.1.12)

Finalmente, E puede seleccionarse como el resto definido por la fórmula parcial (1.1.6) en la que un átomo de nitrógeno de un heterociclo está unido por un enlace directo a la parte restante de un compuesto de fórmula (1.0.0) En algunas realizaciones preferidas, un átomo de carbono en el citado heterociclo que contiene nitrógeno, que está en α al citado átomo de nitrógeno, puede estar sustituido con carbonilo, es decir, oxo (=O). Los significados más preferidos de E en los compuestos de fórmula (1.0.0) son aquellos definidos por las fórmulas parciales (1.1.1), (1.1.10) y (1.1.15).

**5.6.7E 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 E 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 una serie de restos preferidos para la definición del grupo E es aquel de fórmula parcial (1.1.0) en la que $R^7_c$ tiene el significado de -alquilo ($C_1$-$C_4$), preferiblemente metilo, etilo, n-propilo, isopropilo o terc-butilo; cicloalquilo ($C_3$-$C_6$), preferiblemente ciclopropilo, ciclobutilo, ciclpentilo o ciclohexilo, todos los cuales están unidos directamente o mediante un puente de 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 E 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; -alquilo ($C_1$-$C_4$), preferiblemente metilo; -cicloalquilo ($C_3$-$C_7$),

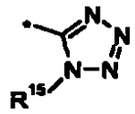
preferiblemente ciclopropilo o ciclopentilo; fenilo; bencilo; piridilo; $-OR^{18}$; -alquil $(C_1-C_2)-OR^{18}$; y -alquil $(C_1-C_2)-C(=O)OR^{18}$; siendo $R^{18}$ -H ó -alquilo $(C_1-C_4)$. $R^{18}$ es preferiblemente -H ó $-CH_3$.

$R^{10}$ es un sustituyente opcional de los restos preferidos anteriormente descritos que definen $R^7_c$, y puede haber hasta tres de dichos sustituyentes cuando están presentes. El significado del sustituyente $R^{10}$ incluye fenilo o piridilo, estando el citado fenilo o piridilo a su vez opcionalmente sustituido con hasta 3 sustituyentes $R^{12}$, siendo $R^{12}$ -F, -Cl, -CN, $-NO_2$, -OH, -alcoxi $(C_1-C_3)$, -alquilo $(C_1-C_3)$ ó $-NR^{16}R^{17}$. En las realizaciones preferidas que incluyen dicha sustitución $R^{12}$, habrá 1 ó 2 sustituyentes $R^{12}$ que tengan el significado de -F, Cl, $-CH_3$, $-OCH_3$, -OH, -CN ó $-N(CH_3)_2$. El significado del sustituyente $R^{10}$ incluye además -F, -Cl, $-CF_3$, oxo (=O), $-OR^{16}$, $-NO_2$, -CN, $-C(O)OR^{16}$, $-O-C(=O)R^{16}$, $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$ ó $-S(=O)_2NR^{16}R^{17}$. Los preferidos entre los significados anteriormente enumerados del sustituyente $R^{10}$ son -F, -Cl, $-CF_3$, oxo (=O), -OH, $-OCH_3$, $-NO_2$, -CN, $-C(=O)OH$, $-C(=O)NH_2$, $-NH_2$, $-N(CH_3)_2$ ó $-NHS(=O)_2CH_3$.

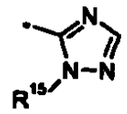
Los subsustituyentes $R^{16}$ y $R^{17}$ comprenden -H; -alquilo $(C_1-$

$C_4$), preferiblemente $-CH_3$; -alquenilo ($C_2$-$C_4$); -cicloalquilo ($C_3$-$C_6$), preferiblemente ciclopropilo; fenilo; bencilo o piridilo. Los citados grupos alquilo, alquenilo, cicloalquilo, fenilo, bencilo o piridilo están a su vez opcionalmente sustituidos con hasta 3 sustituyentes -F, -Cl ó -CN.

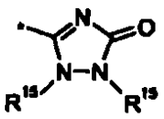
Como ilustración de las realizaciones subgenéricas preferidas de la presente invención en las que el grupo E tiene el significado de un resto de fórmulas parciales (1.1.10) a (1.1.4), se indican a continuación grupos cicloalquilo, fenilo, bencilo y heterocíclicos monocíclicos que definen $R^7_C$, de fórmulas parciales (7.0.1) a (7 0.41):



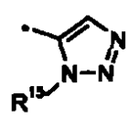
tetrazol-5-ilo
(7 0 1)



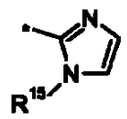
1,2,4-triazol-3-ilo
(7.0 2)



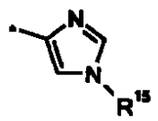
1,2,4-triazol-3-on-5-ilo
(7 0 3)



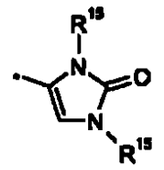
1,2,3-triazol-5-ilo
(7 0 4)



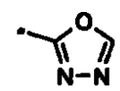
imidazol-2-ilo
(7 0 5)



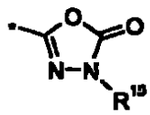
imidazol-4-ilo
(7 0 6)



imidazolidin-2-on-4-ilo
(7 0 7)

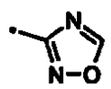


1,3,4-oxadiazolilo
(7 0 8)



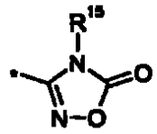
1,3,4-oxadiazol-2-on-5-ilo

(7 0 9)



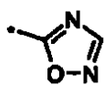
1,2,4-oxadiazol-3-ilo

(7 0 10)



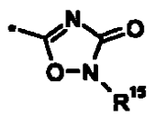
1,2,4-oxadiazol-5-on-3-ilo

(7 0 11)



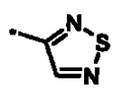
1,2,4-oxadiazol-5-ilo

(7 0 12)



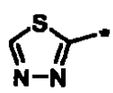
1,2,4-oxadiazol-3-on-5-ilo

(7 0 13)



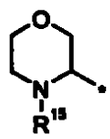
1,2,5-tiadiazol-2-ilo

(7 0 14)



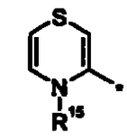
1,3,4-tiadiazolilo

(7 0 15)



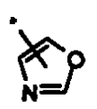
morfolin-3-ilo

(7 0 16)



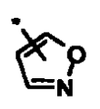
paratiazin-3-ilo

(7 0 17)



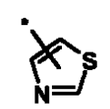
oxazolilo

(7 0 18)



isoxazolilo

(7 0 19)



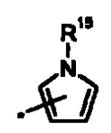
tiazolilo

(7 0 20)



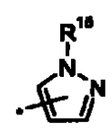
isotiazolilo

(7 0 21)



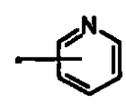
pirrolilo

(7 0.22)



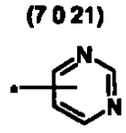
pirazolilo

(7 0 23)



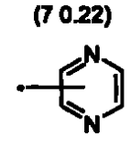
piridilo

(7 0.24)



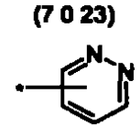
pirimidinilo

(7.0 25)



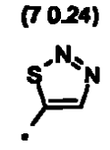
pirazinilo

(7 0 26)



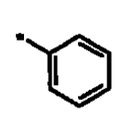
piridazinilo

(7 0 27)



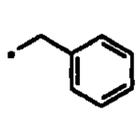
1,2,3-tiadiazol-5-ilo

(7 0 28)



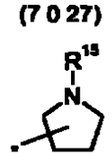
fenilo

(7 0 29)



bencilo

(7 0 30)



pirrolidinilo

(7 0 31)

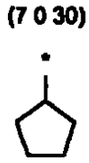


ciclopropilo

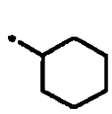
(7 0.32)



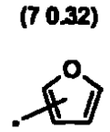
ciclobutilo



ciclopentilo



ciclohexilo



furanilo

(7 0 33)



tetrahidrofuranilo

(7 0 34)



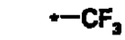
tienilo

(7 0 35)



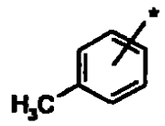
metilo

(7 0 36)



trifluorometilo

(7 0 37)



tolulio

(7 0 38)

(7 0.39)

(7 0 40)

(7 0 41)

en las que "*" indica el punto de unión de cada fórmula parcial (7.0.1) a (7.0.41) a la parte restante de fórmula (1.0.0); en las que cada átomo de carbono de fórmulas parciales (7.0.1) a (7.0.38) está opcionalmente sustituido con un sustituyente $R^{14}$; y en las que cada $R^{14}$ y $R^{15}$ tiene el mismo significado que se definió anteriormente; y todas las formas tautoméricas, y opcionalmente formas N-óxido, de estos.

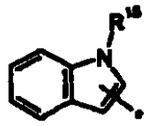
No se muestran sustituyentes $R^9$ en las fórmulas parciales (7.0.1) a (7.0.41) anteriores debido a que el sustituyente $R^9$ está unido sólo a un átomo de nitrógeno que no forma parte

componente integral 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 destaca también la distinción entre los sustituyentes $R^9$ y $R^{15}$, ambos unidos sólo a átomos de nitrógeno en cualquiera de los significados del resto E. El sustituyente $R^{15}$ está unido sólo a un atomo de nitrogeno que sea parte componente integral de cualquier resto heterocíclico que pueda definirse mediante el sustituyente $R^7_c$ en las fórmulas parciales (1.1.9) a (1.1.13), y en particular, con referencia a los restos heterocíclicos más específicos de fórmulas parciales (7.0.1) a (7.0.28) y (7.0.31). El sustituyente $R^9$, por otro lado, está unido sólo a un átomo de nitrógeno que esté a su vez unido a, pero no sea una parte componente integral de, cualquiera de los restos heterocíclicos que se definen 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 los citados 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 pueda caracterizarse por contener o comprender un resto heterocíclico que contenga nitrógeno.

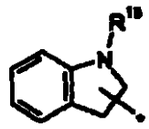
Las realizaciones preferidas de la presente invención en las que el grupo E es un resto de fórmulas parciales (1.1.10) a (1.1.14) incluyen también aquellas en las que el resto $R^7_c$ es un grupo heterocíclico bicíclico seleccionado del grupo constituido por indolilo, indolinilo; isoindolinilo; benzo[b]furanilo, 2,3-dihidrobenzofuranilo, 1,3-dihidroisobenzofuranilo; 2H-1-benzopiranilo; cromanilo; benzotienilo; 1H-indazolilo, bencimidazolilo, benzoxazolilo, benzoisoxazolilo, 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 1H-purinilo.

Para proporcionar una demostración adicional más de las realizaciones preferidas de los compuestos de fórmula (1.0.0) con referencia al grupo E, cuando es un resto de fórmulas parciales (1.1.10) a (1.1.14), y $R^7_c$ es un grupo heterocíclico bicíclico, se indican a continuación los grupos constituidos por las fórmulas parciales (7.5.1) a (7.5.29) de las cuales se selecciona el resto E de dichas realizaciones preferidas:



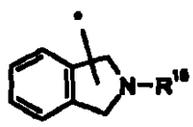
indolilo

(7.5 1)



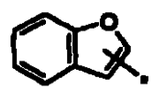
indolinilo

(7 5 2)



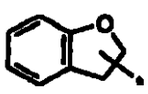
isoindolinilo

(7 5.3)



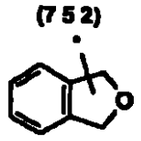
benzo[b]furanilo

(7.5.4)



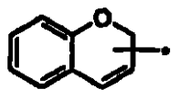
2,3-dihidro-benzofuranilo

(7 5.5)



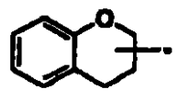
1,3-dihidroisobenzo-furanilo, ftalazinilo

(7.5.6)



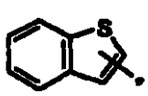
2H-1-benzopiranilo

(7.5 7)



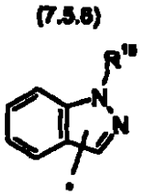
cromanilo

(7 5.8)



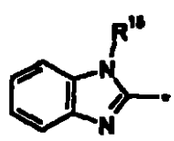
benzotienilo

(7 5.9)



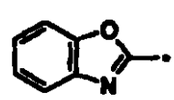
1H-indazolilo

(7.5.10)



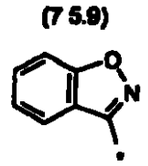
bencimidazolilo

(7 5.11)



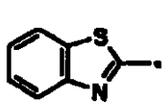
benzoxazolilo

(7 5 12)



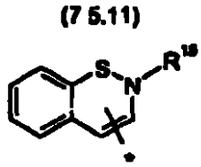
benzoisoxazolilo

(7 5 13)



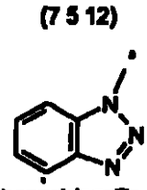
benzotiazolilo

(7 5.14)



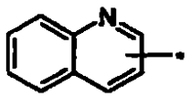
2H-1,2-benzotiazinilo

(7 5 15)



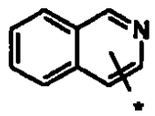
benzotriazolilo

(7 5.16)



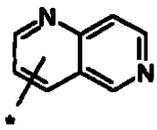
quinolinilo

(7 5 17)



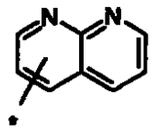
isoquinolinilo

(7 5 18)



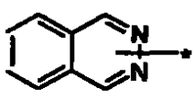
1,6-naftindinilo

(7 5 19)



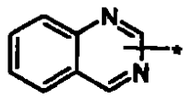
1,8-naftindinilo

(7 5 20)



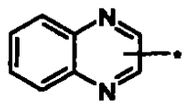
ftalazinilo

(7 5 21)



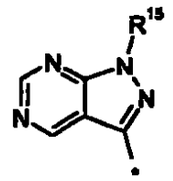
quinazolinilo

(7 5 22)



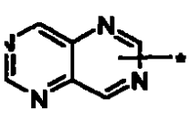
quinoxalinilo

(7 5 23)



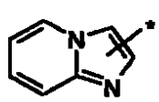
1H-pirazolo[3,4-d]-pirimidinilo

(7 5 24)



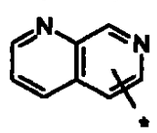
pirimido[5,4-d]-pirimidinilo

(7 5 25)



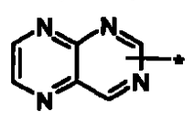
imidazo[1,2-a]-piridinilo

(7 5 26)



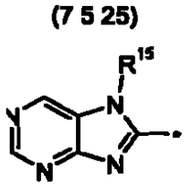
1,7-naftindinilo

(7 5 27)



ptendinilo

(7 5 28)



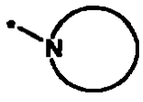
1H-purinilo

(7 5 29)

en las que "*" indica el punto de unión a la parte restante de fórmula (1.0.0); y en las que cada átomo de carbono está opcionalmente sustituido con un sustituyente $R^{14}$, teniendo $R^{14}$ y $R^{15}$ el mismo significado que se definió anteriormente; y todas las formas tautoméricas, y opcionalmente formas N-óxido, de estos.

**5.6.8E 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 la que el resto terminal E entra dentro del alcance de la fórmula parcial (1.1.15), es decir, las realizaciones de este tipo están comprendidas dentro del alcance del resto E cuando tiene el significado de la fórmula parcial (1.1.15):




(1.1.15)

Se comprenderá que cuando el resto terminal E está definido por la fórmula parcial (1.1.15), comprende intrínsecamente un grupo heterocíclico que contiene nitrógeno. Uno cualquiera o más de los átomos de carbono del citado grupo heterocíclico está sustituido con 0 a 3 sustituyentes $R^{14}$. Consiguientemente, $R^{14}$ es un sustituyente opcional de uno

cualquiera o más, hasta un total de tres, de los átomos de carbono de los restos que están incluidos dentro del alcance de la fórmula parcial (1.1.15). El citado sustituyente $R^{14}$ comprende -alquilo ($C_1$-$C_4$), preferiblemente $-CH_3$; -cicloalquilo ($C_3$-$C_7$), preferiblemente ciclopropilo, fenilo; bencilo; piridilo; o quinolinilo; estando los citados restos alquilo, cicloalquilo, fenilo, bencilo, piridilo o quinolinilo a su vez opcionalmente sustituidos con 1 ó 2 sustituyentes -F, -Cl, $-CH_3$, $-OCH_3$, $-OR^{16}$, -CN ó $-NR^{16}R^{17}$. En realizaciones preferidas, $R^{16}$ y $R^{17}$ son independientemente -H ó $-CH_3$. Cuando $R^{14}$ está sustituido, se prefiere que el sustituyente sea -F ó -Cl. El sustituyente $R^{14}$ comprende además -F; -Cl; $-CF_3$; oxo (=O); $-OR^{16}$; -CN; $-NO_2$, $-C(=O)OR^{16}$, $-O-C(=O)R^{16}$, $-C(=O)NR^{16}R^{17}$, $-O-C(=O)NR^{16}R^{17}$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}S(=O)_2R^{17}$ ó $-S(=O)_2NR^{16}R^{17}$. Además de esas realizaciones preferidas indicadas anteriormente, cuando $R^4$ está presente se prefiere también que tenga el significado de -F, -Cl, $-CF_3$, $-OCH_3$, -CN ó $-NO_2$.

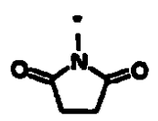
Uno cualquiera o más de los átomos de nitrógeno incluidos en los citados grupos heterocíclicos que contienen nitrógeno incluidos dentro del alcance de la fórmula parcial (1.1.15), con la condición de que no sean un punto de unión del citado grupo heterocíclico, están opcionalmente sustituidos con hasta 3

sustituyentes $R^{15}$. Cualquier átomo de azufre que aparezca en el citado grupo heterocíclico, con la condición de que no sea un punto de unión del citado grupo heterocíclico, está sustituido con 0, 1 ó 2 átomos de oxígeno.

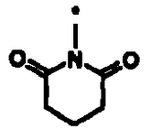
El sustituyente heterociclilo de nitrógeno opcional $R^{15}$ comprende -H; $-C(=O)OR^{16}$, $-C(=O)NR^{16}R^{17}$; -alquilo ($C_1$-$C_4$), preferiblemente $-CH_3$; -alquenilo ($C_2$-$C_4$); -alcoxi ($C_1$-$C_2$), preferiblemente $-OCH_3$; -cicloalquilo ($C_3$-$C_7$), preferiblemente ciclopropilo; fenilo, o bencilo, estando los citados alquilo, alquenilo, alcoxi, cicloalquilo, fenilo o bencilo opcionalmente sustituidos con hasta 2 sustituyentes $R^{11}$.

El subsustituyente $R^{11}$ comprende -F; -Cl; $-CO_2R^{18}$; $-OR^{16}$, -CN; $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$; $-NR^{18}C(=O)OR^{19}$; $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, siendo p 1 ó 2, preferiblemente 2; -alquilo ($C_1$-$C_4$), preferiblemente $-CH_3$; y -alcoxi ($C_1$-$C_4$), teniendo $R^{11}$ el significado de $-OR^{16}$ anterior, y estando definido $R^{16}$ como alquilo ($C_1$-$C_4$), preferiblemente $-OCH_3$; estando los citado alquilo y alcoxi sustituidos opcionalmente a su vez con hasta 3 sustituyentes -F; Cl; -alcoxi ($C_1$-$C_2$)carbonilo; -alquil ($C_1$-$C_2$)carbonilo, y -alquil ($C_1$-$C_2$)carboniloxi. Los sustituyentes $R^{18}$ y $R^{19}$ comprenden -H, ó -alquilo ($C_1$-$C_2$), preferiblemente $-CH_3$; opcionalmente sustituidos con hasta 3 -F; ó -Cl.

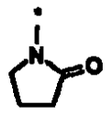
La presente invención se refiere también a un compuesto de fórmula (1.0.0) en la que el grupo E terminal tiene el significado de la fórmula parcial (1.1.15), en la que el número y la posición de los átomos de carbono y reemplazos de estos por uno o más heteroátomos, así como la sustitución de uno o más de los citados átomos de carbono de este con $R^{14}$, siendo $R^{14}$ oxo (=O), se seleccionan de tal modo que E comprende un miembro seleccionado del grupo constituido por las fórmulas parciales (1.7.1) a (1.7.46):



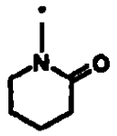
succinimid-1-ilo
(1 7 1)



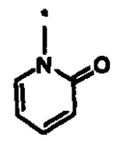
glutarimid-1-ilo
(1 7.2)



pirrolidin-2-on-1-ilo
(1 7 3)



piperid-2-on-1-ilo
(1 7.4)



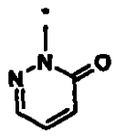
pirid-2-on-1-ilo

(1 7 5)



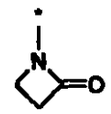
pirid-4-on-1ilo

(1 7 6)



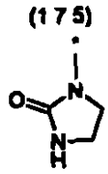
piridazin-3-on-2-ilo

(1 7 7)



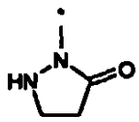
azetidin-2-on-1-ilo

(1 7 8)



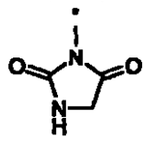
imidazolidin-2-on-1-ilo

(1 7 9)



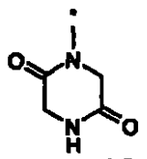
pirazol-5-on-1-ilo

(1 7 10)



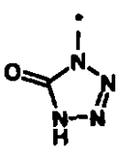
imidazolidin-2,4-dion-1-ilo

(1 7 11)



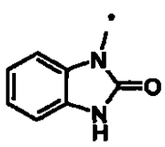
piperazin-2,5-dion-1-ilo

(1 7 12)



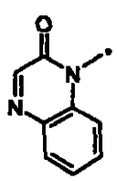
4 5-dihidro-5-oxo-1H-tetrazol-1-ilo

(1 7 13)



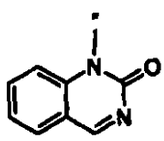
bencimidazolin-2-on-1-ilo

(1 7 14)



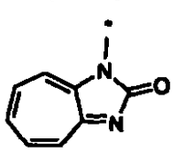
1H-quinoxalin-2-on-1-ilo

(1 7 15)



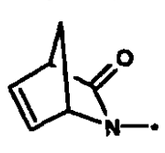
1H-quinazalin-2-on-1-ilo

(1 7 16)



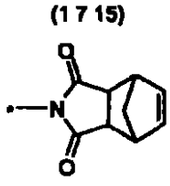
1H-cicloheptamidazol-2-on-1-ilo

(1 7 17)



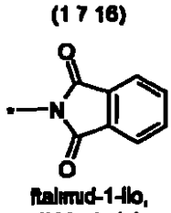
2-azabiciclo[2 2 1]-hept-5-en-3-on-1-ilo

(1 7 18)



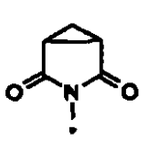
norborn-5-en-2,3-dicarboximid-1-ilo

(1 7 19)



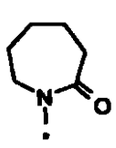
ftalimid-1-ilo, 1H-isoindol-1,3(2H)-dion-1-ilo

(1 7.20)



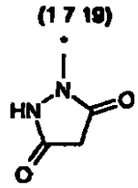
3-azabiciclo[3 1 0]-hexano-2,4-dion-3-ilo

(1 7.21)



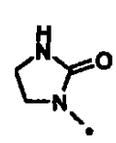
2H-azepin-2-on-1-ilo

(1 7.22)



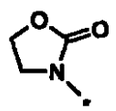
pirazolidin-3,5-dion-1-ilo

(1 7.23)



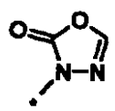
imidazolidin-2-on-1-ilo

(1 7.24)



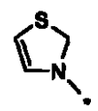
oxazolidin-2-on-1-ile

(1 7 25)



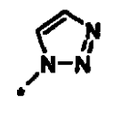
1,3,4-oxadiazol-2(3H)-on-3-ile

(1 7 26)



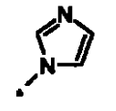
tiazol-3-ile

(1 7.27)



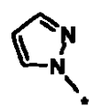
1H-1,2,3-triazol-1-ile

(1 7 28)



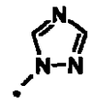
imidazol-1-ile

(1 7.29)



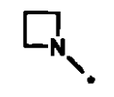
pirazol-1-ile

(1 7 30)



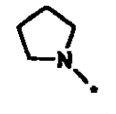
1H-1,2,4-triazol-1-ile

(1 7 31)



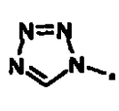
azetidin-1-ile

(1 7.32)



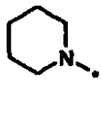
pirrolidin-1-ile

(1 7 33)



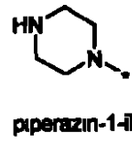
tetrazol-1-ile

(1 7 34)



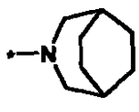
piperidin-1-ile

(1 7 35)



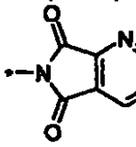
piperazin-1-ile

(1 7 36)



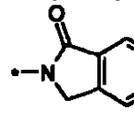
3-azabiciclo[3.2 2]-non-3-ile

(1 7 37)



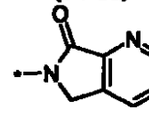
pirrolo[3,4-b]pirdin -5,7-dion-6-ile

(1 7 38)



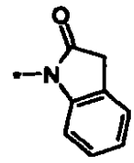
2,3-dihidroisoindol-1-on-2-ile

(1 7 39)



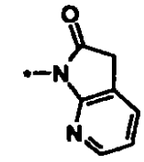
pirrolo[3,4-b]piridin -7-on-6-ile

(1 7.40)



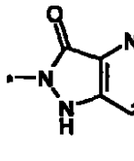
1,3-dihidroindol-2-on-1-ile

(1 7 41)



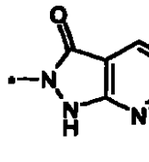
pirrolo[4,5-b]-piridin-3-on-2-ile

(1 7 42)



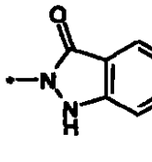
1H-pirazolo[4,5-e] pindin-7-on-2-ile

(1 7 43)



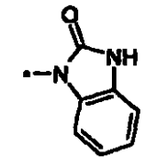
1H-pirazolo[4,5-b] piridin-4-on-2-ile

(1 7 44)



1H-indazol-3-on-2-ile

(1 7 45)

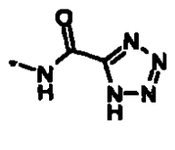


1H-bencimidazol-2-on-3-ile

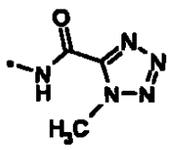
(1 7 46)

Cualquier resto que sea un miembro seleccionado del grupo constituido por las fórmulas parciales (1.7.1) a (1.7.46) descrito anteriormente, incluye la sustitución opcional de éste con respecto a (1) uno cualquiera o más de los átomos de carbono de éste con un sustituyente $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió anteriormente; (2) uno cualquiera o más átomos de nitrógeno de éste con un sustituyente $R^{15}$, teniendo $R^{15}$ el mismo significado que se definió anteriormente, y todas las formas tautoméricas, y opcionalmente formas N-óxido de éstas; ó (3) cualquier átomo de azufre de éste con 0, 1 ó 2 átomos de oxígeno.

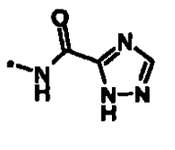
La presente invención se ilustra adicionalmente respecto de los grupos subgenéricos preferidos que comprenden compuestos de fórmula (1.0.0), en la que $R^7_c$ y $R^9$ de fórmulas parciales (1.1.10) a (1.1.15) se seleccionan todos de tal manera que E comprende un miembro seleccionado del grupo constituido por las siguientes fórmulas parciales (8.0.1) a (8.0.139):



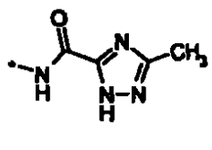
(801)



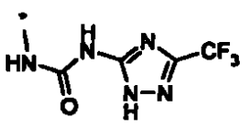
(802)



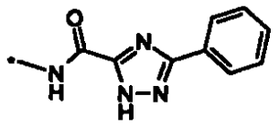
(803)



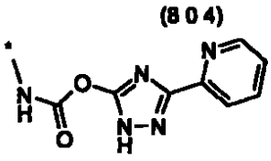
(804)



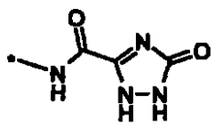
(805)



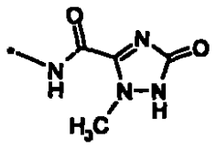
(806)



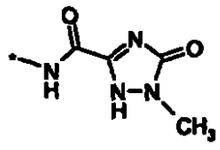
(807)



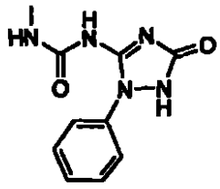
(8.0.8)



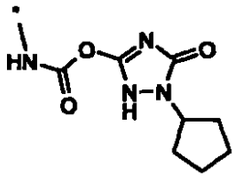
(8 0 9)



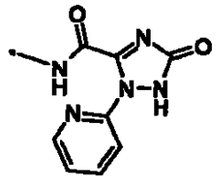
(8 0 10)



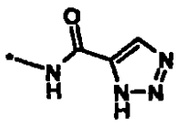
(8 0 11)



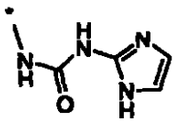
(8 0 12)



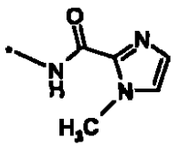
(8 0 13)



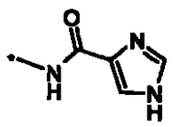
(8 0 14)



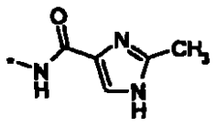
(8 0 15)



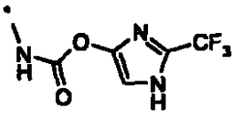
(8 0 16)



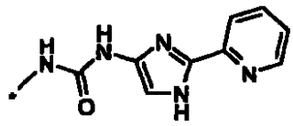
(8 0 17)



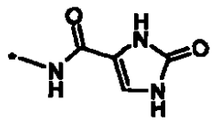
(8 0 18)



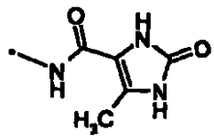
(8 0 19)



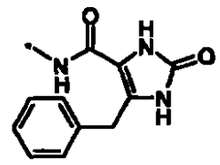
(8 0.20)



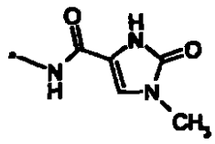
(8.0 21)



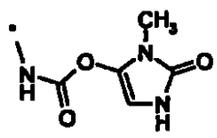
(8 0 22)



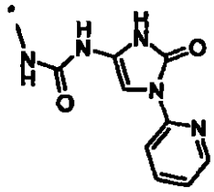
(8 0 23)



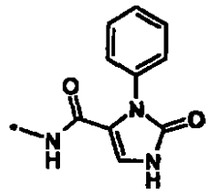
(8.0 24)



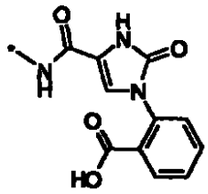
(8 0 25)



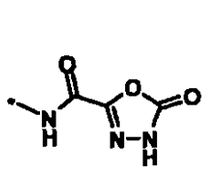
(8 0.26)



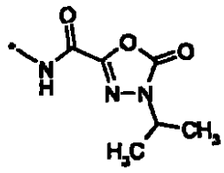
(8 0 27)



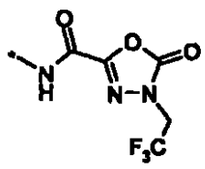
(8 0 28)



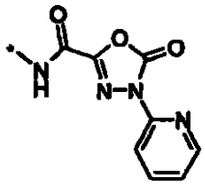
(8.0.29)



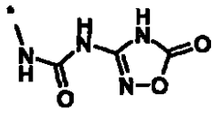
(8.0.30)



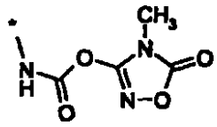
(8.0.31)



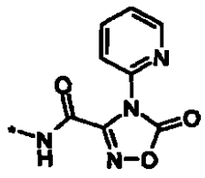
(8.0.32)



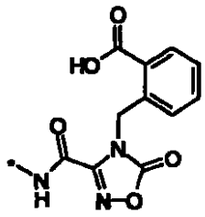
(8.0.33)



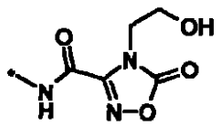
(8.0.34)



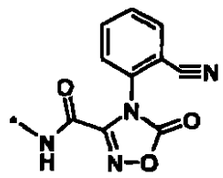
(8.0.35)



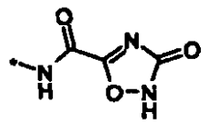
(8.0.36)



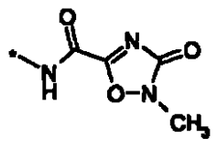
(8.0.37)



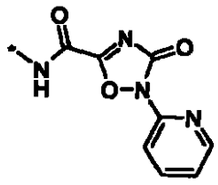
(8.0.38)



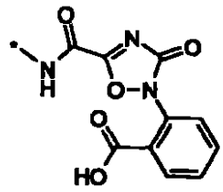
(8.0.39)



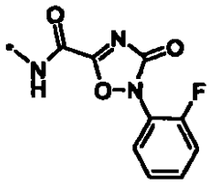
(8.0.40)



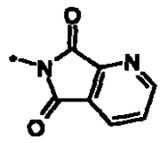
(8.0.41)



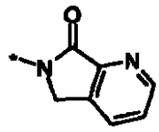
(8.0.42)



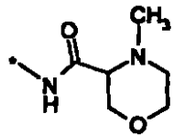
(8.0.43)



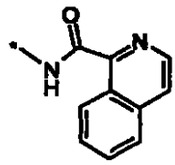
(8.0.44)



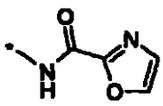
(8.0.45)



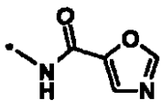
(8.0.46)



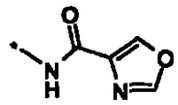
(8.0.47)



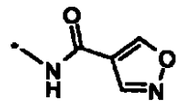
(8.0.48)



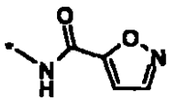
(8.0.49)



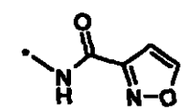
(8.0.50)

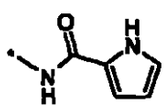


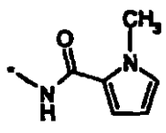
(8.0.51)

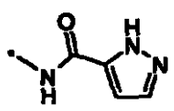


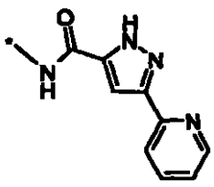
(8.0.52)

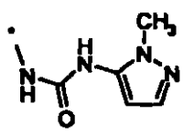

(8 0 53)

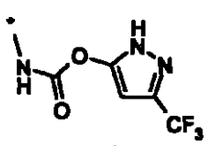

(8 0 54)

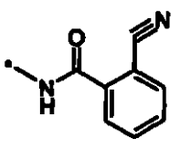

(8.0 55)

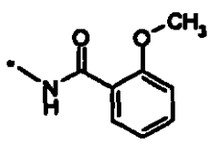

(8 0.56)

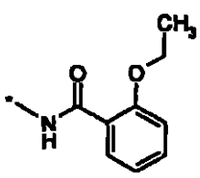

(8 0 57)

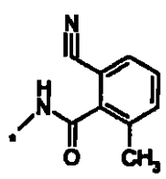

(8 0 58)

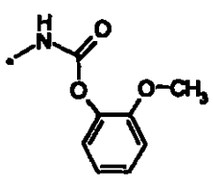

(8 0 59)

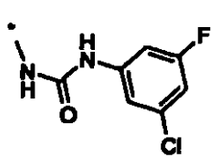

(8 0.60)

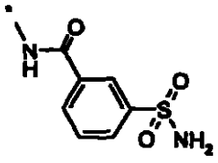

(8 0 61)

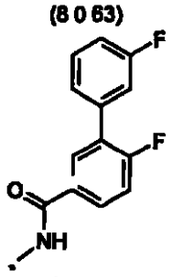

(8 0 62)

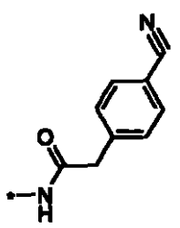

(8 0 63)

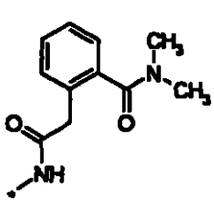

(8 0 64)

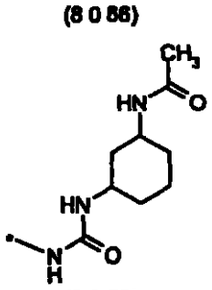

(8 0 65)

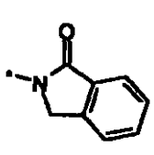

(8 0 66)

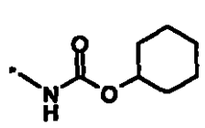

(b 0.67)

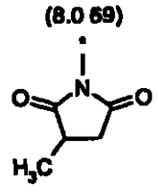

(8 0.68)

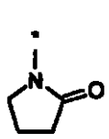

(8.0 69)

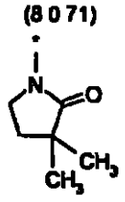

(8 0 70)

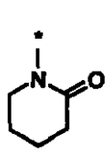

(8 0 71)

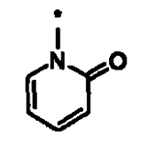

(8 0 72)


(8.0 73)

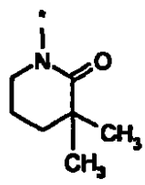

(8.0 74)


(8 0 75)

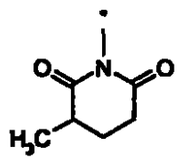

(8 0 76)



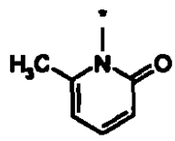
(8 0 77)



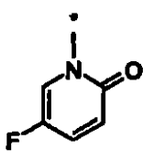
(8 0 78)



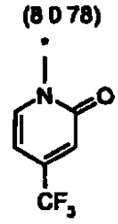
(8 0 79)



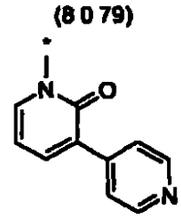
(8 0.80)



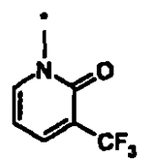
(8 0 81)



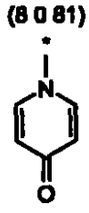
(8 0 82)



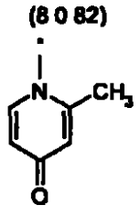
(8 0 83)



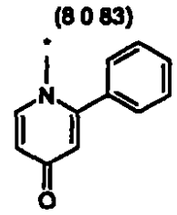
(8 0 84)



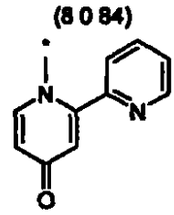
(8.0 85)



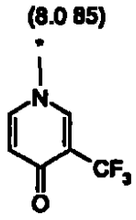
(8 0 86)



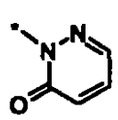
(8.0.87)



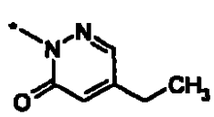
(8 0 88)



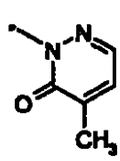
(8 0 89)



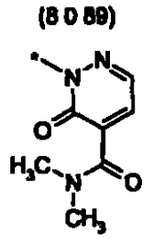
(8 0 90)



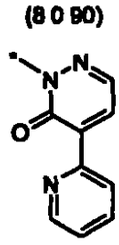
(8 0 91)



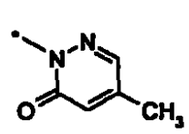
(8 0 92)



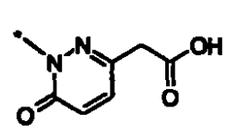
(8.0 93)



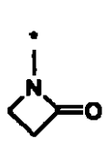
(8 0 94)



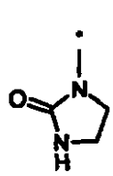
(8 0 95)



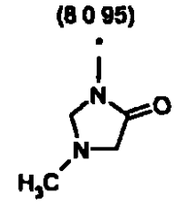
(8 0.96)



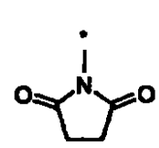
(8.0 97)



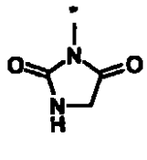
(8 0 98)

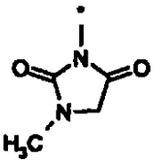


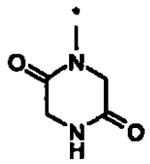
(8 0 99)

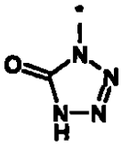


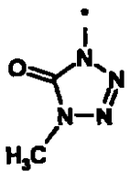
(8 0 100)

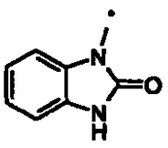

(8 0 101)

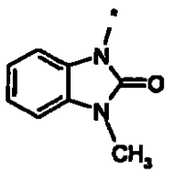

(8 0 102)

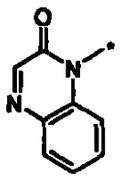

(8 0 103)

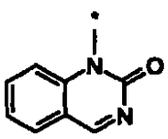

(8 0 104)

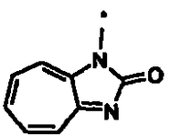

(8 0 105)

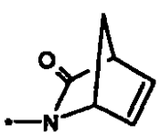

(8 0 106)

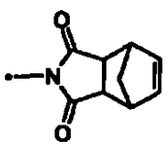

(8 0 107)

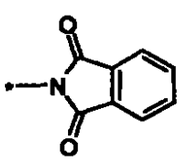

(8 0 108)

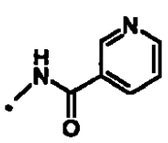

(8 0 109)

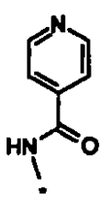

(8 0 110)

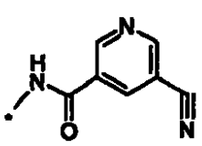

(8 0 111)

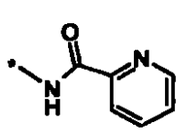

(8 0 112)

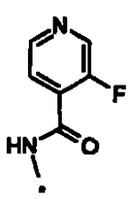

(8 0 113)

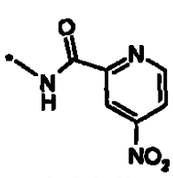

(8 0 114)

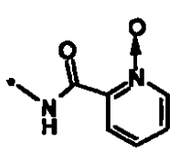

(8 0 115)

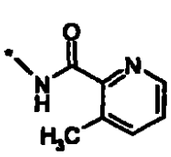

(8.0 116)

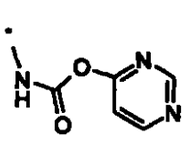

(8 0 117)

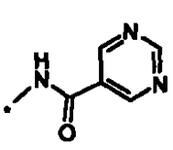

(8 0 118)

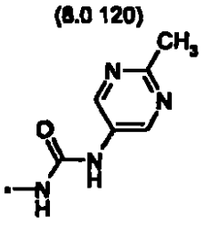

(8 0 119)

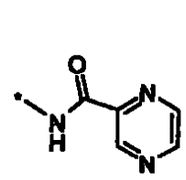

(8.0 120)

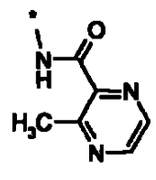

(8 0 121)

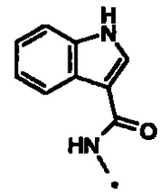

(8 0 122)

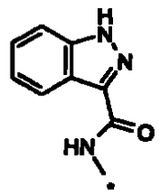

(8 0 123)

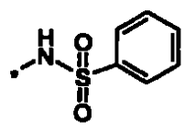

(8 0 124)

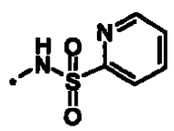

(8 0 125)

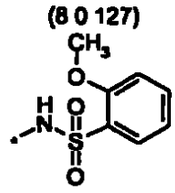

(8 0 126)

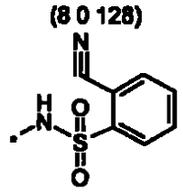

(8 0 127)

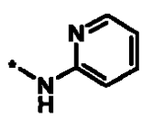

(8 0 128)

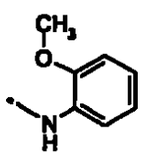

(8 0 129)

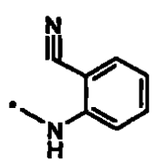

(8 0 130)

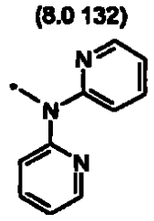

(8 0 131)

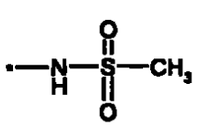

(8.0 132)

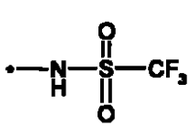

(8 0 133)

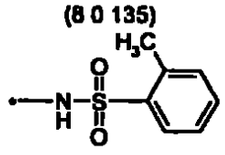

(8 0 134)


(8 0 135)


(8 0 136)


(8 0 137)


(8 0 138)

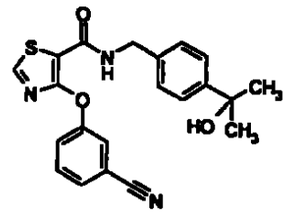
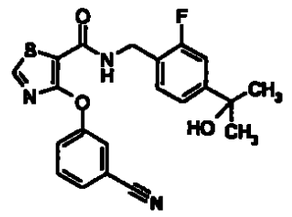

(8 0 139)

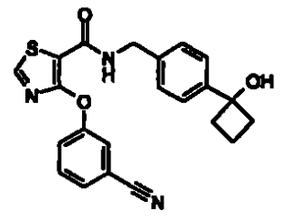
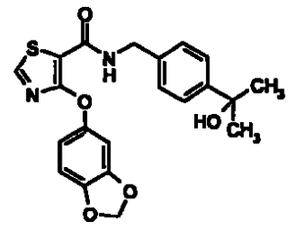
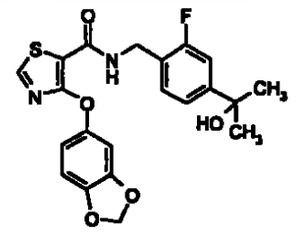
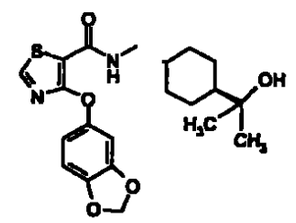
Cualquier resto que sea un miembro seleccionado del grupo constituido por las fórmulas parciales (8.0.1) a (8 0.139) descrito anteriormente incluye la sustitución opcional de este con respecto a· (1) uno cualquiera o más átomos de carbono de éste con un sustituyente $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió anteriormente; (2) uno cualquiera o más de los átomos de nitrógeno de éste con un sustituyente $R^{15}$, teniendo $R^{15}$ el mismo significado que se definió anteriormente, y todas las

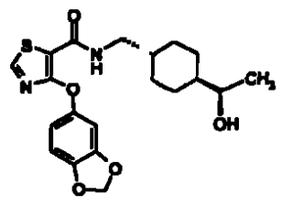
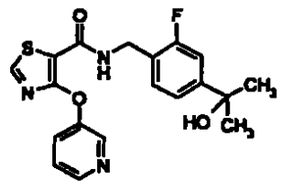
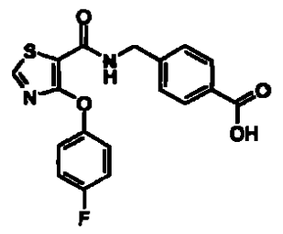
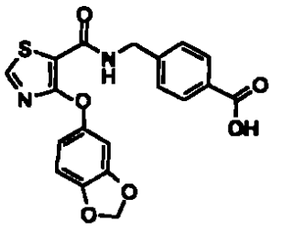
formas tautoméricas, y opcionalmente formas N-óxido de éstos; o (3) cualquier átomo de azufre de éste con 0, 1 ó 2 átomos de oxígeno.

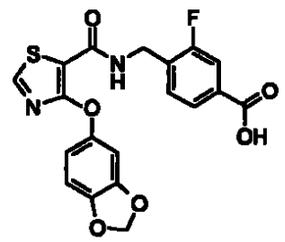
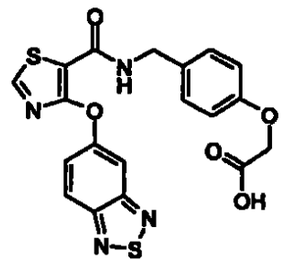
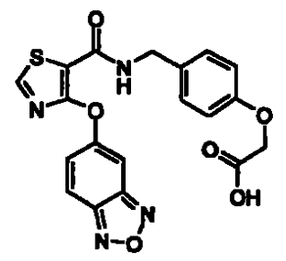
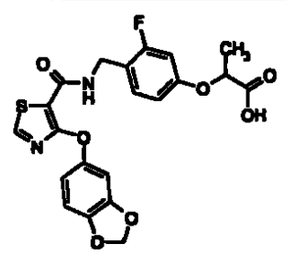
## 5.7 Especies representativas de fórmula (1.0.0)

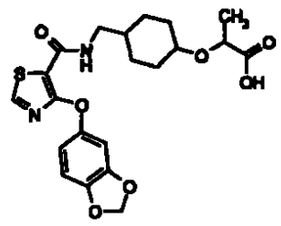
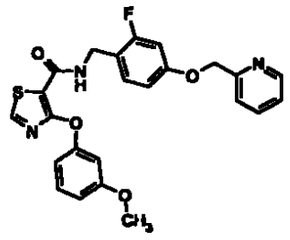
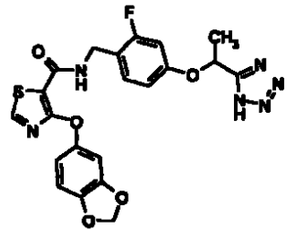
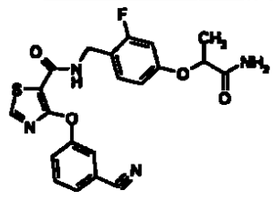
En la descripción anterior, se han indicado varios aspectos preferidos de los compuestos de fórmula (1.0.0). Como demostración adicional del alcance y el contenido de la presente invención, se presentan compuestos específicos que comprenden realizaciones de los compuestos de fórmula (1.0.0). Dichas especies de fórmula (1.0.0) incluyen, pero sin limitación, los siguientes compuestos de fórmulas (8.5.1) a (8.5.44):

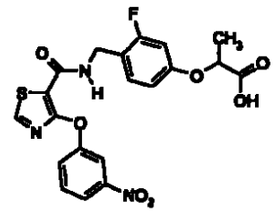
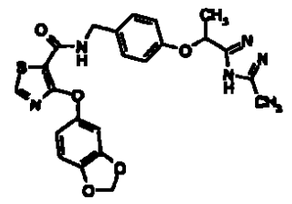
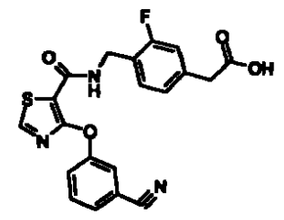
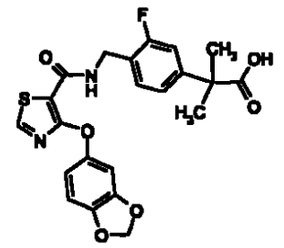
| | | |
|---|---|---|
| (8.5.1) | 4-(1-Hidroxi-1-metiletil)-bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8 5 1) |  |
| (8.5 2) | 2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(3-cianofenoxi)-tiazol-5-carboxílico de fórmula (8 5 2 ) |  |

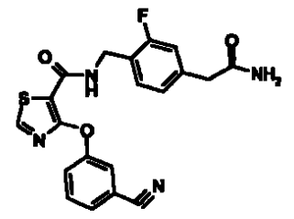
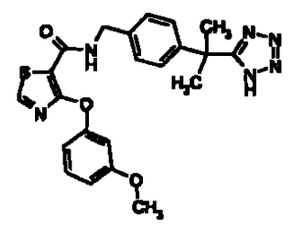
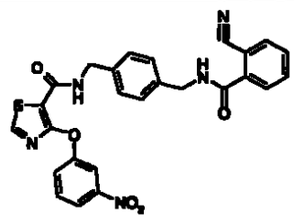
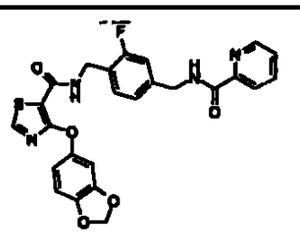
| | | |
|---|---|---|
| (8 5 3) | 4-(1-Hidroxiciclcbutil)-bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8 5 3) |  |
| (8 5 4) | 4-(1-Hidroxi-1-metiletil)-bencilamida del ácido 4-(benzo[1,3]dıoxol-5-ıloxi)tiazol-5-carboxílico de fórmula (8 5 4) |  |
| (8 5 5) | 2-Fluoro-4-(1-hıdroxı-1-metiletil)bencilamida del ácido 4-(benzo[1,3]dıoxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 5) |  |
| (8 5 6) | [4-(1-Hidroxi-1-metiletil)-ciclohexilmetil]amida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 6) |  |

| | | |
|---|---|---|
| (8.5.7) | [4-(1-Hidroxietil)ciclo-hexilmetil]amida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 7) |  |
| (8 5.8) | 2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(piridin-3-iloxi)tiazol-5-carboxílico de fórmula (8 5 8) |  |
| (8 5 9) | Acido 4-({[4-(4-fluorofen-4-iloxi)[1,3]tiazol-5-carbonil]amino}metil)-benzoico de fórmula (8 5 9) |  |
| (8 5 10) | Acido 4-{[(4-benzo[1,3]-dioxol-5-iloxi)[1,3]tiazol-5-carbonil]amino]metil}-benzoico de fórmula (8.5.10) |  |

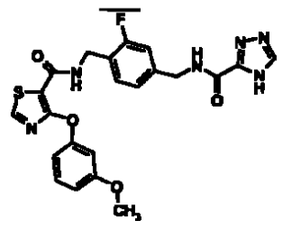
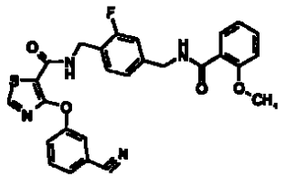
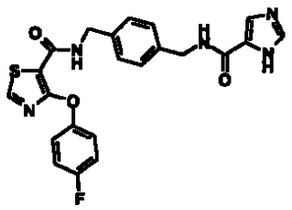
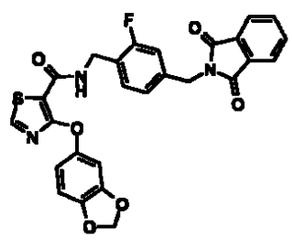
| | | |
|---|---|---|
| (8 5 11) | Acido 4-({[4-(benzo[1,3]-dioxol-5-iloxi)[1,3]tiazol-5-carbonıl]amino}metil)-3-fluorobenzoico de fórmula (8 5 11) |  |
| (8 5 12) | Acıdo [4-({[4-(benzo-[2,1,3]tiadiazol-5-iloxi)[1,3]tiazol-5-carbonıl]amıno}metil)fen-4-iloxi]acético de fórmula (8 5 12) |  |
| (8 5 13) | Acido [4-({[4-(benzo-[2,1,3]oxadiazol-5-iloxi)[1,3]tiazol-5-carbonıl]amıno}metıl)fenil-4-iloxi]acético de fórmula (8 5 13) |  |
| (8 5 14) | Acıdo (±)-2-[4-({[4-(benzo[1,3]-dioxol-5-ıloxi)tiazol-5-carbonil]amino}metil)-3-fluorofenoxi]propiónico de fórmula (8 5 14) |  |

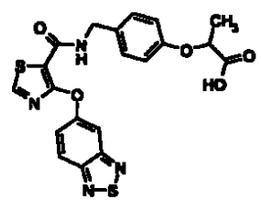
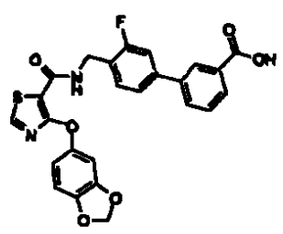
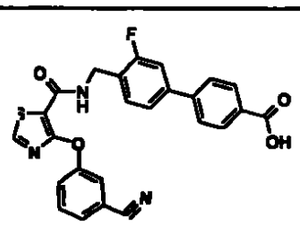
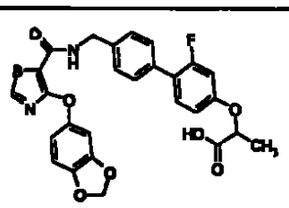
| | | |
|---|---|---|
| (8 5 15) | Acido (±)-2-[4-({[4-(benzo-[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)-ciclohexiloxi]propiónico de fórmula (8 5 15) |  |
| (8 5 16) | 2-Fluoro-4-(piridin-2-ilmetoxi)bencilamida del ácido 4-(3-metoxifenoxi)-tiazol-5-carboxílico de fórmula (8 5 16) |  |
| (8 5 17) | 2-Fluoro-4-[1-(1H-tetrazol-5-il)etoxi]bencilamida del ácido (±)-(4-(benzo[1,3]-dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 17) |  |
| (8 5 18) | 4-(1-Carbamoiletoxi)-2-fluorobencilamida del ácido (±)-4-(3-cianofenoxi)-tiazol-5-carboxílico de fórmula (8 5 18) |  |

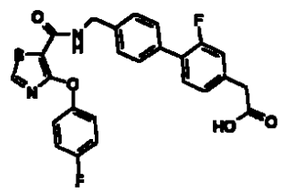
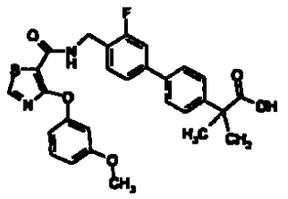
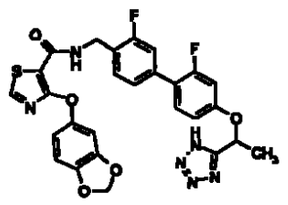
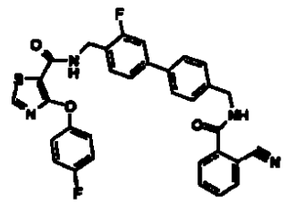
| | | |
|---|---|---|
| (8 5 19) | Acido (±)-2-[3-fluoro-4-({[4-(3-nitrofenoxi)tiazol-5-carbonil]amino}metil)-fenoxi]propiónico de fórmula (8 5 19) |  |
| (8 5 20) | 4-[1-(5-Metil-4H-[1,2,4]-triazol-3-il)etoxi]bencil-amida del ácido (±)-4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 20) |  |
| (8 5 21) | Acido [4-({[4-(3-ciano-fenoxi)tiazol-5-carbonil]-amino}metil)-3-fluoro-fenil]acético de fórmula (8 5 21) |  |
| (8 5 22) | Acido 2-[4-({[4-(benzo-[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)-3-fluorofenil]-2-metil-propiónico de fórmula (8 5 22) |  |

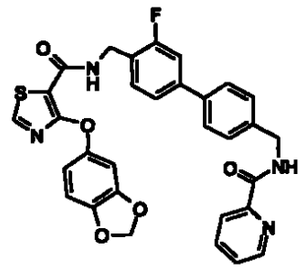
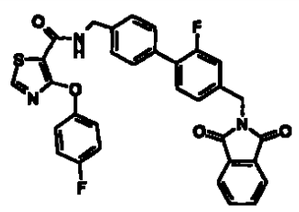
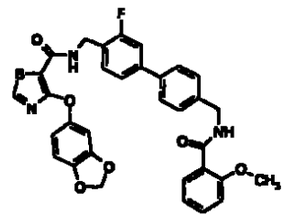
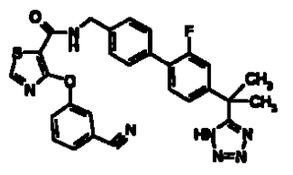
| | | |
|---|---|---|
| (8 5 23) | 4-Carbamoilmetil-2-fluorobencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8 5 23) |  |
| (8 5 24) | 4-[1-Metil-1-(1H-tetrazol-5-il)etil]bencilamida del ácido 4-(3-metoxifenoxi)-tiazol-5-carboxílico de fórmula (8 5 24) |  |
| (8 5.25) | 4-[(2-Cianobenzoilamino)-metil]bencilamida del ácido 4-(3-nitrofenoxi)tiazol-5-carboxílico de fórmula (8.5 25) |  |
| (8 5 26) | 4-({[4-(Benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]-amino}metil)-3-fluoro-bencilamida del ácido piridin-2-carboxílico de fórmula (8 5 26) |  |

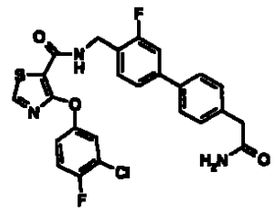
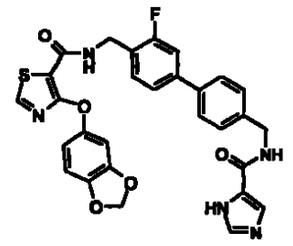
00353

| | | |
|---|---|---|
| (8 5 27) | 3-Fluoro-4-({[4-(3-metoxi-fenoxi)tiazol-5-carbonil]-amino}metil)bencilamida del ácido 4H-[1,2,4]triazol-3-carboxílico de fórmula (8 5 27) |  |
| (8 5 28) | 2-Fluoro-4-[(2-metoxi-benzoilamino)metil]-bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8 5 28) |  |
| (8 5 29) | 4-{[(3H-Imidazol-4-carbonil)amino]metil}bencilamida del ácido 4-(4-fluorofenoxi)tiazol-5-carboxílico de fórmula (8 5 29) |  |
| (8 5 30) | 4-(1,3-Dioxo-1,3-dihidro-isoindol-2-ilmetil)-2-fluorobencilamida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de |  |

| | | |
|---|---|---|
| | fórmula (8.5 30) | |
| (8 5 31) | Acido (±)-2-[4-({[4-(benzo-[2,1,3]tiadiazol-5-iloxi)-tiazol-5-carbonil]amino}-metil)fenoxi]propiónico de fórmula (8 5 31) |  |
| (8 5 32) | Acido 4'-({[4-(benzo-[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)-3'-fluorobifenil-3-carboxilico de fórmula (8 5 32) |  |
| (8 5 33) | Acido 4'-({[4-(3-ciano-fenoxi)tiazol-5-carbonil]-amino}metil)-3'-fluoro-bifenil-4-carboxilico de fórmula (8 5 33) |  |
| (8 5 34) | Acido (±)-2-[4'-({[4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]-amino}metil)-2-fluoro-bifenil-4-iloxi]propiónico de fórmula (8 5 34) |  |

| | | |
|---|---|---|
| (8 5 35) | Acido [2-fluoro-4'-({[4-(4-fluorofenoxi)tiazol-5-carbonil]amino}metil)-bifenil-4-il]acético de fórmula (8 5 35) |  |
| (8 5 36) | Acido 2-[3'-fluoro-4'-({[4-(3-metoxifenoxi)tiazol-5-carbonil]amino}metil)-bifenil-4-il]-2-metil-propiónico de fórmula (8 5 36) |  |
| (8 5 37) | (3,2'-Difluoro-4'-[1-(1H-tetrazol-5-il)etoxi]-bifenil-4-ilmetil}amida del ácido (±)-4-(4-benzo-[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 37) |  |
| (8 5 38) | {4'-[(2-Cianobenzoilamino)-metil]-3-fluorobifenil-4-ilmetil}amida del ácido 4-(4-fluorofenoxi)tiazol-5-carboxílico de fórmula (8.5 38) |  |

| | | |
|---|---|---|
| (8 5 39) | [4'-(([4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]-amino}metil-3'-fluoro-bifenil-4-ilmetil]amida del ácido pirıdın-2-carboxílico de fórmula (8 5 39) |  |
| (8 5 40) | [4'-(1,3-Dioxo-1,3-di-hıdroisoindol-2-ilmetıl)-2'-fluorobifenil-4-ilmetil]amida del ácido 4-(4-fluorofenoxi)tiazol-5-carboxílico de fórmula (8 5 40) |  |
| (8 5 41) | {3-Fluoro-4'-[(2-metoxi-benzoılamino)metil]bifenil-4-ilmetil}amida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 41) |  |
| (8 5.42) | {2'-Fluoro-4'-[1-metil-1-(1H-tetrazol-5-il)etil]-bifenil-4-ilmetıl}amida del ácido 4-(3-cianofenoxi)-tiazol-5- |  |

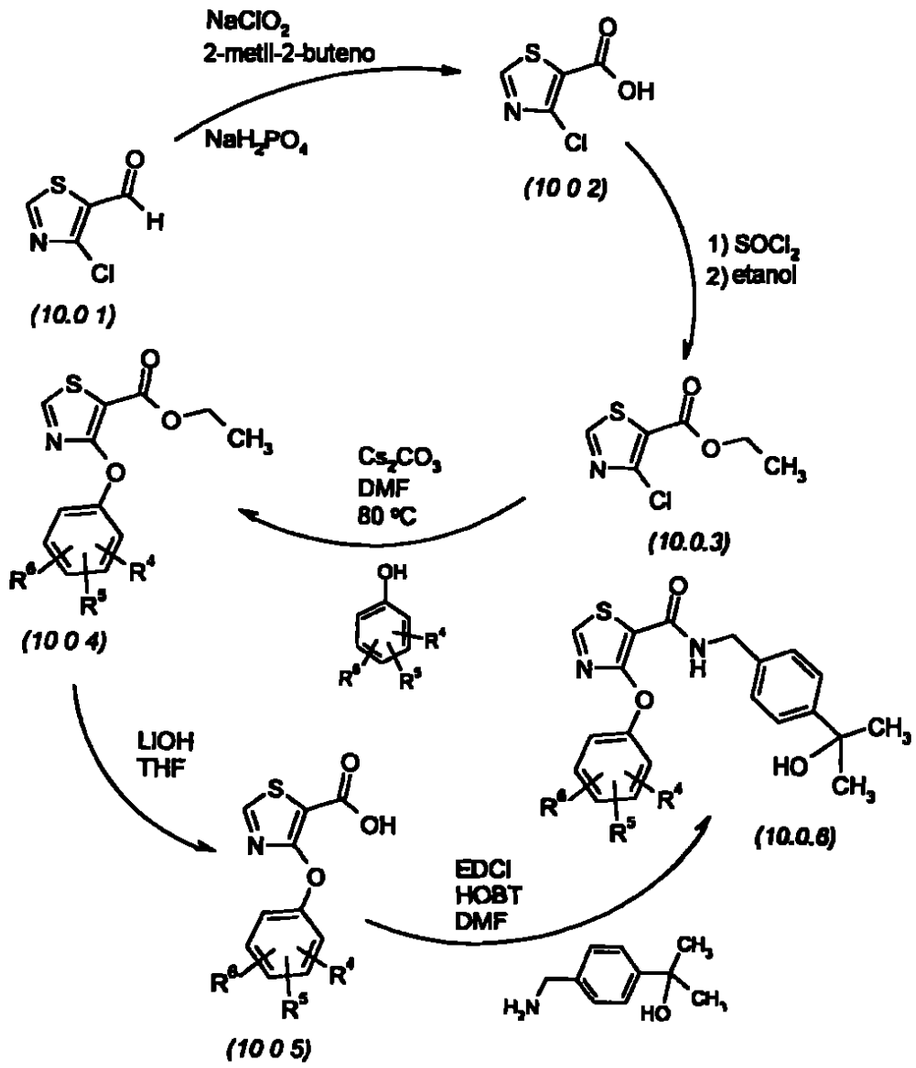
| | | |
|---|---|---|
| | carboxílico de fórmula (8.5 42) | |
| (8 5 43) | (4'-Carbamoilmetil-3-fluorobifenil-4-ilmetil)-amida del ácido 4-(3-cloro-4-fluorofenoxi)tiazol-5-carboxílico de fórmula (8 5 43) |  |
| (8 5 44) | (3-Fluoro-4'-{[(3H-imidazol-4-carbonil)amino]-metil}bifenil-4-ilmetil)-amida del ácido 4-(benzo-[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8 5 44) |  |

**DESCRIPCION DETALLADA DE LA INVENCION**

**6.0 Procedimientos de preparación de los compuestos de fórmula (1.0.0)**

Se ilustra un procedimiento adecuado para la preparación de compuestos de fórmula (1.0.0) en la que ambos grupos $G^1$ y $G^2$ son fenilo, y el grupo E es un resto de fórmula parcial (1.1.8) en el esquema de síntesis (10.0.0) a continuación.

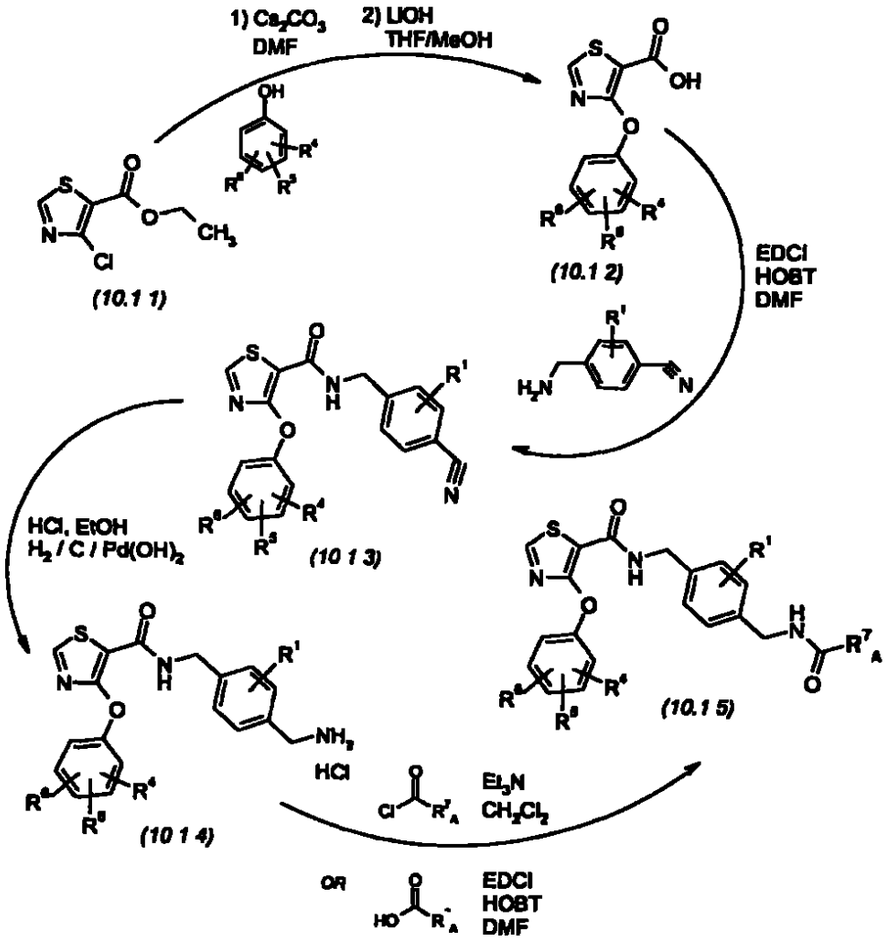
ESQUEMA DE SINTESIS (10.0.0)



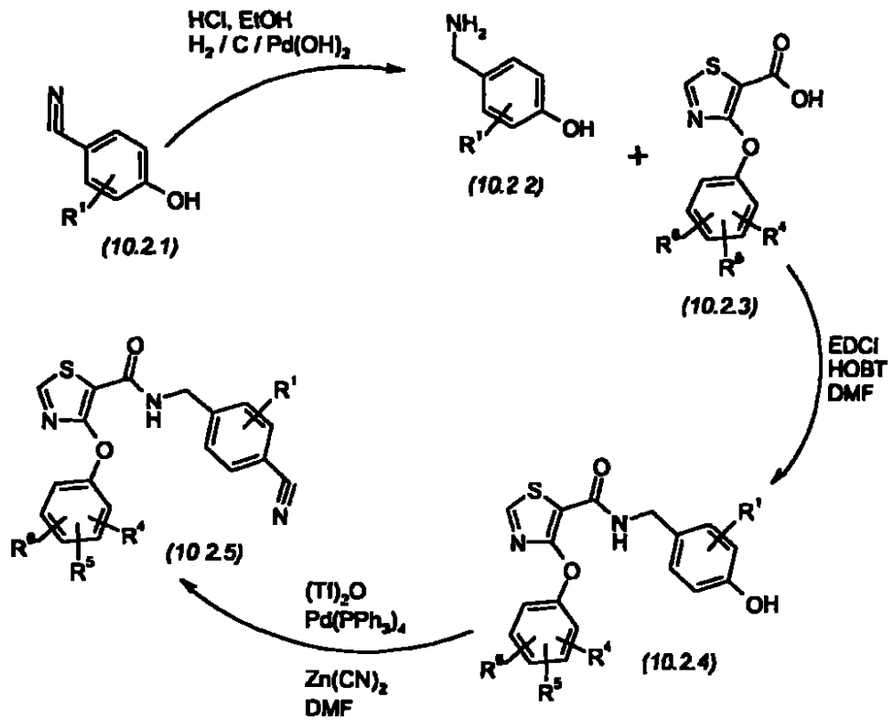
355

08359

## ESQUEMA DE SINTESIS (10.1.0)



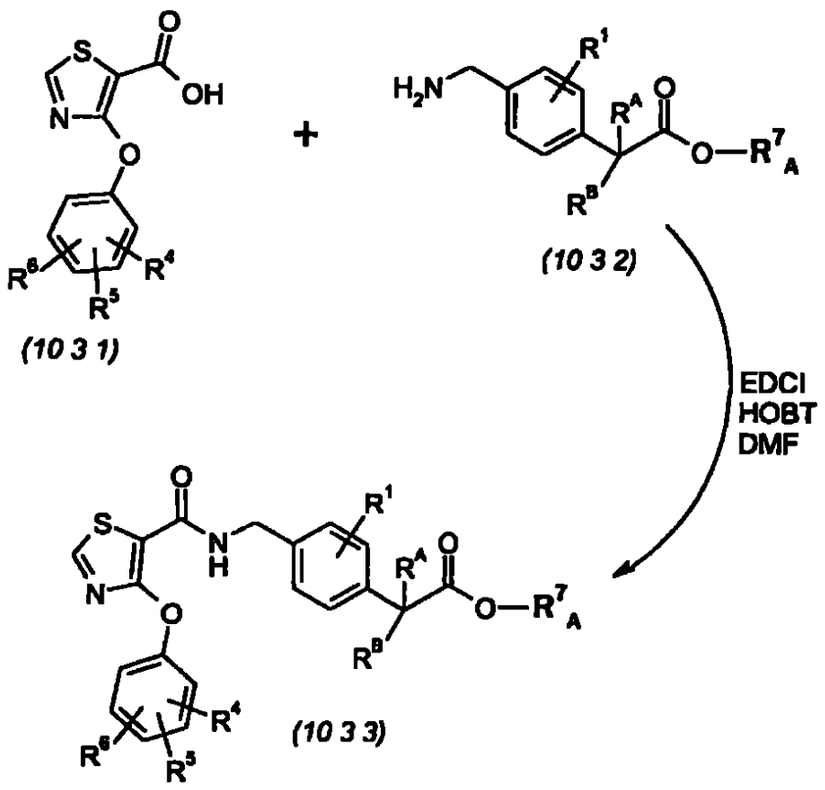
ESQUEMA DE SINTESIS (10.2.0)



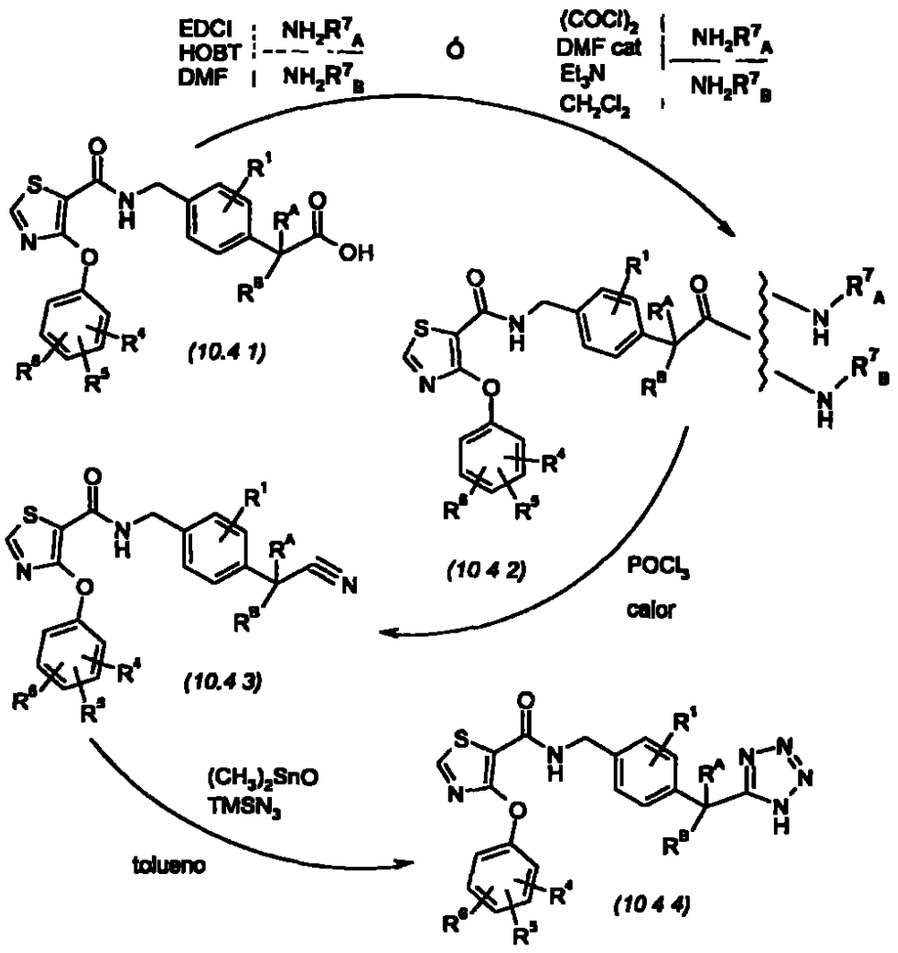
00361

35X

ESQUEMA DE SINTESIS (10 3.0)

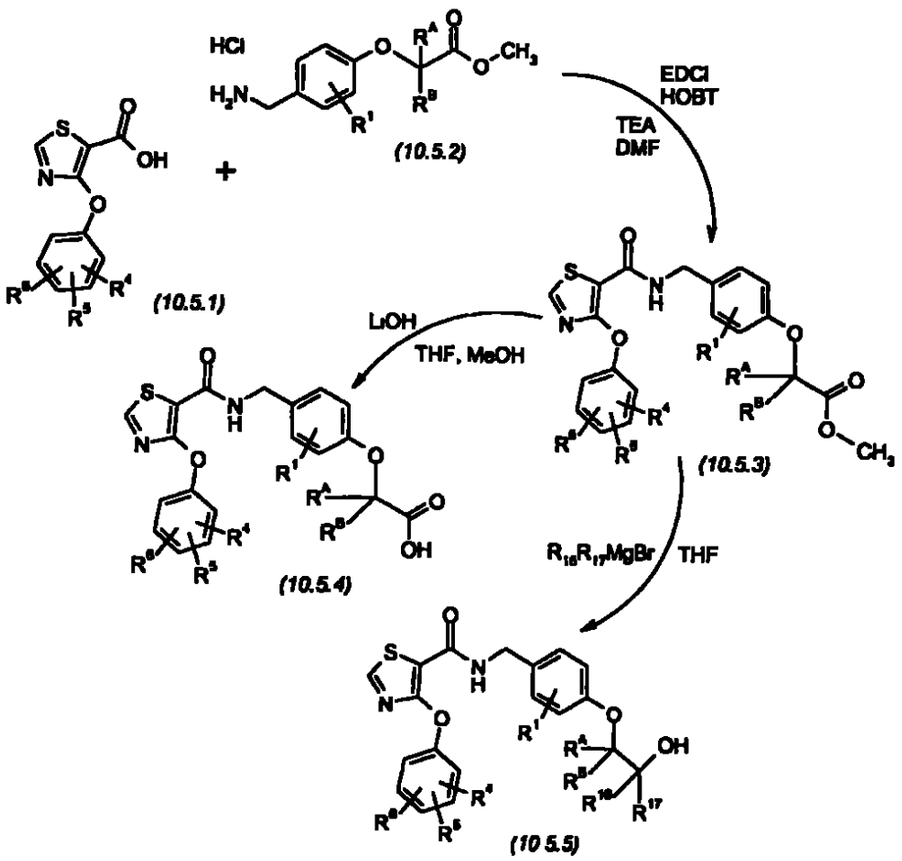


ESQUEMA DE SINTESIS (10.4.0)

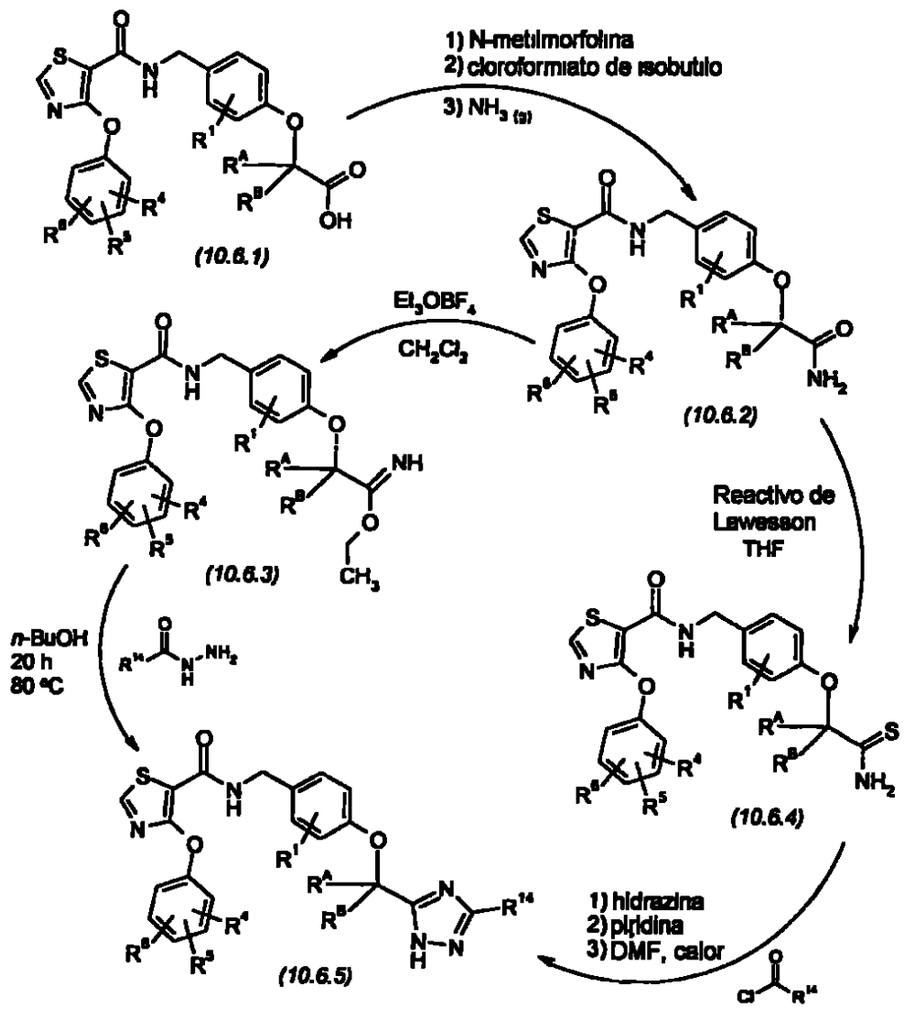


359

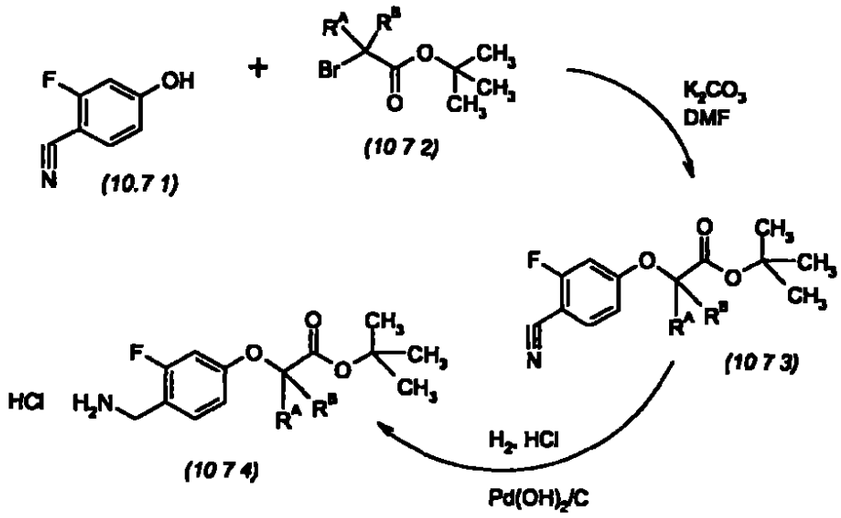
## ESQUEMA DE SINTESIS (10.5.0)



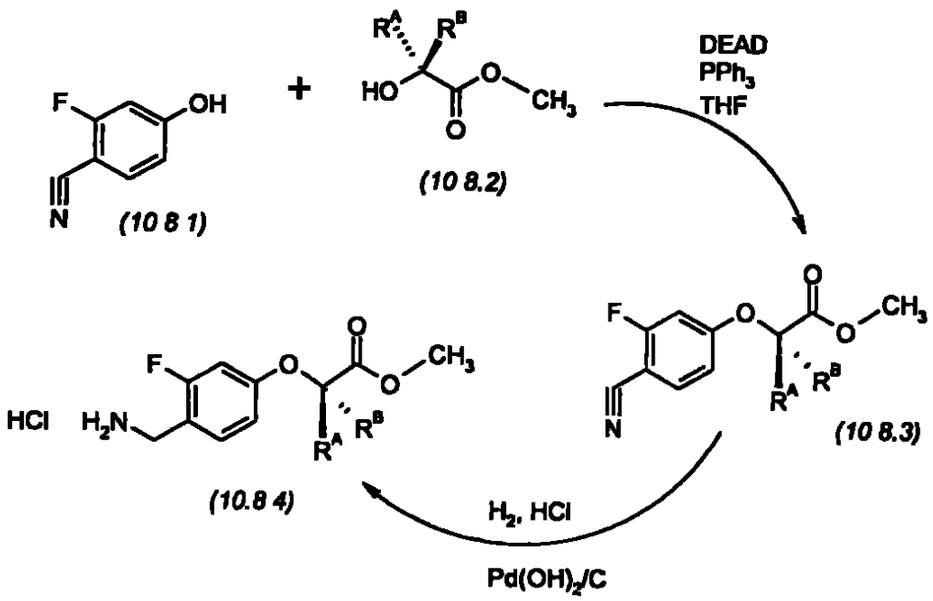
ESQUEMA DE SINTESIS (10.6.0)



ESQUEMA DE SINTESIS (10.7.0)



ESQUEMA DE SINTESIS (10.8.0)



**DESCRIPCION DETALLADA DE LA INVENCION**

**7.0 Sales farmacéuticas y otras formas**

Los compuestos anteriormente descritos de la presente invención pueden utilizarse en forma de ácidos, ésteres u otras clases de compuestos químicos a las que pertenecen los compuestos descritos. Está también dentro del alcance de la presente invención utilizar aquellos compuestos en forma de sus sales farmacéuticamente aceptables derivados de diversos ácidos y bases orgánicos e inorgánicos, según procedimientos bien conocidos en la técnica.

Las formas de sales farmacéuticamente aceptables de los compuestos de fórmula (1.0.0) se preparan en su mayor parte por medios convencionales. Cuando el compuesto de fórmula (1.0.0) contiene un grupo ácido carboxílico, puede formarse una sal adecuada de éste haciendo reaccionar el compuesto con una base apropiada, proporcionando la correspondiente sal de adición de base. Son ejemplos de dichas bases hidróxidos de metal alcalino, incluyendo hidróxido de sodio, hidróxido de potasio e hidróxido de litio; hidróxidos de metal alcalinotérreo, tales como hidróxido de bario e hidróxido de calcio; alcóxidos de metal alcalino, por ejemplo etanolato de potasio y propanolato de sodio; y diversas bases orgánicas, tales como piperidina, dietanolamina y N-metilglutamina. Se incluyen también las sales de aluminio de los compuestos de fórmula (1.0.0).

Para ciertos compuestos de fórmula (1.0.0), pueden formarse las sales de adición de ácidos tratando dichos compuestos con ácidos orgánicos e inorgánicos farmacéuticamente aceptables, por ejemplo, halohidratos tales como clorhidrato, bromhidrato, yodhidrato, otros ácidos minerales y sus correspondientes sales, tales como sulfato, nitrato, fosfato, etc.; y alquil- y monoarilsulfonatos, tales como etanosulfonato, toluenosulfonato y bencenosulfonato; y otros ácidos orgánicos y sus correspondientes sales, tales como acetato, tartrato, maleato, succinato, citrato, benzoato, salicilato, ascorbato, etc

Consiguientemente, 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, bromuro, butirato, canforato, canfosulfonato, caprilato, cloruro, clorobenzoato, citrato, ciclopentanopropionato, digluconato, fosfato diácido, 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, isobutirato, lactato, lactobionato, malato, maleato, malonato, mandelato, metafosfato, metanosulfonato, metilbenzoato, fosfato monoácido, 2-naftalenosulfonato, nicotinato, nitrato, oxalato, oleato, pamoato, pectinato, persulfato, fenilacetato, 3-fenilpropionato, fosfato, fosfonato, ftalato.

Además, las sales de bases de los compuestos de la presente invención incluyen, pero sin limitación, sales de aluminio, de calcio, de cobre, férricas, ferrosas, de litio, de magnesio, mangánicas, manganosas, de potasio, de sodio y de zinc. Las preferidas entre las sales anteriormente enumeradas son las de amonio, las sales de metales alcalinos de sodio y potasio; y las sales de metales alcalinotérreos de calcio y magnesio. Las sales de los compuestos de fórmula (1.0.0) derivadas de bases orgánicas no tóxicas farmacéuticamente aceptables incluyen, pero sin limitación, sales de aminas primarias, secundarias y terciarias, aminas sustituidas, incluyendo aminas sustituidas de origen natural, aminas cíclicas, y resinas básicas de intercambio iónico, por ejemplo arginina, betaína, cafeína, cloroprocaína, colina, N,N'-dibenciletilendiamina (benzatina), diciclohexilamina, dietanolamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina,

hidrabamina, isopropilamina, 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, isopropilo y terc-butilo; sulfatos de dialquilo ($C_1$-$C_4$), 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. Dichas sales permiten la preparación tanto de compuestos hidrosolubles como liposolubles de la presente invención

Entre las sales farmacéuticas anteriormente enumeradas, aquellas preferidas incluyen, pero sin limitación, acetato, besilato, citrato, fumarato, gluconato, hemisuccinato, hipurato, clorhidrato, bromhidrato, isetionato, mandelato, meglumina, nitrato, oleato, fosfonato, pivalato, fosfato de sodio, 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, produciendo la sal de manera convencional. La base libre puede regenerarse poniendo en contacto la forma de sal con una base, y aislando la base libre de manera convencional. Las formas de base libre se diferencian algo de sus respectivas formas de sal en ciertas propiedades físicas, tales como la solubilidad en disolventes polares, pero por lo demás, son equivalentes a sus respectivas formas de base libre para los fines de la presente invención.

Como se indicó, las sales de adición de bases farmacéuticamente aceptables de los compuestos de fórmula (1.0.0) se forman con metales o aminas, tales como aminas de metales alcalinos y metales alcalinotérreos u orgánicas. Los metales preferidos son sodio, potasio, magnesio y calcio. Las aminas orgánicas preferidas son N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina, N-metil-D-glucamina y procaína.

Las sales de adición de bases de compuestos ácidos de la presente invención se preparan poniendo en contacto la forma de

ácido libre con una cantidad suficiente de la base deseada, produciendo la sal de manera convencional. La forma de ácido libre puede regenerarse poniendo en contacto la forma de sal con un ácido, y aislando la forma de ácido libre de manera convencional. Las formas de ácido libre se diferencian algo de sus respectivas formas de sal en propiedades físicas tales como la solubilidad en disolventes polares, pero por lo demás son equivalentes a sus respectivas formas de ácido libre para los fines de la presente invención.

Se incluyen formas de sales múltiples dentro del alcance de la presente invención cuando un compuesto de la presente invención contiene más de un grupo capaz de formar dichas sales farmacéuticamente aceptables. Los ejemplos de formas de sales múltiples típicas incluyen, pero sin limitación, bitartrato, diacetato, difumarato, dimeglumina, difosfato, disodio y triclorhidrato.

A la vista de lo anterior, puede observarse que la expresión "sal farmacéuticamente aceptable", como se utiliza en la presente descripción, se pretende que signifique un ingrediente activo que comprende un compuesto de fórmula (1.0.0) utilizado en forma de una sal de este, especialmente cuando dicha forma de sal confiere propiedades farmacocinéticas mejoradas al citado ingrediente activo en comparación con la

forma libre del citado ingrediente activo o alguna otra forma de sal del citado ingrediente activo utilizada previamente. La forma de sal farmacéuticamente aceptable del citado ingrediente activo puede también conferir inicialmente una propiedad farmacocinética deseable al citado ingrediente activo que no poseía previamente, y puede incluso afectar positivamente la farmacodinámica del citado ingrediente activo con respecto a su actividad terapéutica en el cuerpo.

Las propiedades farmacocinéticas del citado ingrediente activo que pueden verse afectadas favorablemente incluyen, por ejemplo, la manera en que se transporta el citado ingrediente activo a través de las membranas celulares, que a su vez puede afectar directa y positivamente a la absorción, distribución, biotransformación y excreción del citado 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 del citado ingrediente activo depende habitualmente del carácter de la forma de sal particular de éste que se utiliza. Además, como observará el experto, una solución acuosa del citado ingrediente activo proporcionará la absorción más rápida del citado ingrediente activo en el cuerpo de un paciente que se esté tratando, mientras que las soluciones y suspensiones lipídicas, así como las formas de dosificación sólidas, darán

como resultado una absorción menos rápida del citado 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 dicha forma de dosificación oral puede verse afectada adversamente por características físicas, tales como polaridad, émesis causada por la irritación de la mucosa gastrointestinal, destrucción por enzimas digestivas y bajo pH, absorción irregular o propulsión en presencia de comida u otros fármacos, y metabolismo por enzimas de la mucosa, la flora intestinal o el hígado. La formulación del citado ingrediente activo en diferentes formas de sales farmacéuticamente aceptables puede ser eficaz para superar o mitigar uno o más de los problemas anteriormente enumerados hallados con una absorción de formas de dosificación oral.

Finalmente, puede separarse un compuesto de fórmula (1.0.0), preparado según los procedimientos descritos en la presente descripción, de la mezcla de reacción en la que se produce mediante cualquier medio ordinario conocido por el químico experto en la preparación de compuestos orgánicos. Después de separado, el citado compuesto puede purificarse por procedimientos conocidos. Pueden utilizarse diversos

procedimientos y técnicas como medio de separación y purificación, que incluyen, por ejemplo, destilación; recristalización; cromatografía en columna; cromatografía de intercambio iónico; cromatografía en gel; cromatografía de afinidad; cromatografía de capa fina preparativa; y extracción con disolvente.

**7.1. Estereoisómeros**

Un compuesto dentro del alcance de la fórmula (1.0.0) puede ser tal que sus átomos constituyentes puedan disponerse en el espacio en dos o más formas diferentes, a pesar de tener conexiones idénticas. Como consecuencia, el citado compuesto existe en forma de estereoisómeros. La isomería cis-trans es sólo un tipo de estereoisomería. Cuando los estereoisómeros son imágenes especulares no superponibles entre sí son enantiómeros, que tienen quiralidad o sentido de la mano debido a la presencia de uno o más átomos de carbono asimétricos en su estructura constituyente. Los enantiómeros son ópticamente activos, y por tanto distinguibles debido a que rotan el plano de la luz polarizada en grados iguales, pero en direcciones opuestas.

Cuando están presentes dos o más átomos de carbono asimétricos en un compuesto de fórmula (1.0.0), existen dos configuraciones posibles en cada átomo de carbono. Cuando está presentes dos átomos de carbono asimétricos, por ejemplo,

existen cuatro posibles estereoisómeros. Además, estos cuatro posibles estereoisómeros 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. Aquellos pares que no estén relacionados como enantiómeros tienen una relación estereoquímica diferente, a la que se denomina relación diastereomérica. Los estereoisómeros que no son enantiómeros se denominan diastereoisómeros, o más habitualmente, diastereómeros.

Todos estos aspectos bien conocidos de la estereoquímica de los compuestos de fórmula (1.0.0) se contemplan como parte de la presente invención. Se incluyen por tanto dentro del alcance de la presente invención compuestos de fórmula (1.0.0) que son estereoisómeros, y cuando estos son enantiómeros, los enantiómeros individuales, las mezclas racémicas de los citados enantiómeros y las mezclas artificiales, es decir fabricadas, que contienen proporciones de los citados enantiómeros que son diferentes de las proporciones de los citados enantiómeros encontradas en una mezcla racémica. Cuando un compuesto de fórmula (1 0.0) comprende estereoisómeros que son diastereómeros, se incluyen dentro del alcance del citado compuesto los diastereómeros individuales, así como sus mezclas, de cualesquiera dos o más de los citados diastereómeros en

cualquier proporción de estos.

A modo de ilustración, en el caso de que exista un solo átomo de carbono asimétrico en un compuesto de fórmula (1.0.0), que dé como resultado los enantiómeros (-)(R) y (+)(S) de este, se incluyen dentro del alcance del citado compuesto todas las formas de sales farmacéuticamente aceptables, profármacos y metabolitos de éste que sean terapéuticamente activos y útiles en el tratamiento o la prevención de las enfermedades y afecciones descritas más adelante en la presente descripción. Cuando existe un compuesto de fórmula (1.0 0) en forma de los enantiómeros (-)(R) y (+)(S), se incluyen también dentro del alcance del citado compuesto el enantiómero (+)(S) solo, o el enantiómero (-)(R) solo, en el caso en que toda, sustancialmente toda o una parte predominante de la actividad terapéutica resida en sólo uno de los citados enantiómeros, y/o los efectos secundarios indeseados residan en sólo uno de los citados enantiómeros. En el caso de que no haya sustancialmente diferencia entre las actividades biológicas de ambos enantiómeros, se incluye además dentro del alcance del citado compuesto de fórmula (1.0.0), el enantiómero (+)(S) y el enantiómero (-)(R) presentes conjuntamente en forma de una mezcla racémica, o en forma de una mezcla no racémica, en cualquier relación de cantidades proporcionadas de estos.

Por ejemplo, las actividades biológicas y/o físicas y químicas particulares de un par o conjunto de enantiómeros de un compuesto de fórmula (1.0.0), en el que tales existan, pueden sugerir el uso de los citados enantiómeros en ciertas proporciones para constituir un producto terapéutico final. A modo de ilustración, en el caso en que haya un par de enantiómeros, pueden emplearse en relaciones tales como 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); y 10% (R)- 90% (S). Después de evaluar las propiedades de los diversos enantiómeros de un compuesto de fórmula (1.0.0) en el que tales existan, puede determinarse de manera directa la cantidad proporcional de uno o más de los citados enantiómeros con ciertas propiedades deseadas, que constituirán el producto terapéutico final.

**7.2 Isótopos**

Se contempla además incluir dentro del alcance de un compuesto de fórmula (1.0.0) formas marcadas isotópicamente de éste. Una forma marcada isotópicamente de un compuesto de fórmula (1.0.0) es idéntica al citado compuesto, excepto por el hecho de que uno o más átomos del citado compuesto se han reemplazado por un átomo o átomo de masa atómica o número másico diferente de la masa atómica o número másico de dicho átomo que se encuentra habitualmente en la naturaleza. Los ejemplos de

isótopos que están fácilmente asequibles comercialmente, y que pueden incorporarse a un compuesto de fórmula (1.0.0) según procedimientos 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 de éste o una sal farmacéuticamente aceptable de cualquiera, que contenga uno o más de los isótopos anteriormente citados y/o otros isótopos de otros átomos, están contemplados dentro del alcance de la presente invención.

Puede utilizarse un compuesto marcado isotópicamente de fórmula (1.0.0) de una serie de modos beneficiosos. Por ejemplo, un compuesto marcado isotópicamente de fórmula (1.0.0), por ejemplo, uno en el que se ha incorporado un isótopo radiactivo tal como $^{3}H$ ó $^{14}C$, será útil en ensayos de distribución de fármaco y/o tejido sustrato. Estos isótopos radiactivos, es decir, tritio, $^{3}H$ y carbono-14, $^{14}C$, son especialmente preferidos por su facilidad de preparación y su extrema detectabilidad. La incorporación de isótopos más pesados, por ejemplo deuterio, $^{2}H$, a un compuesto de fórmula (1.0.0) proporcionará ventajas terapéuticas basadas en la mayor estabilidad metabólica del citado compuesto isotópicamente marcado. Una mayor estabilidad metabólica se traduce directamente en una semivida in vivo aumentada o en requisitos de dosificación reducidos, que en la

mayoría de las circunstancias constituirán una realización preferida de la presente invención. Un compuesto marcado isotópicamente de fórmula (1.0.0) puede prepararse habitualmente llevando a cabo los procedimientos descritos en los esquemas de síntesis y descripción, ejemplos y preparaciones relacionadas de la presente descripción, sustituyendo por un reactivo marcado isotópicamente fácilmente asequible su correspondiente reactivo no marcado isotópicamente.

El deuterio, $^{2}H$, puede incorporarse también a un compuesto de fórmula (1.0.0) para fines de manipulación del metabolismo oxidativo del citado compuesto mediante el efecto isotópico cinético primario El efecto isotópico cinético primario es un cambio de la velocidad de una reacción química como resultado de la sustitución de núcleos isotópicos, que a su vez está causada por el cambio de las energías de estado fundamental requeridas para la formación de un enlace covalente posterior a la citada sustitución isotópica. La sustitución de un isótopo más pesado dará habitualmente como resultado una reducción de la energía de estado fundamental para un enlace químico, causando así una reducción de la velocidad de una etapa de rotura de un enlace limitante de la velocidad. Si el suceso de rotura del enlace aparece en o cerca de una región de punto de silla de montar a lo largo de la coordenada de una reacción multiproducto, las relaciones de distribución del producto pueden alterarse

sustancialmente. A modo de ilustración, cuando el deuterio está unido a un átomo de carbono en un sitio no intercambiable, son típicas diferencias de velocidades de $k_H/k_D$ = 2-7. Esta diferencia de velocidad, aplicada con éxito a un compuesto oxidativamente lábil de fórmula (1.0.0), puede afectar drásticamente al perfil del citado compuesto in vivo, y dar como resultado propiedades farmacocinéticas mejoradas.

Al descubrir y desarrollar agentes terapéuticos, el experto busca optimizar los parámetros farmacocinéicos reteniendo las propiedades deseables in vitro. Es una suposición razonable que muchos compuestos con malos perfiles farmacocinéticos sufran de labilidad ante el metabolimo oxidativo. Los ensayos microsomales in vitro ahora asequibles proporcionan información valiosa sobre el transcurso de este metabolismo oxidativo, que a su vez permite el diseño racional de compuestos deuterados de fórmula (1 0.0) con una estabilidad mejorada por su resistencia ante dicho metabolismo oxidativo. Se obtienen así mejoras significativas en los perfiles farmacocinéticos de los compuestos de fórmula (1.0.0), que pueden expresarse cuantitativamente en términos de aumentos de la semivida in vitro (t/2), de la concentración al efecto terapéutico máximo ($c_{máx}$), del área bajo la curva de respuesta a la dosis (AUC) y F; y en términos de reducciones de aclaramiento, dosis y costes de materiales.

A modo de ilustración de lo anterior, se prepara un compuesto de fórmula (1.0 0) que tiene múltiples sitios potenciales para metabolismo oxidativo, por ejemplo átomos de hidrógeno bencílicos y átomos de hidrógeno α a un átomo de nitrógeno, en forma de una serie de análogos en los que se reemplazan combinaciones diversas de átomos de hidrógeno por átomos de deuterio, de modo que algunos, la mayoría o todos los citados átomos de hidrógeno estén reemplazados por átomos de deuterio. Las determinaciones de la semivida proporcionan una determinación conveniente y exacta de la extensión de la mejora de la resistencia ante el metabolismo oxidativo. De esta manera, se determina que la semivida del compuesto original puede extenderse tanto como un 100% como resultado de dicha sustitución de hidrógeno por deuterio.

La sustitución de hidrógeno por deuterio en un compuesto de fórmula (1.0.0) puede utilizarse también para conseguir una alteración favorable del perfil de metabolitos del compuesto original, como forma de reducir o eliminar metabolitos tóxicos indeseados. Por ejemplo, cuando surge un metabolito tóxico por escisión oxidativa de un enlace carbono-hidrógeno C-H, se espera razonablemente que el análogo deuterado reduzca en gran medida o elimine la producción del metabolito indeseado, incluso en el caso de que la oxidación particular no sea una etapa

determinante de la velocidad.

Puede encontrarse información adicional referente al estado de la técnica con respecto a la sustitución de hidrógeno por deuterio, por ejemplo en 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; y Jarman et al., *Carcinogenesis* **16**(4), 683-688, 1993.

**DESCRIPCION DETALLADA DE LA INVENCION**

**8.0. Aplicaciones terapéuticas y resultados clínicos**

La descripción siguiente se refiere a las aplicaciones terapéuticas para las que pueden servir los compuestos de fórmula (1 0.0), y cuando sea aplicable, la explicación de los resultados clínicos asociados con dichas aplicaciones terapéuticas. Se expone también una descripción de diversos ensayos in vitro y experimentos de modelos animales que pueden 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 aquejado por una enfermedad o afección como las indicadas en la presente descripción, y por lo tanto, necesitado de dicho tratamiento.

Los resultados beneficiosos son terapéuticos si se administran a animales o humanos. Como se utilizan en la presente descripción, los términos "animal" o "animales" se utilizan simplemente para fines de destacar a los seres humanos en oposición a los demás miembros del reino animal. Los compuestos de fórmula (1.0.0) tienen aplicabilidad terapéutica en el tratamiento de mamíferos, y particularmente de humanos Todas las subdivisiones principales de la clase de mamíferos (*Mammalia*) están incluidas dentro del alcance de la presente invención respecto a que son receptores del tratamiento terapéutico como se describe en la presente descripción. Los mamíferos tienen valor como mascotas para humanos, y es por tanto probable que sean sujetos de tratamiento. Esto se aplica especialmente a los grupos canino y felino de mamíferos. Otros mamíferos tienen valor como animales domesticados, y su tratamiento según la presente invención es probable en vista del impacto económico adverso de no tratar las enfermedades y afecciones descritas en la presente descripción. Esto se aplica especialmente a los grupos equino, bovino, porcino y ovino de mamíferos.

Los compuestos de fórmula (1.0.0) inhiben la isozima PDE4 y tienen por ello un amplio campo de aplicaciones terapéuticas, como se describe con detalle a continuación, debido al papel esencial que desempeña la familia de isozimas PDE4 en la fisiología de todos los mamíferos. El papel enzimático realizado

por las isozimas PDE4 es la hidrólisis intracelular de 3',5'-monofosfato de adenosina (AMPc) en leucocitos pro-inflamatorios. El AMPc, a su vez, es el responsable de mediar los efectos de numerosas hormonas en el cuerpo, y como consecuencia, la inhibición de PDE4 desempeña un papel significativo en una serie de procesos fisiológicos. Existe una extensa bibliografía en la técnica que describe los efectos de los inhibidores de PDE sobre diversas respuestas celulares inflamatorias que, además de la elevación del nivel de AMPc, incluyen la inhibición de la producción de superóxido, la desgranulación, la quimiotaxia y la liberación de factor de necrosis tumoral (TNF) en eosinófilos, neutrófilos y monocitos.

La PDE4 se identificó por primera vez en 1985, Nemoz et al., *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. Posteriormente, se estableció que la PDE4 es la fosfodiesterasa principal en leucocitos inflamatorios. Los cuatro subtipos de PDE4 es decir, PDE4A, PDE4B, PDE4C y PDE4D, están ampliamente distribuidos en tejidos humanos, como se determina por la presencia de sus ARNm. La PDE4D se expresa en tejidos de riñón, timo, intestino delgado y colon, y se expresa fuertemente en tejidos de cerebro, pulmón, músculo esquelético, próstata y leucocito de sangre periférica (PBL). Se expresa sólo

débilmente en tejido de corazón, placenta, hígado, páncreas, bazo, testículos y ovarios. Las PDE4A y PDE4B se expresan también fuertemente en tejidos de cerebro y músculo esquelético, y se expresan sólo débilmente en tejidos de placenta, hígado y ovario. La PDE4C se expresa fuertemente en tejido de músculo esquelético también, y se expresa débilmente también en tejido de ovario. La PDE4C no es habitualmente detectable en la mayoría de los tejidos anteriormente citados.

La familia PDE4 de isozimas es la forma predominante de fosfodiesterasa encontrada en los tipos celulares implicados en enfermedades inflamatorias crónicas, y entre los tipos celulares derivados de médula ósea, sólo las plaquetas no expresan PDE. La PDE4 es la enzima metabolizante de AMPc principal en las células inflamatorias e inmunes, y es una de las dos enzimas principales metabolizantes de AMPc en músculo liso de las vías aéreas. La PDE4 está presente exclusivamente en neutrófilos, eosinófilos, basófilos y monocitos, mientras que en macrófagos se ha demostrado también actividad de PDE3 y PDE1, y en linfocitos T, actividad de PDE7. Los efectos anti-inflamatorios beneficiosos de los inhibidores de PDE se han demostrado hasta ahora utilizando experimentos in vitro, que han establecido que dichos compuestos inhiben la generación de superóxido en monocitos, eosinófilos y neutrófilos humanos; la liberación de mediador en basófilos, macrófagos y neutrófilos; y la liberación de TNFα en

monocitos y macrófagos. Los inhibidores de PDE inhiben también la liberación de mediador de células inflamatorias como monocitos y macrófagos derivados de monocitos, mastocitos pulmonares, linfocitos T, linfocitos B, macrófagos alveolares y eosinófilos.

Se han observado también efectos anti-inflamatorios beneficiosos in vivo hasta la fecha, incluyendo la inhibición de la infiltración microvascular en pulmones de conejillos de indias sensibilizados, y la reducción de hiperreactividad bronquial y eosinofilia en monos cynomolgus, después de una repetida aplicación provocada de antígeno. Se ha demostrado también hasta la fecha que los inhibidores de PDE4 suprimen con potencia la liberación de TNFα de fagocitos mononucleares.

**8.1 Asma**

Una de las enfermedades respiratorias más importantes tratables con PDE4, especialmente con inhibidores de PDE4D del tipo dentro del alcance de los compuestos de fórmula (1.0.0) es el asma, una enfermedad crónica cada vez más común que se encuentra por todo el mundo y se caracteriza por una obstrucción de las vías aéreas reversible intermitente, hiperrespuesta e inflamación de las vías aéreas. La causa del asma está por determinar todavía, pero la expresión patológica más común del asma es la inflamación de las vías aéreas, que puede ser

significativa incluso en las vías aéreas de pacientes con asma leve. Basándose en estudios de biopsias y lavados bronquiales, se ha mostrado claramente que el asma implica la infiltración de mastocitos, eosinófilos y linfocitos T en las vías aéreas del paciente. El lavado broncoalveolar (LBA) en asmáticos atópicos muestra la activación de interleuquina (IL)-3, IL-4, IL-5 y factor estimulante de colonias de granulocitos/macrófagos (GM-CSF), lo que sugiere la presencia de una población de células T similares a auxiliares de células T (Th-2).

Los compuestos de fórmula (1 0.0) inhiben la PDE4 en eosinófilos humanos, y por tanto son útiles en el tratamiento de asma atópico y no atópico. El término "atopía" representa una predisposición genética hacia el desarrollo de reacciones de hipersensibilidad de tipo I (inmediata) frente a antígenos ambientales comunes. La manifestación clínica más común es la rinitis alérgica, aunque aparecen menos frecuentemente asma bronquial, dermatitis atópica y alergia alimentaria. Consiguientemente, el término "asma atópica", como se utiliza en la presente descripción, se pretende que sea sinónimo de "asma alérgica", es decir, asma bronquial que es una manifestación alérgica de una persona sensibilizada. El término "asma no atópica", como se utiliza en la presente descripción, se pretende que represente todas las demás asmas, especialmente el asma esencial o "verdadera", que está provocada por una serie de

factores, incluyendo ejercicio vigoroso, partículas irritantes, estrés psicológico, etc.

El uso de los compuestos de fórmula (1.0.0) para tratar asma atópica o asma no atópica está establecido y demostrado por los modelos de inhibición de PDE, la inhibición de la activación de eosinófilos, y los modelos de infiltración celular descritos a continuación.

Inflamación pulmonar en monos cynomolgus alérgicos. Se evalúa en este procedimiento la capacidad de las combinaciones de agentes terapéuticos de la presente invención de inhibir aumentos del contenido celular inflamatorio inducidos por antígeno de *Ascaris* del fluido de lavado alveolar bronquial de sujetos monos cynomolgus Utilizando un diseño cruzado, se tratan 8-10 monos cynomolgus sensibles a Ascaris con vehículo o fármaco Se anestesia cada mono en un momento adecuado del pretratamiento (cetamina 10 mg/kg + xilacina 1 mg/kg, i.m.), y se intuban con un tubo endotraqueal. Se realiza al lavado broncoalveolar (LBA) utilizando un lavado de 15 ml de solución salina tamponada con fosfato (PBS), suministrada mediante un broncoscopio pediátrico de fibra óptica insertado a través del tubo endotraqueal, y fijado en un bronquio de tercera a quinta generación. Se aspira suavemente el fluido de lavado y se recoge en una jeringa. Después de completar el LBA, cada animal recibe

una exposición de 2 minutos a una concentración de aerosol de *Ascaris suum* que duplica la resistencia del sistema respiratorio determinada en experimentos previos. Se devuelve cada mono a su jaula, y se realiza 24 horas después un segundo lavado, utilizando 15 ml de PBS, en el lado opuesto del pulmón. Una semana después del primer ensayo, se intercambian los monos control y tratados y se repite el experimento. Para determinar la composición porcentual de cada tipo de leucocito, se obtienen dos portaobjetos de cada muestra LBA de mono por centrifugación de 2 x 150 µl de fluido de lavado durante 2 minutos a 500 rpm en una centrífuga Cytosporin. Se tiñen los portaobjetos con Diff-Quick para recuento celular diferencial y se identifican las células por criterios morfológicos estándares. Se determinan los números totales de leucocitos por mililitro de BAL mediante la dilución de 20 µl de muestra en 20 ml de Isoton, añadiendo 3 gotas de Zapoglobin para lisar los eritrocitos, y leyendo la muestra utilizando un contador Coulter. Se realizan las comparaciones entre la relación del aumento de los niveles de eosinófilo, citocina o mediador del lavado bronquial alveolar antes de la aplicación provocada de antígeno, frente a 24 horas después de la aplicación provocada de antígeno, con y sin tratamiento con fármaco.

En el modelo de ensayo anterior, las combinaciones de agentes terapéuticos de la presente invención exhiben actividad

anti-inflamatoria a dosificaciones en el intervalo de 0,001 a 0,1 mg/kg i.v. ó 0,01 a 10,0 mg/kg p.o. ó 0,001 a 0,1 mg/kg i.t.

Otro ensayo útil, basado en el uso de primates, es el descrito en Turner et al., "Characterization of a primate model of asthma using anti-allergy/anti-asthma agents", *Inflammation Research* **45**, 239-245, 1996.

Actividad anti-inflamatoria. Se demuestra la actividad anti-inflamatoria de las combinaciones de agentes terapéuticos de la presente invención mediante la inhibición de la activación de eosinófilos medida mediante la producción de LTE4 estimulado por perlas de Sephadex en sangre humana entera.

Ensayo de sangre humana entera por LTE4 utilizando perlas de Sephadex como estimulante. El día antes del ensayo, se siliconizan tubos de vidrio con Sigmacote (Sigma, N° Cat. SL-2). Antes de extraer la sangre, se diluyen los compuestos en DMSO 1000x, se añade 1 µl de DMSO o de compuesto a cada tubo respectivo, y se coloca el soporte de tubos de ensayo en un baño de agua a 37°C. Se extrae la sangre en tubos Vacutainer heparinizados n° 6480 (heparina de sodio, 143 unidades USP, 10 ml), 10 tubos= 100 ml de sangre. Se reúnen los tubos de sangre en dos tubos cónicos de 50 ml. Se añade 1 ml de sangre entera a cada tubo siliconizado que contiene DMSO o compuesto, se agita

con vórtex y se incuba después a 37°C durante 15 minutos. Para preparar la suspensión de perlas de Sephadex G-15, (Pharmacia, n° Cat 17-0020-01), se añaden 3,3 g de Sephadex G-15, se mezclan con 20 ml de PBS en un vaso de 100 ml, y se mezclan después con una barra de agitación magnética. Después de 15 minutos, se añaden 100 µl de perlas de Sephadex G-15 a cada tubo, excepto a los tubos de Sephadex que proporcionarán el valor de línea base para la liberación de LTE4 Se agitan con vórtex y se incuban durante 90 minutos a 37°C. Al final de la incubación de 90 minutos, se añaden 20 µl de EDTA al 15%, se agita con vórtex y se centrifuga durante 5 minutos a 1000 rpm. Después, se retira y guarda la muestra de plasma para análisis. Se determinan los niveles de LTE4 mediante el estuche ELISA cisteinil-LT de Cayman (N° cat. 520501). Se calcula el porcentaje de inhibición como 100 x 1 - (concentración de LTE4 en la muestra tratada con fármaco dividida 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 a concentraciones en el intervalo de 0,0001 µM a 20,0 µM, siendo activas las realizaciones preferidas a concentraciones en el intervalo de 0,5 nM a 1000 nM.

De lo anterior puede observarse que los compuestos de

fórmula (1.0.0) son útiles para el tratamiento de enfermedades inflamatorias u obstructivas de las vías aéreas, u otras afecciones que impliquen la obstrucción de las vías aéreas. En particular, son útiles para el tratamiento de asma bronquial.

A la vista de su actividad anti-inflamatoria, su influencia sobre la hiperreactividad de las vías aéreas y sus perfiles en relación con la inhibición de isoenzima PDE, en particular como inhibidores selectivos de PDE4, los compuestos de fórmula (1.0.0) son útiles para el tratamiento, en particular el tratamiento profiláctico, de enfermedades obstructivas o inflamatorias de las vías aéreas. Así, mediante una administración continuada y regular durante periodos prolongados de tiempo, los compuestos de fórmula (1.0.0) son útiles para proporcionar una protección avanzada frente a la recurrencia de broncoconstricción u otros ataques sintomáticos consecuencia de enfermedades obstructivas o inflamatorias de las vías aéreas. Los compuestos de fórmula (1.0.0) son también útiles para el control, la mejora o la reversión del estado basal de dichas enfermedades.

Con respecto a su actividad broncodilatadora, los compuestos de fórmula (1.0.0) son útiles como broncodilatadores, por ejemplo, en el tratamiento de broncoconstricción crónica o aguda, y para el tratamiento sintomático de enfermedades

obstructivas o inflamatorias de las vías aéreas.

Las palabras "tratamiento" y "tratar", como se utilizan a lo largo de la presente descripción y reivindicaciones respecto de enfermedades obstructivas e inflamatorias, se comprende consiguientemente que comprenden ambos modos profiláctico y sintomático de terapia.

A la vista de la descripción anterior, puede observarse que la presente invención se refiere también a un procedimiento para el tratamiento de hiperreactividad de las vías aéreas en mamíferos, a un procedimiento para producir la broncodilatación en mamíferos; y en particular, a un procedimiento de tratamiento de enfermedades obstructivas o inflamatorias de las vías aéreas, especialmente asma, en un sujeto mamífero necesitado de ello, comprendiendo dicho procedimiento la administración al citado sujeto mamífero de una cantidad eficaz de un compuesto de fórmula (1.0.0).

Las enfermedades obstructivas o inflamatorias de las vías aéreas a las que se aplica la invención incluyen asma; neumoconiosis; neumonía eosinófila crónica; enfermedad obstructiva crónica de las vías aéreas o pulmonar (EVAOC ó EPOC); y síndrome del distrés respiratorio en adultos (SDRA), así como exacerbación de la hiperreactividad de las vías aéreas

consecuencia de otra terapia de fármacos, por ejemplo, aspirina o terapia de β-agonista.

Los compuestos de fórmula (1.0.0) son útiles en el tratamiento de asma de cualquier tipo, etiología o patogénesis; incluyendo asma intrínseca atribuida a perturbaciones patofisiológicas, asma extrínseca causada por algún factor del ambiente, y asma esencial de causa desconocida o no evidente. Los compuestos de fórmula (1.0.0) son útiles en el tratamiento de asma alérgica (atópica/bronquial/mediada por IgE); y son útiles también en el tratamiento de asma no atópica, incluyendo por ejemplo asma bronquítica, enfisematosa, inducida por ejercicio y ocupacional; asma infecciosa, que es una secuela de infección microbiana, especialmente bacteriana, fúngica, protozooaria o viral, y otras asmas no alérgicas, por ejemplo asma incipiente (síndrome de jadeos en infantes).

Los compuestos de fórmula (1.0 0) son además útiles en el tratamiento de neumoconiosis de cualquier tipo, etiología o patogénessis; 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 causada por la inhalación del polvo de plumas de avestruz; siderosis, causada por la inhalación de partículas de hierro, silicosis (enfermedad

00346 392

del molinero); bisinosis (asma de polvo de algodón) y neumoconiosis de talco.

**8.2 Enfermedad pulmonar obstructiva crónica (EPOC)**

Los compuestos de fórmula (1.0.0) son útiles además en el tratamiento de EPOC o EVAOC, incluyendo bronquitis crónica, enfisema pulmonar o disnea asociada a estos. La EPOC se caracteriza por una obstrucción irreversible progresiva de las vías aéreas. La bronquitis crónica está asociada a hiperplasia e hipertrofia de las glándulas secretoras de mucosidad de la submucosa de las vías aéreas cartilaginosas grandes. Se encuentran en los bronquiolos terminales y respiratorios hiperplasia de células cáliz, infiltración celular inflamatoria mucosa y submucosa, edema, fibrosis, tapones de mucosidad y aumento del músculo liso. Las vías aéreas pequeñas son conocidas por ser un sitio importante de obstrucción de las vías aéreas. El enfisema se caracteriza por la destrucción de la pared alveolar y la pérdida de la elasticidad del pulmón. Se han identificado también una serie de factores de riesgo ligados a la incidencia de la EPOC. La relación entre fumar tabaco y EPOC está bien establecida. Otros factores de riesgo incluyen la exposición a polvo de carbón y diversos factores genéticos. Véase Sandford et al., "Genetic risk factors for chronic obstructive pulmonary disease", *Eur. Respir. J* **10** 1380-1391, 1997. La incidencia de EPOC está aumentando, y representa una carga económica significativa sobre las poblaciones de las

naciones industrializadas. La EPOC se presenta también clínicamente con un amplio espectro de variación, desde una simple bronquitis crónica sin incapacidad a pacientes en un estado gravemente incapacitado con insuficiencia respiratoria crónica.

La EPOC se caracteriza por la inflamación de las vías aéreas, como es el caso del asma, pero las células inflamatorias que se han encontrado en el fluido de lavado broncoalveolar y el esputo de pacientes son neutrófilos en vez de eosinófilos. Se han encontrado también niveles elevados de mediadores inflamatorios en los pacientes con EPOC, incluyendo IL-8, $LTB_4$ y TNF-α, y se ha encontrado que el epitelio y subepitelio de superficie está infiltrado con linfocitos T y macrófagos. Puede proporcionarse un alivio sintomático a los pacientes con EPOC mediante el uso de β-agonistas y broncodilatadores anticolinérgicos, pero el progreso de la enfermedad permanece sin alterar. La EPOC se ha tratado utilizando teofilina, pero sin mucho éxito, aunque reduce el recuento de neutrófilos en el esputo de pacientes con EPOC. Los esteroides ha fracasado también en mantener las promesas de agentes de tratamiento satisfactorios de EPOC.

Consiguientemente, el uso de los compuestos de fórmula (1.0.0) para tratar EPOC y sus enfermedades obstructivas de las

vías aéreas relacionadas e incluidas, representa un avance significativo en la técnica. La presente invención no está limitada a ningún modo particular de acción o a ninguna hipótesis sobre el modo en que se han obtenido los objetivos terapéuticos mediante la utilización de compuestos de fórmula (1.0.0). Sin embargo, se reconoce en la técnica que la PDE4 es la PDE predominante en neutrófilos y macrófagos; 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 $^{3}$[H]rolipram binding site", *Bioorg. Med Chem. Lett* **5** 1969-1972; 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, y Tenor et al., "Cyclic nucleotide phosphodiesterase isoenzyme activities in human alveolar macrophages", *Clin. Exp. Allergy* **25** 625-633, 1995.

Para proporcionar una mejor comprensión de la presente invención, se hace aquí la deducción de que los compuestos de fórmula (1.0.0) inhiben las PDE4 en neutrófilos, dando como resultado una quimiotaxia, activación, adherencia y

desgranulación reducidas; 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; y Bloeman et al., "Increased cAMP levels in stimulated neutrophils inhibit their adhesion to human bronquial epithelial cells", *Am. J. Physiol.* **272** L580-587, 1997.

Se deduce también que los compuestos de fórmula (1.0.0) reducen la producción de anión superóxido mediada por PDE4 en neutrófilos de sangre periférica, y que regulan la síntesis mediada por PDE4 de leucotrienos; 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; y 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.

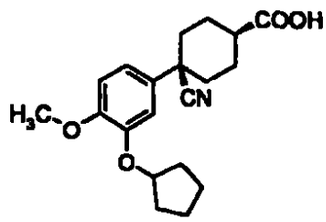
Se deduce también que los compuestos de fórmula (1.0.0)

inhiben la expresión de CD11b/CD18; 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, y Derian et al., "Inhibition of chemotactic peptide-induced neutrophil adhesion to vascular endothelium by cAMP modulators", *J. Immunol* **154** 308-317, 1995.

Se deduce además que los compuestos de fórmula (1.0.0) inhiben las PDE4 de macrófago alveolar, reduciendo así los factores quimiotácticos y el TNF-α; y que los compuestos de fórmula (1.0.0) aumentan la síntesis y facilitan la liberación de monocitos de la citocina anti-inflamatoria IL-10, que a su vez es capaz de reducir la generación de TNF-α, IL-1β y GM-CSF por células mononucleares en fluido sinovial, aumentando así el perfil anti-inflamatorio general de los inhibidores de PDE4 de fórmula (1.0.0), Schudt et al., "PDE isoenzymes as targets for anti-asthma drugs", *Eur Respir. J.* **8** 1179-1183, 1995; y 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.

Se ha demostrado la aplicación de inhibidores de PDE4 al tratamiento de EPOC en pacientes humanos en ensayos clínicos. El

tratamiento con SB-207.499, representado por la fórmula (0.1.9) anterior, a una dosis de 15 mg dos veces al día durante seis semanas, se ha mostrado que da como resultado aumentos de $FEV_1$ y de la capacidad vital forzada (FVC); Brown, W.M., "SB-207.499" *Anti-inflamm. Immunomodulatory Invest. Drugs* 1 39-47, 1999. Se ha demostrado también la eficacia clínica del SB-207.499 em un ensayo de cuatro semanas que ha proporcionado evidencias de un $FEV_1$ mejorado; y en un estudio de seis semanas en pacientes con EPOC que recibieron 15 mg dos veces al día, que ha proporcionado evidencias también de un $FEV_1$ mejorado; Brown, ibid. Se ha descrito también anteriormente el SB-207.499, y representado por la fórmula (0 1.9):




SB-207 499 (0 1 9)

**8.3 Bronquitis y bronquiectasis**

Según las actividades inhibitorias particulares y distintas descritas anteriormente que poseen los compuestos de fórmula (1.0.0), son útiles en el tratamiento de bronquitis de cualquier tipo, etiología o patogénesis, incluyendo, por ejemplo, bronquitis aguda que tiene un curso corto pero grave, y

está causada por la exposición a frío, la respiración de sustancias irritantes o una infección aguda; bronquitis laringotraqueal aguda, que es una forma de crup no diftérico; bronquitis araquídica, que está causada por la presencia de un grano de cacahuete en un bronquio, bronquitis catarral, que es una forma de bronquitis aguda con descarga mucopurulenta abundante; bronquitis crónica, que es una forma continuada de bronquitis con una tendencia más o menos marcada a la recurrencia después de etapas de inactividad, debido a ataques repetidos de bronquitis aguda o enfermedades generales crónicas caracterizadas por ataques de tos, por expectoración escasa o abundante, y por cambios secundarios en el tejido pulmonar; bronquitis crup que se caracteriza por una tos violenta y paroxismos de disnea; bronquitis seca, que se caracteriza por una secreción escasa de esputo duro; bronquitis asmática infecciosa, que es un síndrome caracterizado por el desarrollo de síntomas de broncoespasmo después de infecciones del tracto respiratorio en personas con asma; bronquitis productiva, que es bronquitis asociada a tos productiva; bronquitis de estafilococos o estreptococos, que está causada por estafilococos o estreptococos; y bronquitis vesicular, en la que la inflamación se extiende a los alveolos, que a veces son visibles bajo la pleura como granulaciones amarillo-blanquecinas como semillas de mijo.

La bronquiectasis es una dilatación crónica de los bronquios caracterizada por un aliento fétido y toses paroxísmicas con expectoración de materia mucopurulenta. Puede afectar uniformemente al tubo, en cuyo caso se designa como bronquiectasis cilíndrica, o puede aparecer en bolsas irregulares, en cuyo caso de denomina bronquiectasis en sáculos. Cuando los tubos bronquiales dilatados tiene alargamientos bulbosos terminales, se utiliza el término bronquiectasis fusiforme. En aquellos casos en que la condición de dilatación se extiende hasta los bronquiolos, se designa como bronquiectasis capilar. Si la dilatación de los bronquios es de forma esférica, la afección se designa como bronquiectasis quística. La bronquiectasis seca aparece cuando la infección implicada es episódica y puede estar acompañada de hemoptisis, expectoración de sangre o de esputo manchado de sangre. Durante los periodos inactivos de bronquiectasis seca, la tos que aparece es no productiva. La bronquiectasis folicular es un tipo de bronquiectasis en la que el tejido linfoide de las regiones afectadas aumenta mucho de tamaño, y por proyección en el lumen bronquial, puede deformar gravemente y obstruir parcialmente el bronquio. Consiguientemente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento beneficioso de los diversos tipos anteriormente descritos de bronquiectasis 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 asma bronquial, bronquitis crónica y enfermedades y trastornos relacionados descritos en la presente descripción es demostrable mediante el uso de una serie de diferentes modelos animales in vivo conocidos en la técnica, incluyendo aquellos descritos en los párrafos siguientes.

Actividad broncoespasmolítica in vitro. Se demuestra la capacidad de los compuestos de fórmula (1.0.0) de causar la relajación de músculo liso traqueal de conejillo de indias en el siguiente procedimiento de ensayo. Se sacrifican conejillos de indias (350-500 g) con pentotal de sodio (100 mg/kg i.p.). Se diseccIona la tráquea y se extrae una sección de 2-3 cm de longitud. Se corta en plano transversal la tráquea en placas de cartílago alternadas, de modo que se proporcionan anillos de tejido de 3-5 mm de profundidad. Se desechan los anillos proximal y distal. Se montan los anillos individuales verticalmente en soportes de acero inoxidable, uno de los cuales se fija a la base de un baño de órganos, mientras que el otro se une a un transductor isométrico Se bañan los anillos en solución de Krebs (composición en µM: $NaHCO_3$ 25; NaCl 113; KCl 4,7, $MgSO_4 7H_2O$ 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). Los anillos preparados de esta manera y precargados a 1 g, generan un tono espontáneo y,

después de un periodo de equilibrio (45-60 min), se relajan consistentemente con la adición de fármacos espasmolíticos. Para evaluar la actividad espasmolítica, se disuelven compuestos de ensayo de fórmula (1.0.0) en solución salina fisiológica y se añaden en cantidades crecientes al baño de órganos a intervalos de 5 min, proporcionando una curva acumulativa de concentración-efecto.

En el modelo de ensayo anterior, los compuestos de fórmula (1.0.0) producen la relajación relacionada con la concentración de preparaciones de anillos de tráquea de conejillos de indias a concentraciones en el intervalo de 0,001 a 1,0 μM.

Se demuestra la actividad anti-inflamatoria de las combinaciones de agentes terapéuticos de la presente invención mediante la inhibición de la producción de TNFα en sangre humana entera estimulada por lipopolisacáridos (LPS). Se analizan los compuestos en presencia de agonista beta (10 ng/ml) e indometacina (1 μM). Se preparan 250 ml de tampón de ensayo de HEPES 200 mM en RPMI 1640 filtrado. Se realiza lo siguiente a temperatura ambiente en mesa de trabajo. Se prepara cóctel "IP" en un tubo de polipropileno de 50 ml mediante la adición de 0,4 ml de indometacina (solución madre 4 mM) y 0,4 ml de agonista beta (solución madre 0,04 mg/ml) para 40 ml de v.f. con tampón de ensayo. Se preparan compuestos a partir de soluciones madre

de polvo en DMSO hasta soluciones madre 200 ó 60 mM. Se hacen diluciones en serie semilogarítmicas de ocho puntos en viales o microtubos de vidrio. Se añaden 0,01 ml de cada dilución del compuesto a tubos de polipropileno de 5 ml, a los que se añaden 0,490 ml de tampón de ensayo y 0,50 ml de cóctel "IP" hasta un v.f. de 1,0 ml (una c.f. del compuesto de 100-0,1 µM). Se prepara solución de LPS añadiendo 0,08 ml de LPS (solución madre 1 mg/ml) a 40 ml de tampón de ensayo para una c.f. de 2 µg/ml. 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%. Se utiliza este cóctel para los pocillos de control, de modo que la c.f. de indometacina del ensayo es 1 µM, y la c.f. del agonista beta es de 10 ng/ml. Se realiza lo siguiente en campana de cultivo de tejido. Se añaden 0,0125 ml del compuesto diluido al pocillo apropiado en placa estéril de 96 pocillos Costar nº3790 de fondo en U. Se añaden 0,0125 ml de LPS a todos los pocillos (c.f. 0,1 µg/ml) excepto los pocillos de control negativo. Se extrae sangre humana entera reciente (aprox. 22 ml por placa de 96 pocillos), habitualmente cuatro tubos de tapón verde por donante, en tubos de heparina estériles matenidos a 37°C. Se añaden 0,225 ml de la sangre entera a las placas. Se tapan, se incuban a 37°C, y se agitan durante cuatro horas. Se centrifugan las placas a 2000 rpm durante 10 minutos. Se preparan patrones de ELISA. Se retiran 100 µl de suero en placa de fondo plano. Se diluyen 1:20 retirando 15 µl y

añadiendo 285 µl de diluyente RD6. Se congela a -20°C. Para el análisis, se descongela y se añaden 200 µl a un ELISA de TNFα de R&D Systems. Se procesan las placas según el protocolo de R&D Systems. Se lee la placa a 450 nm utilizando SoftMax Pro. Se analiza e interpreta con Java Fitter para determinar los valores de $CI_{50}$. Se representa una curva de respuesta a la dosis de datos expresados como porcentaje del control. Se genera un mínimo de seis puntos por triplicado para cada compuesto. Se calculan los valores de $CI_{50}$ utilizando el programa de ajuste de curvas Java Fitter con el parámetro "ambas $CI_{50}$ fijadas".

En el modelo de ensayo anterior, las combinaciones de agentes terapéuticos de la presente invención producen la inhibición relacionada con la concentración de la producción de TNFα a concentraciones en el intervalo de 0,001 a 1,0 µM.

**8.4 Rinitis alérgica y otros tipos de rinitis; 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 enfermedades, estacional y perenne, en las que la primera se atribuye al polen o a esporas de mohos del exterior, mientras que la segunda se atribuye a alergenos comunes tales como ácaros del polvo doméstico, escamas animales y esporas de mohos. La rinitis alérgica exhibe generalmente una respuesta de fase temprana y

una respuesta de fase tardía. La respuesta de fase temprana está asociada con desgranulación de mastocitos, mientras que la respuesta de fase tardía se caracteriza por la infiltración de eosinófilos, basófilos, monocitos y linfocitos T. Se liberan también una serie de mediadores de la inflamación por estas células, todos los cuales pueden contribuir a la inflamación exhibida en la respuesta de fase tardía.

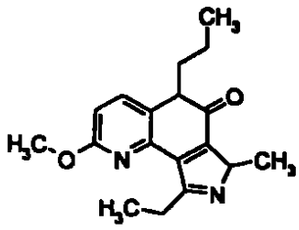
Una forma particularmente prevalente de rinitis alérgica estacional es la fiebre del heno, caracterizada por conjuntivitis aguda con lagrimeo y picor, hinchazón de la mucosa nasal, catarro nasal, ataques súbitos de estornudos y a menudo síntomas asmáticos Los compuestos de fórmula (1.0.0) son especialmente útiles en el tratamiento beneficioso de la fiebre del heno.

Otros tipos de rinitis para los que pueden utilizarse los compuestos de fórmula (1.0.0) como agentes terapéuticos incluyen rinitis catarral aguda, que es un resfriado de cabeza que implica la congestión aguda de la membrana mucosa de la nariz, caracterizada por sequedad, y seguida por secreción mucosa aumentada de la membrana, respiración impedida por la nariz, y algo de dolor, rinitis atrófica, que es una forma crónica caracterizada por el agotamiento de la membrana mucosa y las glándulas; rinitis purulenta, que es rinitis crónica con

formación de pus, y rinitis vasomotora, que es rinitis no alérgica en la que se producen cambios transitorios en el tono y permeabilidad vasculares con los mismos síntomas de la rinitis alérgica por estímulos tales como enfriamiento leve, fatiga, ira y ansiedad.

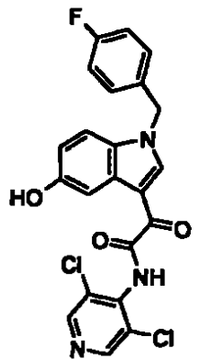
Existe una relación reconocida entre la rinitis alérgica y el asma. La rinitis alérgica es una acompañante frecuente del asma, y se ha demostrado que el tratamiento de la rinitis alérgica mejora el asma. Se han utilizado también datos epidemiológicos para mostrar una relación entre la rinitis grave y el asma más grave. Por ejemplo, el compuesto D-22888, en desarrollo preclínico para el tratamiento de rinitis alérgica, se ha mostrado que exhibe un fuerte efecto antialérgico y que inhibe la rinorrea en cerdo provocado con antígeno. Véase Marx et al., "D-22888, a new PDE4 inhibitos for the treatment of allergic rhinitis and other allergic disorders", *J. Allergy Clin. Immunol.* 99 S444, 1997. Otro compuesto experimental, AWD-12.281, se ha mostrado activo en un modelo de rata de rinitis alérgica. Veáse 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. Los compuestos D-22888 y AWD-12.281 se han descrito ya anteriormente y representado por las fórmulas (0.0.28) y (0.0.34),

respectivamente:



D-22888

(0 0 28)



Loteprednol (AWD - 12 281)

(0 0 34)

La sinusitis está relacionada con la rinitis en términos de proximidad anatómica, así como por una etiología y patogénesis compartida, en algunos casos. La sinusitis es la inflamación de un seno, y esta afección puede ser purulenta o no purulenta, así como aguda o crónica Dependiendo del seno en el que se localice la inflamación, la afección se conoce como sinusitis etmoidea, frontal, maxilar, o esfenoide. El seno etmoideo es un tipo de seno paranasal localizado en el hueso

etmoideo. El seno frontal es un uno de los senos paranasales duplicados localizado en el hueso frontal. El seno maxilar es uno de los senos paranasales duplicados localizado en el cuerpo del maxilar. Consiguientemente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento beneficioso de sinusitis aguda o crónica, pero especialmente de sinusitis crónica.

**8.5 Artritis reumatoide, osteoartritis, dolor, fiebre y gota**

La artritis se define como una inflamación de las articulaciones, y la artritis reumatoide es una enfermedad sistémica crónica principalmente de las articulaciones, habitualmente poliarticular, caracterizada por cambios inflamatorios en las membranas sinoviales y las estructuras articulares, y por atrofia muscular y rarefacción de los huesos. Las últimas etapas de la artritis reumatoide están caracterizadas por anquilosamiento y deformidad. La artritis reumatoide es una enfermedad autoinmune incapacitante de etiología desconocida que afecta a más del 1% de la población.

Como se utiliza en la presente descripción, el término "artritis reumatoide" se pretende que incluya dentro de su alcance, cuando sea aplicable, las formas relacionadas y asociadas de artritis bien conocidas en la técnica, puesto que estas pueden tratarse también con los compuestos de fórmula (1.0.0). Consiguientemente, el término "artritis reumatoide", incluye artritis aguda, que es artritis caracterizada por dolor,

calor, enrojecimiento e hinchazón debido a inflamación, infección o trauma; artritis gotosa aguda, que es artritis aguda asociada a gota; artritis inflamatoria crónica, que es inflamación de las articulaciones en enfermedades crónicas, tales como artritis reumatoide; artritis degenerativa, que es osteoartritis, artritis infecciosa, que es artritis causada por bacterias, ricketsias, micoplasmas, virus, hongos o parásitos; artritis de Lyme, que es artritis de las articulaciones grandes asociada con enfermedad de Lyme; artritis proliferativa, que es inflamación de las articulaciones con proliferación de la sinovia, observada en artritis reumatoide; artritis psoriática, que es un síndrome en el que aparece psoriasis asociada con artritis inflamatoria; y artritis vertebral, que es inflamación que implica los discos invertebrales.

Las tres características patológicas principales de la artritis reumatoide que son las responsables de la progresiva destrucción de las articulaciones son la inflamación, las respuestas anormales celular y humoral y la hiperplasia sinovial. La patología celular particular de la artritis reumatoide incluye la presencia de células T y monocitos. Las células T, que son predominantemente células T de memoria, constituyen hasta el 50% de las células recuperadas del tejido sinovial de pacientes con artritis reumatoide; y de los monocitos encontrados en el mismo tejido, el 30-50% son células

que presentan antígenos, lo que es indicativo del carácter autoinmune de la enfermedad. Las citocinas pro-inflamatorias, por ejemplo, IL-1, IL-4, IL-5, IL-6, IL-9, IL-13 y TNF-α, son los contribuyentes principales al daño, inflamación, hiperplasia, formación de pannus y resorción ósea del tejido de articulaciones. Véase Firestein, G.S. y Zvaifler, W.J., "How important are T-cells in chronic rheumatoid synovitis?", *Arth. Rheum* 33 768-773, 1990. Esto se ha demostrado, por ejemplo, por el hecho de que los anticuerpos monoclonales (MAb) de TNF-α se han mostrado promisorios en ensayos clínicos de AR; Maini et al., "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 útiles en el tratamiento de artritis reumatoide como resultado de su capacidad de suprimir la actividad de una serie de células inflamatorias, incluyendo basófilos, eosinófilos y mastocitos. Estas actividades inhibitorias de los compuestos de fórmula (1.0.0) se han descrito ya anteriormente, así como su amplio espectro de acción anti-inflamatoria in vitro por la liberación de especies de oxígeno reactivo, prostaglandinas y citocinas anti-inflamatorias, por ejemplo, IL-5, IFN-γ y TNF-α. Véase además Cohen et al., "In vitro pharmacology of the novel phosphodiesterase Type IV inhibitor, CP-80.633", *J. Pharm. Exp.*

*Ther.* 278, 1356-1361, 1996; y Barnette et al., "SB207499 (Ariflo), a potent and selective second generation phophodiesterase 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 útiles en el tratamiento de artritis reumatoide como resultado de su eficacia en la inhibición de la proliferación de células T mediada por una serie de agentes diferentes, incluyendo antígenos tales como ácaros del polvo doméstico, que se ha demostrado en la técnica; Barnette et al., ibid. La capacidad de los compuestos de fórmula (1.0.0) de facilitar la liberación la citocina IL-10 de monocitos, que a su vez es capaz de reducir la generación de TNF-α, IL-1, IL-4, IL-5, IL-6, IL-9, IL-13 y GM-CSF por células mononucleares del fluido sinovial, aumenta además el perfil anti-inflamatorio general de los inhibidores de PDE4 de fórmula (1.0.0); Kambayashi et al., ibid. Además, la capacidad de los compuestos de fórmula (1.0.0) de inhibir la liberación de TNF-α de monocitos estimulados, puede correlacionarse con modelos animales de inflamación en los que pueden mostrarse efectos anti-inflamatorios que corresponden a la supresión de la acumulación de TNF-α. Uno de dichos modelos animales implica la inhibición de la liberación de TNF-α inducida por LPS en ratones mediante la administración oral de un inhibidor de PDE4, 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. Otro de dichos modelos animales implica la inhibición de edema de pata de rata inducido por carragenina mediante la administración oral de 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 (supl. 2), S153-S154, 1997.

La gota representa un grupo de trastornos del metabolismo de purina, y la gota desarrollada completamente se manifiesta por diversas combinaciones de hiperuricemia, artritis inflamatoria aguda recurrente característica inducida por cristales de urato de monosodio monohidratado, depósitos tobáceos de los citados cristales en y alrededor de las articulaciones, que pueden conducir a la destrucción de la articulación y a una grave incapacidad, y urolitiasis de ácido úrico. La gota reumática es otro nombre de la artritis reumatoide. La gota tobácea es gota en la que existen tobas o depósitos calcáreos de urato de sodio. Algunos agentes terapéuticos son útiles en el tratamiento tanto de gota como de su inflamación acompañante, por ejemplo fenilbutazona y colchicina; mientras que otros agentes terapéuticos poseen sólo propiedades uricosúricas, por ejemplo, sulfinpirazona y benzobromarona.

La fiebre o pirexia pueden ser el resultado de uno cualquiera de un gran número de factores diferentes, pero con respecto a la presente invención, dicha fiebre es la manifestada en fiebre faringoconjuntiva o reumática, o la manifestada durante la inflamación. Un acompañante de la inflamación es el dolor, especialmente el experimentado en las articulaciones y tejido conectivo de los que sufren artritis reumatoide y gota.

Consiguientemente, los inhibidores de PDE4 de fórmula (1.0.0) proporcionan resultados beneficiosos en el tratamiento de gota, y de fiebre y dolor asociados con la inflamación.

Se han utilizado también modelos animales de artritis reumatoide en la técnica para fines de demostración de la correlación entre la modulación in vivo de TNF-α por inhibidores de PDE4 y su utilidad en el tratamiento de artritis reumatoide. Se ha demostrado en la técnica la actividad del rolipram en modelos animales de inflamación aguda, tales como el modelo de artritis coadyuvante de ratón; 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. Se ha demostrado en la técnica la capacidad del rolipram de reducir la gravedad de la enfermedad en el modelo de artritis inducida por colágeno (II) (CIA) después de inyección

s.c. ó i.p.; Nyman et al., "Amelioration of collagen II induced arthritis in rats by Type IV phosphodiesterase inhibitor rolipram", *Clin. Exp. Immunol.* 108, 415-419, 1997. En este estudio, el régimen de dosificación del rolipram fue 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 de la terminación del tratamiento, los animales ensayados desarrollaron artritis y alcanzaron los mismos máximos de puntuación de artritis que el grupo de control. En el mismo estudio, se administró también rolipram a 3 mg/kg dos veces al día en el mismo momento en que apareció la artritis. Este tratamiento cambió drásticamente el desarrollo de la enfermedad, interrumpiendo la progresión de la gravedad, e incluso después del término del tratamiento, la puntuación de artritis no alcanzó los niveles observados en animales no tratados. Los investigadores fueron capaces también de demostrar una fuerte subrregulación de la expresión de ARNm de TNF-α e IFN-γ en nodos linfáticos regionales, lo que sugiere que el efecto principal del rolipram se ejerce en la fase de efector del proceso inflamatorio. Nyman et al. ibid.

Inhibición de la producción de TNF-α por monocitos humanos in vitro. Puede determinarse el efecto inhibitorio de los compuestos de fórmula (1.0.0) sobre la producción in vitro de TNF-α por monocitos humanos según el protocolo descrito en el

documento EP 411.754 (Badger et al.) y el documento WO 90/15534 (Hanna). Las publicaciones referidas describen también dos modelos de choque endotóxico que pueden utilizarse para determinar la actividad inhibitoria in vivo de los compuestos de fórmula (1.0 0). Se detallan los protocolos utilizados en estos modelos, y los compuestos de ensayo demuestran un resultado positivo en la reducción de los niveles de suero de TNF-α inducido por la inyección de endotoxina.

Se ha mostrado que los inhibidores selectivos de PDE4, tales como RP73401, exhiben una mejora significativa de la enfermedad, especialmente mejoras en la destrucción de articulaciones, sinovitis y fibrosis en modelos animales tales como los que implican artritis inducida por pared celular de estreptococos (SCW); Souness et al., "Potential of phosphodiesterase Type IV inhibitors in the treatment of rheumatoid arthritis", *Drugs* 1, 541-553, 1998.

Es de particular interés para el tratamiento de artritis reumatoide la observación de que los inhibidores de PDE4 tienen efectos positivos en el sitio de acción de la enfermedad. Por ejemplo, el RP73401 se ha demostrado que reduce la expresión de ARNm de TNF-α en la interfaz pannus/cartílago de las articulaciones de las patas de ratones tratados con colágeno II. Souness et al., ibid. Se ha estudiado también clínicamente

RP73401 en pacientes con artritis reumatoide en un estudio controlado por placebo, de doble ciego, de fase II de 35 pacientes con artritis reumatoide administrados con 400 pg del compuesto t.i.d. El compuesto pudo inducir una tendencia positiva hacia la mejora clínica asociada con una reducción de los niveles en suero de proteína reactiva C e IL-6. Chikanza et al. "The clinical effects of RP73401 phosphodiesterase Type 4 inhibitor in patients with rheumatoid arthritis", *Br. J. Rheumatol.* 36, resumen supl. I, 186, 1997.

Ensayo del aumento de la acumulación de AMPc en tejidos intactos utilizando células U-937.

Otro ensayo adecuado para demostrar la actividad inhibitoria de PDE4 de los compuestos de fórmula (1 0.0) es aquel que utiliza células U-937 de una línea celular de monocito humano que ha mostrado 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 a 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 adicionales. Cinco minutos después de iniciar la reacción, se lisan las células por adición de ácido perclórico al 17,5%, después de lo cual se lleva el pH a neutralidad mediante la adición de carbonato de potasio 1 M. Se

mide el contenido en AMPc del tubo de reacción utilizando técnicas RIA. Se describe un protocolo detallado para llevar a cabo este ensayo en Brooker et al., "Radioimmunoassay of cyclic AMP and cyclic GMP"; *Adv. Cyclic Nucleotide Res* 10, 1-33, 1979.

**8.6 Enfermedades relacionadas con eosinófilos**

Se ha descrito anteriormente la capacidad de los compuestos inhibidores de PDE4 de fórmula (1.0.0) de inhibir la activación de eosinófilos como parte de su actividad anti-inflamatoria general. Consiguientemente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento terapéutico de trastornos relacionados con eosinófilos. Dichos trastornos incluyen eosinofilia, que es la formación y acumulación de un número anormalmente alto de eosinófilos en la sangre El nombre del trastorno proviene de "eosina", un tinte o colorante de color rosa que comprende un derivado de bromo de fluoresceína que tiñe fácilmente los "leucocitos eosinófilos" en la sangre de los pacientes, que se identifican así fácilmente. Un trastorno eosinófilo particular que puede tratarse según la presente invención es la eosinofilia de infiltración pulmonar, que se caracteriza por la infiltración del parénquima pulmonar por eosinófilos. Este trastorno incluye especialmente el síndrome de Loffer, que es una afección caracterizada por infiltraciones transitorias de los pulmones, acompañadas por tos, fiebre, disnea y eosinofilia.

Otros trastornos eosinófilos incluyen neumonía eosinófila crónica, que es una enfermedad pulmonar intersticial crónica caracterizada por tos, disnea, malestar, fiebre, sudores nocturnos, pérdida de peso, eosinofilia y una placa de tórax que revela infiltrados no segmentados no migratorios en la periferia pulmonar; eosinofilia pulmonar tropical, que es una forma subaguda o crónica de filariasis oculta, que implica habitualmente *Brugia malayi, Wuchereria bancrofti* ó filarias que infectan animales, aparece en los trópicos, y se caracteriza por jadeos y toses nocturnas episódicas, eosinofilia marcadamente elevada e infiltraciones reticulonodulares difusas; aspergilosis bronconeumónica, que es una infección de los bronquios y pulmones por hongos *Aspergillus* que da como resultado una afección patológica caracterizada por lesiones granulomatosas inflamatorias en los senos nasales y pulmones, pero también en la piel, oído, órbitas y a veces en los huesos y meninges, y que conducen a aspergiloma, el tipo más habitual de nódulo de hongos formado por colonización de *Apergillus* de una cavidad bronquial o pulmonar.

El término "granulomatoso" significa que contiene granulomas, y el término "granuloma" designa cualquier agregación delimitada nodular pequeña de células inflamatorias mononucleares, o una colección tal de macrófagos modificados que parezcan células epiteliales, rodeadas habitualmente de una

franja de linfocitos, con fibrosis observada habitualmente alrededor de la lesión. Algunos granulomas contienen eosinófilos. La formación de granuloma representa una respuesta inflamatoria crónica iniciada por diversos agentes infecciosos y no infecciosos. Una serie de dichas afecciones granulomatosas son tratables utilizando un compuesto de fórmula (1.0.0), por ejemplo, angitis granulomatosa alérgica, también llamados síndrome de Churg-Strauss, que es una forma de vasculitis necrotizante sistémica en la que existe una importante implicación del pulmón, generalmente manifestada por eosinofilia, reacciones granulomatosas y habitualmente asma grave. Un trastorno relacionado es la poliarteritis nodosa (PAN), que se caracteriza por lesiones arteriales inflamatorias múltiples y destructivas y es una forma de vasculitis necrotizante sistémica que implica las arterias de tamaño pequeño y mediano con señales y síntomas resultantes de infarto y cicatrización del sistema de órganos afectado, en particular, los pulmones. Otros trastornos relacionados con eosinófilos que pueden tratarse según la presente invención son aquellos que afectan a las vías aéreas que están inducidos u ocasionados por una reacción frente a un agente terapéutico no relacionado con ningún compuesto de fórmula (1.0.0).

**8.7 Dermatitis atópica, urticaria, conjuntivitis y uveitis**

La dermatitis atópica es una enfermedad dérmica inflamatoria crónica observada en individuos con una

predisposición hereditaria a un umbral cutáneo reducido ante el prurito, que está acompañado a menudo por 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 (DA) es la enfermedad dérmica inflamatoria crónica más habitual en niños pequeños, y afecta del 10% al 15% de la población durante la niñez. La dermatitis atópica está asociada frecuentemente a asma y alergias, y por tanto se le ha conocido como un componente de la denominada "triada atópica", puesto que aparece frecuentemente en individuos con asma y/o rinitis alérgica. Véase Leung Dym, *Atopic Dermatitis: From Pathogenesis To Treatment*, R.G. Landes Co., Austin, Tejas, 1-226, 1996. Consiguientemente, la disfunción inmune asociada con la dermatitis atópica es tratable con agentes terapéuticos que son inhibidores de PDE4. Por ejemplo, se ha informado de que el rolipram, Ro-201724, y la denbufilina producen una inhibición relacionada con la concentración de la proliferación de células mononucleares de sangre periférica humana (HPBM) en pacientes normales, así como en sujetos con dermatitis atópica. Véanse, respectivamente, Torphy et al., *Drugs and the Lung*, Eds. Page y Metzger, Raven Press, Nueva York, 1994; y O'Brien, *Mol. Medicine Today*, 369, 1997. Estos estudios determinaron también que la respuesta

proliferativa de HPBM en pacientes con dermatitis atópica era más sensible a la inhibición de PDE4 que la proliferación observada en HPBM en sujetos normales.

Las células T que segregan citocina de tipo Th2 que expresan el antígeno asociado a linfocito cutáneo desempeñan un papel crucial en la inducción de las respuestas de IgE locales y en la agrupación de eosinófilos en esta enfermedad. La inflamación crónica observada en la dermatitis atópica se considera que es el resultado de varios factores interdependientes, tales como la repetida o persistente exposición a alergenos, que puede conducir a la expansión de células Th2. Se ha demostrado que existe un aumento de la frecuencia de células T específicas de alergeno que producen niveles aumentados de IL-4, IL-5 e IL-3 en la sangre de pacientes con dermatitis atópica. Véase Leung Dym et al , "Allergic and immunological skin disorders", *JAMA* **278**(22), 1914-1923, 1197. Esto es significativo debido a que IL-4 e IL3 inducen la expresión de la molécula de adhesión vascular 1 (VCAM-1), una molécula de adhesión implicada en la migración de células mononucleares y eosinófilos a sitios de inflamación de tejido. Además, el IL-5 es un mediador clave de la activación de eosinófilos, que es una característica habitual de la enfermedad atópica.

Se sabe desde hace mucho que el aumento de la concentración de AMPc en linfocitos y basófilos está asociado con una reducción de la liberación de mediador de estas células, y más recientemente se ha informado de que la histamina que actúa sobre los receptores H2 aumenta los niveles de AMPc e inhibe la producción de IL-4 en células Th2 de ratón. Consiguientemente, se supone que están presentes en las enfermedades atópicas, tales como dermatitis atópica, respuestas β-adrenérgicas deficientes o actividad de PDE4 aumentada de respuestas inflamatorias de leucocitos. Una respuesta de AMPc reducida puede ser el resultado de una actividad de PDE4 potenciada que tenga una base genética o que sea una afección adquirida.

Se han llevado a cabo estudios que comparan los diferentes tipos celulares de pacientes atópicos con aquellos de voluntarios sanos, y los resultados han mostrado que el aumento de actividad de AMPc-PDE en células atópicas se correlaciona con una función celular inflamatoria e inmune anormal en dermatitis atópica. Además, la enzima PDE4 de leucocitos atópicos es más sensible a los inhibidores de PDE4 que la enzima PDE4 de leucocitos normales, y se ha demostrado una diferencia de hasta 14 veces. 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 un aumento de la sensibilidad en la inhibición de la proliferación de células mononucleares de sangre periférica de donantes atópicos en tratamiento con inhibidores de PDE4. Por ejemplo, se ha encontrado que el rolipram es más eficaz en la inhibición de la proliferación de PBMC de dermatitis atópica estimuladas por PHA que en la inhibición de la proliferación de PBMC normales estimuladas por PHA, con una $CI_{50}$= 280 nM en comparación con una $CI_{50}$= 2600 nM, respectivamente.

Además, se ha mostrado que una gama estructuralmente diversa de inhibidores selectivos de PDE4 son eficaces en la reducción de eosinofilia dérmica en conejillos de indias que se han mediado por una serie de agentes tales como PAF, ácido araquidónico, plasma activado con zimosán y proteína de anafilaxis cutánea. Véase 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. Dichos datos muestran la utilidad de los inhibidores de PDE4 en el tratamiento de enfermedades dérmicas causadas por eosinófilos. Dicho tratamiento es mediante administración tópica, por ejemplo, se ha encontrado que atizoram tópico administrado bilateralmente durante ocho días a veinte pacientes en un ensayo clínico inhibe eficazmente todos los parámetros inflamatorios ensayados, mostrando mejoras tanto

cualitativas como cuantitativas sin efectos adversos. Véase Hanifin et al. "Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis", *J. Invest. Dermatol.* **197**, 51-56, 1996.

Consiguientemente, los inhibidores de PDE4 de fórmula (1.0.0) son útiles para el tratamiento beneficioso de dermatitis atópica como se describió anteriormente. Un área relacionada de aplicación terapéutica para la que los compuestos de fórmula (1.0.0) producen también efectos beneficiosos es en el tratamiento de urticaria. La urticaria es una reacción vascular, habitualmente transitoria, que implica la dermis superior, que representa edemas localizados causados por la dilatación y el aumento de la permeabilidad de los capilares, y caracterizada por el desarrollo de ronchas o erupciones. Muchos estímulos diferentes pueden inducir una reacción urticaria, y puede clasificarse, según las causas precipitantes, como: mediada por sistema inmune; mediada por complemento, que puede implicar mecanismos inmunológicos o no inmunológicos, inducida por material urticariogénico, inducida por agentes físicos, inducida por estrés o idiopática. La afección puede designarse también como aguda o crónica dependiendo de la duración de un ataque. El angioderma es la misma respuesta en los tejidos de dermis profunda o subcutáneos o submucosos.

Los tipos más habituales de urticaria que son tratables con los compuestos de fórmula (1.0.0) son urticaria colinérgica, que se caracteriza por la presencia de ronchas puntuales distintivas rodeadas por áreas de eritema, que se cree que es una reacción de hipersensibilidad no inmunológica en la que la acetilcolina liberada por terminales nerviosas pasasimpáticas o motoras induce la liberación de mediadores de mastocitos, y provocada por condiciones de ejercicio, estrés o aumento del calor ambiental; urticaria de frío, que es urticaria precipitada por aire, agua u objetos fríos, que aparece en dos formas: en la forma autosómica dominante, que está asociada a fiebres, artralgias y leucocitosis, las lesiones presentes son eritematosas, pápulas y máculas con escozor, y en la forma más habitual adquirida, que es habitualmente idiopática y autolimitada; urticaria de contacto, que es una respuesta localizada o generalizada transitoria de ronchas y erupciones desencadenada por la exposición a agentes urticariogénicos rápidamente absorbibles; urticaria gigante, que es angioderma; y urticaria papular, que es una erupción cutánea persistente que representa una reacción de hipersensibilidad frente a picaduras de insectos.

Consiguientemente, los inhibidores de PDE4 de fórmula (1.0.0) son útiles para el tratamiento beneficioso de los diversos tipos de urticaria descritos anteriormente. Un área

relacionada de aplicación terapéutica para la que los compuestos de fórmula (1.0.0) producen también resultados beneficiosos es en diversos usos oftálmicos, en particular, en el tratamiento de conjuntivitis y uveitis.

La conjuntiva es una membrana delicada que recubre los párpados y que cubre la superfice expuesta de la esclerótica. La conjuntivitis es una inflamación de la conjuntiva que consiste generalmente en hiperemia conjuntiva asociada con descarga. Los tipos más habituales de conjuntivitis que son tratables con los compuestos de fórmula (1.0.0) son: conjuntivitis actínica, producida por la luz ultravioleta; conjuntivitis catarral aguda, que es una conjuntivitis infecciosa aguda asociada con resfriados o catarros y caracterizada por una vívida hiperemia, edema, pérdida de translucidez, y descarga mucosa o mucopurulenta; conjuntivitis contagiosa aguda, que es una conjuntivitis epidémica mucopurulenta causada por *Haemophilus aegyptius*, que tiene los mismos síntomas que la conjuntivitis catarral aguda, y se denomina también "ojos rojos"; conjuntivitis alérgica, que es un componente de la fiebre del heno, conjuntivitis atópica, que es conjuntivitis alérgica de tipo inmediato causado por alergenos de transporte aéreo, por ejemplo, pólenes, polvos, esporas y escamas animales; conjuntivitis catarral crónica, que es una conjuntivitis crónica leve con sólo una ligera hiperemia y descarga mucosa;

conjuntivitis purulenta, que es una conjuntivitis aguda causada por bacterias o virus, particularmente gonococos, meningococos, neumococos y estreptococos, y caracterizada por una grave inflamación de la conjuntiva y una copiosa descarga de pus, y conjuntivitis primaveral, que es una conjuntivits bilateral de aparición estacional, de causa desconocida, que afecta a niños, especialmente varones, y caracterizada por pápulas aplanadas y un exdudado espeso gelatinoso. Consiguientemente, los inhibidores de PDE4 de fórmula (1.0.0) son útiles para el tratamiento beneficioso de los diversos tipos de conjuntivitis descritos anteriormente. Un área relacionada de aplicación terapéutica para la que los compuestos de fórmula (1.0.0) producen también resultados beneficiosos es en el tratamiento de uveitis.

La úvea es la capa o túnica media vascular del ojo, que comprende iris, cuerpo ciliar y coroide. La uveitis es una inflamación de toda o parte de la úvea e implica habitualmente las demás túnicas del ojo, es decir, la esclerótica y la córnea, así como la retina. Los tipos más habituales de uveitis, que son tratables con los compuestos de fórmula (1.0.0), son uveitis anterior, que es uveitis que implica las estrcuturas de iris y/o cuerpo ciliar, incluyendo iritis, ciclitis e iridociclitis, uveitis granulomatosa, que es uveitis de cualquier parte del tracto uveal, pero particularmente de la parte posterior,

caracterizada por colecciones nodulares de células epiteliales y células gigantes rodeadas por linfocitos; uveitis no granulomatosa, que es inflamación de la parte anterior del tracto uveal, es decir, iris y cuerpo ciliar; uveitis facoantigénica, que es una de las uveitis inducidas por lentes, es una uveitis anterior grave similar a la oftalmia simpática, observada semanas o incluso meses después de cirugía de lentes extracapsulares u otro trauma de la cápsula; e uveitis posterior, que es uveitis que implica la parte posterior del ojo, incluyendo coroiditis y coriorretinitis. Consiguientemente, los inhibidores de PDE4 de fórmula (1.0.0) son útiles para el tratamiento beneficioso de los diversos tipos de uveitis descritos anteriormente.

**8.8 Psoriasis**

La psoriasis es una dermatosis escamosa crónica común con herencia poligénica y un curso fluctuante, que se caracteriza por microabscesos y pústulas espongiformes, así como parches eritematosos, secos y escamosos de diversos tamaños. La psoriasis es una enfermedad dérmica común que afecta aproximadamente al 2% de la población, y más de 1,5 millones de pacientes en los EE.UU. consultan anualmente a médicos para tratamiento. La psoriasis es habitualmente recurrente, y en algunos casos, puede ser muy debilitante. La etiología de la psoriasis es desconocida, pero parece ser una enfermedad autoinmune con predisposición genética.

La psoriasis implica una gran infiltración de células T en las regiones afectadas de la piel, con linfocitos CD4+ en la dermis, y linfocitos CD8+ en la epidermis. Estos linfocitos segregan IL-2, IFN-γ y TNF-α, que alteran la proliferación y diferenciación de los queratinocitos. Además, del 5% al 10% de los pacientes con psoriasis desarrollan artritis psoriática, los síntomas de la cual son muy similares a los de artritis reumatoide. El amplio espectro de actividades anti-inflamatorias mostrado por los inhibidores de PDE4, ya discutidas anteriormente, posibilitan que dichos inhibidores se utilicen beneficiosamente en el tratamiento de la psoriasis.

Se ha demostrado que el tratamiento de células basales epidérmicas en cultivos primarios con el inhibidor de PDE4, Ro 20-1724, conduce a un aumento de tres veces en las concentraciones de AMPc. Se ha mostrado también que el tratamiento de las láminas epidérmicas psoriáticas y las láminas epidérmicas psoriáticas queratomizadas con Ro 20.1724 da como resultado una elevación muy marcada de las concentraciones de AMPc frente a los controles. Específicamente, se ha observado un aumento del 1395% en la concentración de AMPc en epidermis psoriática queratomizada. Los inhibidores de PDE4 han mostrado inhibir también la respuesta inflamatoria de una serie de mediadores por administración tópica o sistémica. Por ejemplo,

se ha mostrado que el rolipram inhibe la inflamación del oído inducida por aceite de ricino en ratón a dosis tópicas tan bajas como de 0,03 mg por oído. El inhibidor selectivo de PDE4 Ro 20-1724 se ha investigado también en dos estudios de doble ciego que comparan su eficacia respecto del vehículo, en los que se ha mostrado que mejora las lesiones psoriáticas sin efectos sistémicos o cutáneos adversos.

**8.9 Esclerosis múltiple y otras enfermedades autoinmunes inflamatorias**

Una esclerosis es una induración o endurecimiento, y representa especialmente el endurecimiento de una parte de la sustancia intersticial por inflamación, y por el aumento de la formación de tejido conectivo y en enfermedades intersticial. El término "esclerosis" se utiliza principalmente para dicho endurecimiento del sistema nervios debido al depósito de tejido conectivo, o para designar el endurecimiento de los vasos sanguíneos La esclerosis múltiple (EM) es una enfermedad en la que existen focos de desmielinización de diversos tamaños a lo largo de la materia blanca del sistema nervioso central, que se extienden a veces a la materia gris, dando como resultado debilidad, descoordinación, parestesias, trastornos del habla y problemas 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 autoinmune que, además de inflamación crónica y desmielinización, da como resultado también gliosis en el sistema nervioso central. Existen varios subtipos de enfermedad, incluyendo esclerosis múltiple progresiva primaria, y esclerosis múltiple con remisión y recaídas. Estos subtipos de enfermedad pueden distinguirse entre sí basándose en el curso de la enfermedad, en el tipo de inflamación implicada y mediante el uso visualización por resonancia magnética (MRI). También es posible que el mecanismo básico de la enfermedad cambie durante el curso de la esclerosis múltiple, reemplazándose un proceso basado en inflamación después por uno que implique desmielinización y daño axónico. Véase Weilbach y Gold, "Disease modifying treatments for multiple sclerosis. What is on the horizon?", *CNS Drugs* 11, 133-157, 1999.

En esclerosis múltiple, las lesiones inflamatorias se localizan, pero con prevalencia, por toda la materia blanca del sistema nervioso central, aunque las placas escleróticas caracterizadas por la desmielinización son una marca de la enfermedad. El desarrollo de la desmielinización, a su vez, está causado por la necrosis de oligodendrocitos, y la desmielinización está asociada con un infiltrado compuesto principalmente de células T y macrófagos, que junto con las

células locales tales como astrocitos, microglía y células endoteliales cerebrales microvasculares, expresan el complejo de histocompatibilidad principal (MHC) de clase II. Estas células están así implicadas en la presentación de antígenos y se ha identificado una respuesta inflamatoria, y una serie de citocinas pro-inflamatorias, que incluyen TNF-α, TNF-β, IL-1, IL-6 e IFN-γ en el tejido cerebral de los pacientes con esclerosis múltiple, y su presencia está generalmente asociada con lesiones activas. En particular, el TNF-α ha sido el foco de atención debido a que media el daño a mielina y oligodendrocito in vitro, induce a los astrocitos a expresar moléculas de adhesión a superficie y está asociado con la ruptura de la barrera hematoencefálica.

Se han utilizado modelos animales para demostrar el papel del TNF-α en esclerosis múltiple, por ejemplo, en encefalomielitis alérgica experimental (EAE), la administración de anticuerpos anti-TNF o receptores de TNF soluble ha mostrado que proporciona un efecto protector. Véase Selmaj et al., "Prevention of chronic relapsing experimental autoimmune encephalomyelitis by soluble tumor necrosis factor", *J. Neuroimmunol.* **56**, 135-141, 1995. Se ha informado también de una correlación directa entre el nivel de ARNm de TNF-α y la progresión de la EAE. Véase 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. Es una evidencia adicional de que el TNF-α es un mediador de la esclerosis múltiple el aumento de la concentración de TNF-α en el fluido cerebroespinal de pacientes con esclerosis múltiple durante el curso de la enfermedad. Además, un ratón transgénico que sobreexpresa TNF-α en el sistema nervioso central ha mostrado signos de desmielinización espontánea, mientras que un ratón transgénico deficiente en TNF-α ha mostrado un efecto protector. Véase Probert et al., "Spontaneous inflammatory demyelinating disease in transgenic mice showing central nervous system-specific expression of tumour necrosis factor alpha", *Proc. Natl. Acad. Sci. USA* **92**, 11294-11298, 1995; y Liu et al., "TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination", *Nature Med.* **4** 76-83, 1988.

Puesto que los inhibidores de PDE4 reducen también el TNF-α, son beneficiosos en el tratamiento de esclerosis múltiple, porque el TNF-α desempeña un papel clave en la mediación de esclerosis múltiple, como se discutió anteriormente. Por ejemplo, en un modelo de mono tití de encefalomielitis alérgica experimental, se ha encontrado que el rolipram suprime la aparición de síntomas clínicos y cancela las anormalidades según se observa por visualización por MRI. En otro estudio de los

efectos del rolipram sobre encefalomielitis alérgica experimental con recaídas crónica en ratones SJL, se ha mostrado que el rolipram mejora los síntomas clínicos y los cambios patológicos en este modelo. Véase Genain et al., "Prevention of autoimmune demyelination in non-human primates by a cAMP-specific phophodiesterase", *Proc Natl Acad. Sci. USA* **92**, 3601-3605, 1995; y Sommer et al., "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 TNF-α, los compuestos de fórmula (1.0.0) poseen también actividad como agentes inmunosupresores, y son especialmente útiles para tratar enfermedades autoinmunes en las que la inflamación sea una parte componente de la enfermedad autoinmune, o en las que la inflamación sea parte de la etiología de la enfermedad autoinmune, o en las que la inflamación esté implicada de otra manera con la enfermedad autoinmune. Como alternativa, los compuestos de fórmula (1.0.0) son agentes antiinflamatorios útiles en el tratamiento de enfermedades inflamatorias en las que las reacciones autoinmunes sean parte de la enfermedad inflamatoria, o en las que las reacciones autoinmunes sean parte de la etiología de la enfermedad inflamatoria, o en las que las reacciones autoinmunes estén implicadas de otra manera con la enfermedad inflamatoria.

Consiguientemente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento de esclerosis múltiple, como se discutió con detalle anteriormente.

Otras enfermedades autoinmunes/inflamatorias que pueden tratarse por agentes terapéuticos que comprenden los compuestos de fórmula (1.0.0) incluyen, pero sin limitación, dolencias hematológicas autoinmunes tales como anemia hemolítica, anemia aplásica, anemia pura de glóbulos rojos y púrpura trombocitopénica idiopática; lupus sistémico eritematoso; policondritis, escleroderma; granulomatosis de Wegner; dermatomiositis, hepatitis activa crónica; miastenia grave; síndrome de Stevens-Johnson; esprúe idiopático, enfermedades intestinales inflamatorias tales como colitis ulcerosa y enfermedad de Crohn; oftamopatía endocrina; enfermedad de Grave, sarcoidosis, alveolitis; neumonitis por hipersensibilidad crónica, cirrosis biliar primaria; diabetes juvenil (diabetes mellitus de tipo I); uveitis anterior e uveitis granulomatosa (posterior); queratoconjuntivitis seca y queratoconjuntivitis epidémica; fibrosis pulmonar intersticial difusa (fibrosis pulmonar intersticial); fibrosis pulmonar idiopática; fibrosis quística; artritis psoriática; glomerulonefritis con y sin síndrome nefrótico, incluyendo glomerulonefritis aguda, síndrome nefrótico idiopático y nefropatía con cambios mínimos; enfermedades dérmicas inflamatorias/hiperproliferativas,

incluyendo psoriasis y dermatitis atópica; discutidas con 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 utilizarse como agentes inmunosupresores para la prevención de rechazo de injerto alogénico después de un trasplante de órganos, incluyendo típicamente dichos órganos: tejido de médula ósea, intestino, corazón, riñón, hígado, pulmón, páncreas, piel y córnea.

**8.10 Enfermedad intestinal inflamatoria**

La colitis ulcerosa (CU) es una ulceración recurrente crónica del colon, principalmente de la mucosa y submucosa, que es de causa desconocida, y que se manifiesta clínicamente por un dolor abdominal de tipo retortojón, hemorragia rectal y descargas sueltas de sangre, pus y mucosidad con escasas partículas fecales. Las enfermedades relacionadas del intestino incluyen colitis colágena, que es un tipo de colitis de etiología desconocida que se caracteriza por depósitos de material colágeno debajo del epitelio del colon, y caracterizada por dolores abdominales de tipo retortijón con una clara reducción de la absorción de fluidos y electrolitos que conduce a diarrea acuosa; colitis poliposa, que es una colitis ulcerosa asociada con la formación de pseudopólipos, es decir, islas

inflamadas edematosas de mucosa entre las áreas de ulceración; y colitis transmural, que es la inflamación de todo el grosor del intestino, en vez de la enfermedad de mucosa y submucosa, habitualmente con la formación de granulomas no caseificantes; que se parece clínicamente 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 contracturas es habitual, y las fístulas, particularmente en el perineo, son una complicación frecuente.

La enfermedad de Crohn (EC) es una enfermedad inflamatoria granulomatosa crónica de etiología desconocida que implica cualquier parte del tracto gastrointestinal, pero que implica habitualmente el íleo terminal con cicatrización y engrosamiento de la pared intestinal, que conduce frecuentemente a obstrucción intestinal y a 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 discutidas anteriormente se representan colectivamente como enfermedad intestinal inflamatoria (EII). Estas enfermedades son crónicas, trastornos de recaída espontánea de causa desconocida que están mediados inmunológicamente y cuya patogénesis se ha establecido mediante el 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 et al, "Inflammatory bowel disease: A new wave of therapy", *Exp. Opin. Ther. Patents* **8**(7), 785-818, 1998. Aunque la incidencia de colitis ulcerosa ha permanecido relativamente estable, la incidencia de enfermedad de Crohn ha aumentado significativamente.

La terapia actual para enfermedad intestinal inflamatoria incluye ácido 5-aminosalicílico, corticosteroides e inmunomodulantes tales como azatioprina, 6-mercaptopurina y metotrexato. Estos agentes tienen un amplio espectro de efectos secundarios adversos y mo modifican la enfermedad misma, por lo que existe una necesidad continua de agentes de tratamiento más eficaces. Los compuestos de fórmula (1 0.0) son capaces de tratar beneficiosamente la enfermedad intestinal inflamatoria como resultado de su capacidad de inhibir la producción de TNF-α, debido a que el TNF-α causa la activación, proliferación y liberación del mediador de células inmunes en la enfermedad intestinal inflamatoria. Véase Radford-Smith y Jewell, "Cytokines and inflammatory bowel disease"; *Bailleres Clin. Gastroenterol* **10**, 151-164, 1996. El TNF-α se ha detectado también en las heces y mucosa intestinal de pacientes con enfermedad intestinal inflamatoria. Además, estudios clínicos iniciales de la enfermedad de Crohn utilizando anticuerpos monoclonales de TNF se han mostrado significativamente prometedores.

Como ya se detalló adicionalmente antes, los inhibidores selectivos de PDE4 tienen un efecto marcado sobre la inhibición de la liberación de TNF-α de células mononucleares de sangre periférica después de que dichas células se hayan estimulado con una amplia serie de mediadores, tanto in vitro como in vivo. El inhibidor selectivo de PDE4 arofilina se ha mostrado que proporciona efectos beneficiosos cuando se ensayó en modelos de colitis en rata. Además, en un modelo de colitis inducida por sulfato de dextrano en rata, el rolipram y el inhibidor selectivo de PDE4 LAS31025 han demostrado efectos beneficiosos comparables a la prednisolona. Ambos compuestos de ensayo han mostrado que mejoran la hemorragia y las marcas inflamatorias. Véase Puig et al , "Curative effects of phosphodiesterase 4 inhibitors in dextran sulfate sodium induced colitis in the rat", *Gastroenterology* **114**(4), A1064, 1998. Otros investigadores han utilizado modelos adicionales para demostrar la capacidad de los inhibidores selectivos de PDE4 de proporcionar protección gastrointestinal. Por ejemplo, se ha mostrado que la extravasación de eritrocitos inducida por lipopolisacáridos en ratas y la hipoperfusión intestinal en perros puede atenuarse con los inhibidores selectivos de PDE4 rolipram y denbufilina. Véase 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; y Cardelus et al., "Protective effects of denbufylline against endotoxin induced bowel hyperplasia", *Met. 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 una infección abrumadora, lo más habitualmente una infección con bacterias gram negativas, aunque puede producirse por otras bacterias, virus, hongos y protozoos. El choque séptico se considera el resultado de la acción de endotoxinas u otros productos del agente infeccioso sobre el sistema vascular, causando el secuestro de grandes volúmenes de sangre en los capilares y venas. Está también implicada la activación de los sistemas de complemento y cinina y la liberación de histamina, citocinas, prostaglandinas y otros mediadores.

Se ha mostrado en un modelo de insuficiencia renal aguda inducida por endotoxina en ratas que el inhibidor selectivo de PDE4, Ro-201734, administrado como post-tratamiento a 10 µg/kg/min, aumenta significativamente la excreción de AMPc urinario, atenúa notablemente los aumentos inducidos por endotoxina en la resistencia vascular renal, y reduce el flujo renal y la tasa de filtración glomerular. Se ha mostrado también que Ro-201734 mejora las tasas de supervivencia de ratas tratadas con endotoxinas. Véase Carcillo et al., *Pharmacol. Exp. Ther.* **279**, 1197, 1996. Se ha estudiado también la pentoxifilina

en pacientes que sufren choque séptico. En este estudio, se han seleccionado 24 pacientes 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 12 han servido como grupo de control. Después de 24 horas, se ha encontrado que los niveles de TNF-α en el grupo de terapia se han reducido significativamente, mientras que los niveles de IL-6 han aumentado significativamente.

En otro estudio, se ha mostrado que el pretratamiento 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 de eritrocitos de intestino inducida por lipopolisacáridos, y que la denbufilina es 100 veces más potente que la pentoxifilina en la inhibición de la caída del flujo sanguíneo mesentérico inducida por lipopolisacáridos, sin afectar al flujo renal ni al índice cardiaco. Véase Cardelus et al., ibid., *Eur. J Pharmacol*.

La insuficiencia renal es la incapacidad del riñón de excretar metabolitos a niveles de plasma normales en condiciones de carga normal, o la incapacidad de retener electrolitos en condiciones de ingesta normal. En la forma aguda, se caracteriza por uremia y habitualmente por oliguria o anuria, con

hipercalemia y edema pulmonar. Basándose en las actividades anteriormente descritas de los inhibidores selectivos de PDE4, se ha demostrado que los inhibidores selectivos de PDE4 son útiles en el tratamiento de insuficiencia renal, especialmente insuficiencia renal aguda. Véase 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. Véase también el documento WO 98/00135, cedido a la Universidad de Pittsburgh. Consiguientemente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento de insuficiencia renal, particularmente de insuficiencia renal aguda.

La caquexia es un estado profundo y marcado de trastorno constitutivo caracterizado por una mala salud general y desnutrición. La caquexia puede ser el resultado final de una serie de factores causantes, por ejemplo, puede ser el resultado de infección por uno cualquiera de una serie de diferentes organismos o microorganismos unicelulares que incluyen bacterias, virus, hongos y protozoos. La caquexia de malaria es representativa, y comprende un grupo de síntomas de naturaleza crónica que son el resultado de ataques previos de malaria grave, siendo las principales señales anemia, piel descolorida, escleróticas amarillas, esplenomegalia y hepatomegalia. Otra causa de caquexia es la cesación o deterioro de las funciones humorales u otras orgánicas, por ejemplo, la caquexia

hipofisaria comprende una serie de síntomas que son el resultado de la cesación 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 caquexia asociada con otros síntomas de insuficiencia renal avanzada. La caquexia cardiaca comprende emaciación debida a enfermedad cardiaca. La caquexia suprarrenal, o enfermedad de Addison, es un trastorno caracterizado por hipotensión, pérdida de peso, anorexia y debilidad, causada por deficiencia de la hormona suprarrenal. Se debe a la destrucción inducida por tuberculosis o autoinmune de la corteza suprarrenal, que da como resultado la deficiencia en aldosterona y cortisona.

La caquexia puede ser también el resultado de estados patológicos de diversos tipos. La caquexia cancerosa comprende el estado débil, emaciado observado en casos de tumores malignos. La caquexia puede ser también la consecuencia de infección por el virus de la inmunodeficiencia humana (VIH), y comprende los síntomas representados habitualmente como síndrome de inmunodeficiencia adquirida (SIDA). Los compuestos de fórmula (1.0.0) son útiles en el tratamiento de caquexia de los diferentes tipos descritos anteriormente como resultado de su capacidad de proporcionar una subrregulación 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 células mononucleares de sangre periférica, después de que dichas células se hayan estimulado con una amplia gama de mediadores. La liberación de TNF-α está implicada o desempeña un papel mediador en enfermedades o afecciones cuya etiología implica o comprende la liberación morbosa, es decir, patológica, excesiva o no regulada de TNF-α.

Los compuestos inhibidores de PDE4 de fórmula (1.0.0) son útiles además en el tratamiento de infección, especialmente de infección por virus en la que dichos virus aumentan la producción de TNF-α en su huésped, o en la que dichos virus son sensibles a la sobrerregulación de TNF-α en su huésped, de modo que su replicación u otras actividades vitales se vean afectadas adversamente. Dichos virus incluyen, por ejemplo, VIH-1, VIH-2 y VIH-3, citomegalovirus, CMV; gripe; adenovirus, y herpesvirus, especialmente *Herpes zoster* y *Herpes simplex*.

Los compuestos inhibidores de PDE4 de fórmula (1.0.0) son útiles además en el tratamiento de infecciones por levaduras y hongos en las que las citadas levaduras u hongos son sensibles a la sobrerregulación por TNF-α o desencadenan la producción de TNF-α en su huésped. Una enfermedad particular que es tratable de esta manera es la meningitis fúngica. Los compuestos de fórmula (1.0.0) proporcionan también efectos beneficiosos cuando

se combinan con, es decir se administran conjuntamente con, otros fármacos a elegir para el tratamiento de infecciones sistémicas por levaduras y hongos. Dichos fármacos a elegir 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 liposómica B. El término "administración conjunta" como se utiliza en la presente descripción con referencia a los compuestos de fórmula (1.0.0), y a los fármacos a elegir para el tratamiento de infecciones sistémicas por levaduras y hongos, se pretende que signifique e incluya (a) la administración simultánea de dicho(s) compuesto(s) y fármaco(s) a un sujeto cuando se formulan conjuntamente en una forma de dosificación única; (b) la administración sustancialmente simultánea de dicho(s) compuesto(s) y fármaco(s) a un sujeto cuando se formulan por separado en formas de formas de dosificación separadas; y (c) la administración secuencial de dicho(s) compuesto(s) y fármaco(s) a un sujeto cuando se formulan por separado y se administran consecutivamente con cierto intervalo de tiempo significativo entre ellos.

**8 12 Daño hepático**

Además de los efectos adversos descritos anteriormente del TNF-α, causa también insuficiencia hepática en humanos, un fenómeno que se ha mostrado en una serie de modelos animales.

Por ejempo, en un modelo agudo de insuficiencia hepática mediada por células T, el rolipram administrado de 0,1 a 10 mg/kg i.p. 30 minutos antes de la provocación con concavalina A ó enterotoxina estafilocóccica B, se ha mostrado que reduce significativamente las concentraciones en plasma de TNF-α e INF-γ, mientras que eleva también significativamente los niveles de IL-10. Véase Gantner et al., *J, Pharmacol. Exp. Ther.* **280**, 53, 1997. En este mismo estudio, se ha mostrado también que el rolipram suprime la liberación de IL-4 inducida por concavalina A. Se han evaluado las actividades en plasma de las enzimas específicas de hígado ALT, AST y SDH en este estudio, puesto que cualquier aumento de sus niveles indicaría una destrucción masiva de células hepáticas. Se ha encontrado que en el pretratamiento de ratones no tratados que recibían concavalina A, o ratones sensibilizados con galactosamina que recibían galactosamina/endotoxina estafilocócica B, con rolipram de 0,1 a 10 mg/kg i.p, el rolipram ha inhibido de forma dependiente de la dosis las actividades enzimáticas en plasma anteriormente citadas. Consiguientemente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento de trastornos de células T, tales como insuficiencia hepática.

**8.13 Hipertensión pulmonar**

Es conocido que la actividad de las fosfodiesterasas, que hidrolizan los segundos mensajeros vasodilatadores AMPc y GMPc, puede aumentarse mediante hipertensión pulmonar inducida por

hipoxia (HPH). La hipoxia es una reducción del suministro de oxígeno al tejido por debajo de los niveles fisiológicos a pesar de una perfusión adecuada del tejido por la sangre. La hipertensión pulmonar resultante se caracteriza por un aumento de la presión, es decir, por encima de 30 mm Hg sistólica y por encima de 12 mm Hg diastólica, en la circulación arterial pulmonar. Utilizando un modelo que utiliza anillos arteriales pulmonares aislados de ratas normales y de ratas con hipertensión pulmonar inducida por hipoxia, se ha mostrado que el inhibidor selectivo de PDE4 rolipram potencia las actividades relajantes del isoprotereneol y forscolina. Se ha observado el mismo efecto con milrinona, que es un inhibidor selectivo de PDE3, apoyando así la inhibición tanto de PDE3 como PDE4 para mejorar significativamente la relajación arterial pulmonar en hipertensión pulmonar inducida por hipoxia. Véase Wagner et al., *J Pharmacol Exp. Ther* **282**, 1650, 1997. Consiguientemente, los compuestos de fórmula (1.0.0) son útiles en el tratamiento de hipertensión pulmonar, especialmente de hipertensión pulmonar inducida por hipoxia

**8.14 Enfermedad de pérdida ósea**

La enfermedad de pérdida ósea, designada más habitualmente como osteoporosis, es una afección de baja masa ósea y ruptura de la microarquitectura que da como resultado fracturas con un trauma mínimo. La osteoporosis secundaria es debida a enfermedad sistémica o medicamentos tales como glucocorticoides. Se ha

sostenido que la osteoporosis primaria debe considerarse que comprende dos afecciones: osteoporosis de tipo I, que es la pérdida de hueso trabecular debido a la deficiencia de estrógenos en la menopausia, y la osteoporosis de tipo II, que es la pérdida de hueso cortical y trabecular debido a ineficacia de la remodelación a largo plazo, dietas inadecuadas y la activación del eje paratiroideo con la edad. Los reguladores primarios de la masa ósea en adultos incluyen la actividad física, el estado endocrino reproductor y la ingesta de calcio, y un mantenimiento óptimo del hueso requiere suficiencia en las tres áreas.

Se ha demostrado que los inhibidores selectivos de PDE4 son útiles en el tratamiento beneficioso de enfermedad de pérdida ósea, particularmente osteoporosis. Se ha estudiado el efecto de la denbufilina sobre la pérdida ósea en ratas Walker que llevan 256/S, y sobre la formación de nódulos mineralizados y la formación de células similares a osteoclastos en sistemas de cultivo de médula ósea. Se ha descubierto que la administración oral en serie de denbufilina inhibe la reducción de la densidad mineral ósea de fémures de ratas Walker que llevan 256/S, y restablece la masa ósea y el número de osteoclastos y osteoblastos por superficie trabecular en la metáfisis del fémur. Se ha encontrado también que la administración de denbufilina da como resultado un aumento del

número de los nódulos mineralizados y una reducción del número de células similares a osteoclastos en el sistema de cultivo de médula ósea in vitro. Estos efectos beneficiosos son específicos de la inhibición de PDE4, y se imitan por el dibutiril-AMPc, demostrando que la isozima PDE4 desempeña un papel importante en el recambio óseo mediante AMPc. Veáse 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, 199, y el documento JP 9169665 cedido a Miyamoto (1997). Consiguientemente, los inhibidores selectivos de PDE4 de fórmula (1.0.0) son útiles en el tratamiento de enfermedades que implican pérdida ósea, especialmente osteoporosis.

**8.15 Trastornos del SNC**

El inhibidor selectivo de PDE4, rolipram, se desarrolló inicialmente como antidepresivo, y sigue estudiándose en ensayos clínicos para esta indicación. Además, se ha demostrado que los inhibidores selectivos de PDE4 proporcionan efectos beneficiosos en otros trastornos del sistema nervioso central, incluyendo enfermedad de Parkinson, Hulley et al.; "Inhibitors of Type IV phosphodiesterase reduce the toxicity of MPTP in substantia nigra neurons in vivo", *Eur. J. Neurosci.* 7 2431-2440, 1995; así como deterioro de la memoria y el aprendizaje en ratas, 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; y Barad et al., "Rolipram, a Type IV-specific phosphodiesterase inhibitor, facilates the establishment of long-lasting long-term potentiation and improves memory", *Proc. Natl. Acad Sci. USA* **95**, 15020-15025, 1998.

Se ha descrito también el uso de inhibidores de PDE4 para tratar discinesia tardía y dependiencia de fármacos en la técnica, documentos WO 95/28177 y JP 92221423 (1997), ambos cedidos a Meiji Seika Kaisja Ltd. Se ha encontrado que la isozima PDE4 desempeña un papel importante en el control de la biosíntesis de dopamina en neuronas mesencefálicas; consiguientemente, los inhibidores de PDE4 son útiles en el tratamiento de enfermedades y trastornos que están asociados con o mediados por dopamina en y alrededor de neuronas mesencefálicas; 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. Pharmacol.* **75**, 91-95, 1997.

Los compuestos inhibidores de PDE4 de fórmula (1.0.0) son además útiles en el tratamiento de demencia arteriosclerótica y demencia subcortical. La demencia arteriosclerótica, también denominada demencia vascular y demencia multi-infarto, es una demencia con un curso de deterioro por etapas en forma de una serie de pequeñas apoplejías, y una distribución irregular de déficits neurológicos causados por enfermedad cerebrovascular. La demencia subcortical está causada por lesiones que afectan a las estructuras cerebrales subcorticales, y se caracteriza por pérdida de memoria con lentitud en el procesamiento de información, o de producir respuestas intelectuales Están incluidas las demencias que acompañan la corea de Huntigton, enfermedad de Wilson, parálisis agitante y atrofias talámicas.

**8.16 Otras aplicaciones terapéuticas**

Se ha demostrado que los inhibidores de PDE4 son útiles en el tratamiento de daño por reperfuión-isquemia, Block et al., "Delayed treatment with rolipram protects against neuronal damage following global isquemia in rats", *NeuroReport* **8** 3829-3832, 1997 y 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, en el tratamiento de diabetes autoinmune, Liang et al., "The phosphodiesterase inhibitors pentoxifylline and rolipram prevent diabetes in NOD mice", *Diabetes* **47**, 570-575, 1998, en el tratamiento de autoinmunidad

retinal, Xu et al., "Protective effect of the Type IV phosphodiesterase inhibitor rolipram in EAU: protection is independent of the IL-10-inducing activity", *Invest. Ophtalmol. 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 et al., "Rolipram, a specific Type IV phosphodiesterase inhibitor, is a potent inhibitor of HIV-1 replication", *AIDS* **9** 1137-1144, 1995 y 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; en el tratamiento de lupus eritematoso, documento JP 10067682 (1998) cedido a Fujisawa Pharm. Co. Ltd.; en el tratamiento de enfermedades de riñón y uréter, documento DE 4230755 (1994) cedido a Schering AG; en el tratamiento de trastornos urogenitales y gastrointestinales, documento WO 94/06423 cedido a Schering AG; y en el tratamiento de enfermedades de la próstata, documento WO 99/02161, cedido a Porssmann y documento WO99/02161 cedido a Stief.

Según las descripciones anteriores, se comprenderá que los compuestos de fórmula (1.0.0) son útiles 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 selecionado del grupo constituido por asma atópica; asma no atópica; asma alérgica; asma mediada por IgE bronquial atópica; asma bronquial, asma esencial; asma verdadera; asma intrínseca causada por perturbaciones patofisiológicas, asma extrínseca causada por factores medioambientales; asma esencial de causa desconocida o no evidente; asma no atópica, asma bronquítica, asma enfisematosa, asma inducida por ejercicio; asma ocupacional; asma infecciosa causada por infección bacteriana, fúngica, protozooaria o viral; asma no alérgica, asma incipiente, síndrome de jadeos en infantes;

- broncoconstricción crónica o aguda, bronquitis crónica; obstrucción de las vías aéreas pequeñas; y enfisema;

- enfermedades obstructivas o inflamatorias de las vías aéreas de cualquier tipo, etiología o patogénesis; o una enfermedad inflamatoria u obstructiva de las vías aéreas que es un miembro seleccionado del grupo constituido por asma; neumoconiosis; neumonía eosinófila crónica, enfermedad pulmonar

obstructiva crónica (EPOC); EPOC que incluye bronquitis crónica, enfisema pulmonar o disnea asociadas con ésta; EPOC que se caracteriza por una obstrucción irreversible progresiva de las vías aéreas; síndrome del distrés respiratorio en adultos (SDRA) y exacerbación de la hiperreactividad de las vías aéreas posterior a otra terapia de fármacos;

- neumoconiosis de cualquier tipo, etiología o patogénesis; o neumoconiosis que es un miembro seleccionado del grupo constituido por aluminosis o enfermedad de los trabajadores con bauxita; antracosis o asma de los mineros, asbestosis o asma de los montadores de calderas; calicosis o enfermedad del sílex; ptilosis causada por la inhalación de polvo de plumas de avestruz; siderosis causada por la inhalación de partículas de hierro; silicosis o enfermedad de los molineros, bisinosis o asma de polvo de algodón y neumoconiosis de 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 de crup; bronquitis seca; bronquitis asmática infecciosa; bronquitis productiva; bronquitis por estafilococo o estreptococo; y bronquitis vesicular,

- bronquiectasis de cualquier tipo, etiología o patogénesis; o bronquiectasis que es un miembro seleccionado del grupo constituido por bronquiectasis cilíndrica; bronquiectasis de sáculos; bronquiectasis fusiforme, bronquiectasis capilar; bronquiectasis quística; bronquiectasis seca; y bronquiectasis 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 etmoidea, frontal, maxilar o esfenoide;

- 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 psoriática y artritis vertebral:

- gota, y fiebre y dolor asociados con inflamación;

- un trastorno relacionado con eosinófilos de cualquier tipo, etiología o patogénesis, o un trastorno relacionado con

eosinófilos que es un miembro seleccionado del grupo constituido por eosinofilia; eosinofilia de infiltración pulmonar; síndrome de Loffler; neumonía eosinófila crónica; eosinofilia pulmonar tropical; aspergilosis bronconeumónica; aspergiloma; granulomas que contienen eosinófilos; angitis granulomatosa o síndrome de Churg-Strauss; poliarteritis nodular (PAN); y vasculitis necrotizante 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 mediada por sistema inmune; urticaria mediada por complemento, urticaria inducida por material urticariogénico, urticaria inducida por un agente físico; urticaria inducida por el estrés; urticaria idiopática; urticaria aguda; urticaria crónica; angioedema; urticaria colinérgica; urticaria por el frío en la forma autosómica dominante o en la forma adquirida; urticaria de contacto, urticaria gigante; 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; conjuntitivitis contagiosa aguda; conjuntivitis

alérgica; conjuntivitis atópica; conjuntivitis catarral crónica; conjuntivitis purulenta; y conjuntitivitis primaveral:

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

- psoriasis,

- 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 de remisión recurrente;

- enfermedades autoinmunes/inflamatorias de cualquier tipo, etiología o patogénesis; o una enfermedad autoinmune/ inflamatoria que es un miembro seleccionado del grupo constituido por trastornos hematológicos autoinmunes; anemia hemolítica; anemia aplásica, anemia pura de glóbulos rojos; púrpura trombocitopénica idiopática; lupus sistémico eritematoso; policondritis; escleroderma, granulomatosis de

Wegner; dermatomiositis; hepatitis activa crónica; miastenia grave; síndrome de Stevens-Johnson; esprúe idiopático; enfermedad inflamatoria intestinal autoinmune; colitis ulcerosa, enfermedad de Crohn; oftamopatía endocrina; enfermedad de Grave; sarcoidosis; alveolitis, neumonitis de hipersensibilidad crónica; cirrosis biliar primaria; diabetes juvenil o diabetes mellitus tipo I; uveitis anterior; uveitis granulomatosis o posterior; queratoconjuntivitis seca; queratoconjuntivitis epidérmica; fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial; fibrosis pulmonar idiopática; fibrosis quística, artritis psoriática, glomerulonefritis con y sin síndrome nefrótico; glomerulonefritis aguda; síndrome nefrótico idiopático; nefropatía con cambios mínimos; enfermedades dérmicas inflamatorias/hiperproliferativas; psoriasis; dermatitis atópica, dermatitis de contacto, dermatitis de contacto alérgico; pénfigo familiar benigno, pénfigo eritematoso; pénfigo foliáceo y pénfigo vulgar;

- prevención de rechazo de injertos alogénicos después de un trasplante de órganos;

- enfermedad inflamatoria del intestino (EII) de cualquier tipo, etiología o patogénesis; o enfermedad inflamatoria del intestino que es un miembro del grupo constituido por colitis ulcerosa (CU), colitis colágena; colitis poliposa; colitis

transmural; y enfermedad de Crohn (EC);

- 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 de 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 la inmunodeficiencia humana (VIH):

- daño hepático,

- 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 de aprendizaje y memoria; discinesia tardía; dependencia de drogas, demencia arterioscleróticа y demencias que acompañan a la corea

de Huntigton, enfermedad de Wilson, parálisis agitante y atrofias talámicas;

- infección, especialmente infección por virus en la que dichos virus aumentan la producción de TNF-α en su huésped, o en la que dichos virus son sensibles a la sobrerregulación de TNF-α en su huésped de modo que su replicación u otras actividades vitales se ven afectadas adversamente, incluyendo un virus que es un miembro seleccionado del grupo constituido por VIH-1, VIH-2 y VIH-3; citomegalovirus, CMV; gripe; adenovirus, y herpesvirus, incluyendo *Herpes zoster* y *Herpes simplex*;

- infecciones por levaduras y hongos en las que las citadas levaduras y hongos son sensibles a la sobrerregulación por TNF-α o desencadenan la producción de TNF-α en su huésped, por ejemplo, meningitis fúngica, particularmente cuando se administra en combinación con otros fármacos de elección para el tratamietno de infecciones sistémicas por 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, anfotericina B y anfotericina B liposómica; y

- daños de reperfusión por isquemia; diabetes autoinmune;

autoinmunidad retinal; leucemia linfocítica crónica; infecciones por VIH; lupus eritematoso; enfermedades renalcs y de uréter; trastornos urogenitales y gastrointestinales; y enfermedades de próstata.

**DESCRIPCION DETALLADA DE LA INVENCION**

**9.0 Combinación con otros fármacos y terapias**

La presente invención contempla realizaciones en las que un compuesto de fórmula (1.0.0) es el único agentc terapéutico que se emplea en un procedimiento de tratamiento descrito en la presente descripción, utilizado solo, o más habitualmente, junto con un vehículo farmacéuticamente aceptable para producir una forma de dosificación adecuada para administración a un paciente. Otras realizaciones de la presente invención contemplan una combinación de un compuesto de fórmula (1.0.0) junto con un o más agentes terapéuticos adicionales para administrar conjuntamente a un paciente para obtener cierto resultado final terapéutico particularmente deseado. 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 con detalle en la presente descripción. Más típicamente, el segundo, etc., agente terapéutico se seleccionará de una clase diferente de agentes terapéuticos. Estas selecciones se describen con detalle a continuación.

Como se utiliza en la presente descripción, los términos "administración conjunta", "administrado conjuntamente" y "en combinación con", referidos a los compuestos de fórmula (1.0.0) y a uno o más de otros agentes terapéuticos, se pretende que signifique e incluya lo siguiente: (a) la administración simultánea de dicha combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente necesitado de tratamiento, cuando dichos componentes se formulan conjuntamente en una sola forma de dosificación que libera los citados componentes sustancialmente en el mismo momento al citado paciente; (b) la administración sustancialmente simultánea de dicha combinación de compuesto(s) y agentes(s) terapéuticos a un paciente necesitado de tratamiento, cuando dichos componentes se formulan por separado en formas de dosificación separadas, que se ingieren sustancialmente en el mismo momento por el citado paciente, liberándose los citados componentes sustancialmente en el mismo momento al citado paciente, (c) la administración secuencial de dicha combinación de compuesto(s) y agente(s) terapéutico(s) a un paciente necesitado de tratamiento, cuando dichos componentes se formulan por separado en formas de dosificación separadas, que se ingieren en momentos consecutivos por el citado paciente con un intervalo significativo de tiempo entre cada ingestión, liberándose los citados compuestos sustancialmente en momentos diferentes al citado paciente; y (d) la administración secuencial de dicha combinación de

compuesto(s) y agente(s) terapéutico(s) a un paciente necesitado de tratamiento, cuando dichos componentes se formulan conjuntamente en una sola forma de dosificación que libera los citados componentes de manera controlada, ingiriéndose de forma concurrente, consecutiva y/o superpuesta en el mismo y/o diferentes momentos por el citado paciente.

**9.1 Con inhibidores de la biosíntesis de leucotrienos: inhibidores de 5-lipooxigenasa (5-LO) y antagonistas de proteína activadora de 5-lipooxigenasa (FLAP)**

Se utiliza uno o más compuestos de fórmula (1.0.0) en combinación con inhibidores de la biosíntesis de leucotrienos, es decir, inhibidores de 5-lipooxigenasa y/o antagonistas de proteína activadora de 5-lipooxigenasa, para formar realizaciones de la presente invención. Como ya se ha advertido anteriormente, la 5-lipooxigenasa (5-LO) es uno de los dos grupos de enzimas que metabolizan ácido araquidónico, siendo el otro grupo las ciclooxigenasas, COX-1 y COX-2. La proteína activadora de 5-lipooxigenasa es una proteína de 18 kDa unida a membrana, de unión a araquidonato que estimula la conversión de ácido araquidónico celular por 5-lipooxigenasa. El ácido araquidónico se convierte en ácido 5-hidroperoxieicosa-tetraenoico (5-HPETE), y esta ruta conduce eventualmente a la producción de leucotrienos inflamatorios; consiguientemente, el bloqueo de la proteína activadora de 5-lipooxigenasa o de la enzima 5-lipooxigenasa misma proporciona una diana deseable para

interferir beneficiosamente esta ruta. Uno de dichos inhibidores de 5-lipooxigenasa es el zileutón, representado por la fórmula (0.1.14), que puede encontrarse tanto anteriormente como a continuación. Entre las clases de inhibidores de la síntesis de leucotrienos que son útiles para formar combinaciones terapéuticas con los compuestos de fórmula (1.0.0) están los siguientes:

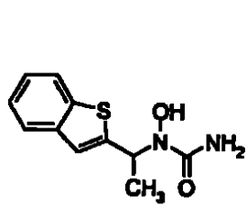
(a) agentes rédox activos, que incluyen N-hidroxiureas; ácidos N-alquilhidroxámicos; selenita; hidrobenzofuranos; hidroxilaminas y catecoles, véase Ford-Hutchinson et al., "5-Lipoxygenase", *Ann. Rev Biochem.* **63**, 383-417, 1994; Weitzel y Wendel, "Selenoenzymes regulate the activity of leukocyte 5-lipooxigenase via the peroxide tone", *J. Biol. Chem.* **268**, 6288-6292, 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**, 8511-8516, 1996; y Stewart et al., "Structure-activity relationships of N-hydroxyurea 5-lipoxygenase inhibitors", *J. Med. Chem.* **40**, 1955-1968, 1997;

(b) se ha mostrado que agentes alquilantes y compuestos que reaccionan con grupos SH inhiben la síntesis de leucotrieno in vitro; véase Larsson et al., "Effects of 1-chloro-2,4,6-

trinitrobenzene on 5-lipoxygenase activity and cellular leukotriene synthesis", *Biochem. Pharmacol.* **55**, 863-871, 1998; y

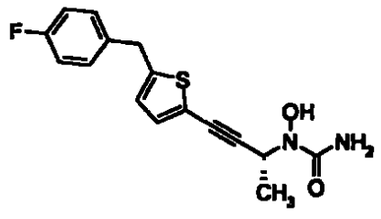
(c) inhibidores competitivos de 5-lipooxigenasa, basados en estructuras tiopiranoindol y metoxialquiltiazol, que pueden actuar como inhibidores no rédox de 5-lipooxigenasa, véase Ford-Hutchinson et al., ibid., y Hamel et al., "Substituted (pyridylmethoxy)naphtalenes as potent and orally active 5-lipoxygenase inhibitors- synthesis, biological profile, and pharmacokinetics of L-739.010", *J. Med. Chem.* **40**, 2866-2875, 1997.

La observación de que el hidroxamato de araquidonoílo inhibe la 5-lipooxigenasa ha conducido al descubrimiento de inhibidores selectivos de 5-lipooxigenasa clínicamente útiles, tales como los derivados de N-hidroxiurea zileutón y ABT-761, representados por las fórmulas (0.1.14) y (5.2.1):




zileutón

(0 1 14)

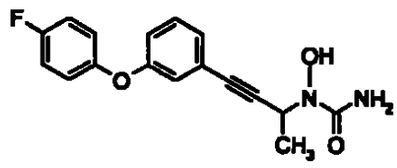



ABT-761

(5.2 1)

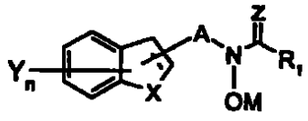
Otro compuesto de N-hidroxiurea es el fenleutón (Abbott-

76745), que se representa por la fórmula (5.2.2):



fenleutón (5.2.2)

El zileutón está cubierto por el documento US 4.873.259 (Summers et al.) cedido a Abbott Laboratories, que describe compuestos inhibidores de lipooxigenasa que contienen indol, benzofirano y benzotiofeno, que pueden representarse por la fórmula (5.2 3):



(5.2.3)

en la que $R_1$ es H; alquilo ($C_1$-$C_4$); alquenilo ($C_2$-$C_4$); ó $NR_2R_3$, siendo $R_2$ y $R_3$ H, alquilo ($C_1$-$C_4$) ó OH; X es O; S; $SO_2$; ó $NR_4$, siendo $R_4$ H, alquilo ($C_1$-$C_6$), alcanoílo ($C_1$-$C_6$); aroílo ó alquilsulfonilo, A es alquileno ($C_1$-$C_6$) ó 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; aril ($C_1$-$C_{12}$)alquilo; aril ($C_2$-$C_{12}$)alquenilo; aril ($C_1$-$C_{12}$)alcoxi; aril ($C_1$-$C_{12}$)tioalcoxi ó derivados sustituidos de arilo; ariloxi; ariloílo; aril ($C_1$-$C_{12}$)alquilo; aril ($C_2$-$C_{12}$)alquenilo; aril ($C_1$-$C_{12}$)alcoxi; aril ($C_1$-$C_{12}$)tioalcoxi, siendo el citado sustituyente halo; $NO_2$; CN ó alquilo ($C_1$-$C_{12}$), alcoxi ($C_1$-$C_{12}$) y alquilo ($C_1$-$C_{12}$) sustituido con halo; E es O ó S; y M es H; un catión farmacéuticamente aceptable; aroílo ó alcanoílo ($C_1$-$C_{12}$).

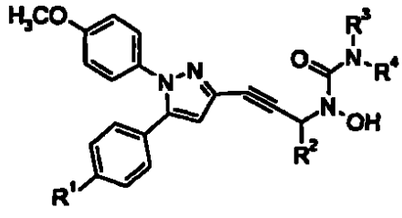
Se describen compuestos relacionados en los documentos US 4.769.387 (Summers et al.); US 4.822.811 (Summers); US 4.822.809 (Summers y Stewart); US 4.897.422 (Summers); US 4.992.464 (Summers et al.), y US 5.250.565 (Brooks y Summers); cada uno de los cuales se incorpora a la presente descripción en su totalidad como si se expusieran completamente en la presente descripción.

El zileutón o cualquiera de los derivados anteriormente descritos de éste se combina con los compuestos de fórmula (1.0.0) para formar realizaciones de la presente invención.

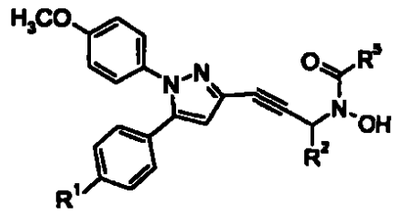
El fenleutón se describe en los documentos US 5.432.194; US 5.446.062; US 5.484.786; US 5.559.144; US 5.616.596; US 5.668.146; US 5 668.150; US 5.843.968; US 5.407.959; US

5.426.111, US 5.446.055; US 5.475.009; US 5.512.581; US 5.516.795; US 5.476.873· US 5.714.488; 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 a la presente descripción en su totalidad como si se expusieran completamente en la presente descripción. Pueden encontrarse descripciones adicionales de dicha N-hidroxiurea e inhibidores relacionados de 5-lipooxigenasa y de la síntesis de leucotrienos inflamatorios en los documentos WO 95/30671, WO 96/02507; WO 97/12865; WO 97/12866; WO 97/12867; WO 98/04555 y WO 98/14429.

La tepoxalina es un inhibidor dual de COX/5-LO con una actividad in vivo de corta vida que ha conducido al desarrollo de dos series de compuestos híbridos, que son N-hidroxiureas y ácidos hidroxámicos de fórmulas (5.2.4) y (5.2.5), respectivamente:



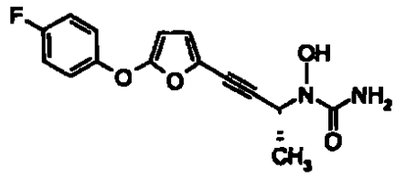

(524)




(525)

en las que de $R^1$ a $R^4$ son H; Cl; $CH_3$; etilo; isopropilo ó n-propilo; ó $R^3$ y $R^4$ son conjuntamente $(CH_2)_5$ ó $(CH_2)_2O(CH_2)_2$; y $R^5$ es metilo; etilo; isopropilo, metoxi, trifluorometilo; clorometilo; propionato de etilo; fenilo; 2-furilo; 3-piridilo ó 4-piridilo. Véase Connolly et al., "N-Hydroxyurea and hydroxamic acid inhibitors of cyclooxygenase and 5-lipoxygenase", *Bioorganic & Medicinal Chemistry Letters* **9**, 979-984, 1999.

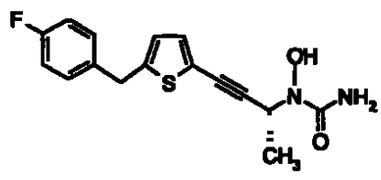
Otro compuesto N-hidroxiurea es Abbott-79175, que se representa por la fórmula (5 2 6):




Abbott-79175 (5 2 6)

Abbott-79175 tiene una duración de acción más larga que el zileutón, Brooks et al, *J. Pharm Exp. Therapeut.* **272**, 724, 1995.

Un compuesto más de N-hidroxiurea es Abbott-85761, que se representa por la fórmula (5 2 7):



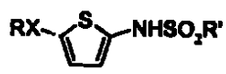

Abbott-85781 (527)

Abbott-85761 se suministra al pulmón mediante administración de aerosol de una formulación homogénea, físicamente estable y casi monodispersada; Gupta et al., "Pulmonary delivery of the 5-lipoxygenase inhibitor, Abbott-85761, in beagle dogs"; *International Journal of Pharmaceuticals* **147**, 207-218, 1997.

Fenleutón, Abbott-79175, Abbott-85761 o cualquier de los derivados anteriormente descritos de éstos o de tepoxalina se combinan con los compuestos de fórmula (1 0.0) para formar realizaciones de la presente invención.

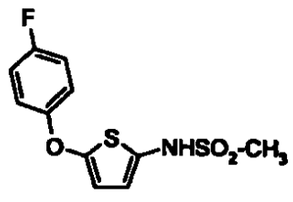
Desde la elucidación de la ruta biosintética de la 5-LO, ha habido un debate continuo sobre si es más ventajoso inhibir la enzima 5-lipooxigenasa o antagonizar los receptores de leucotrieno peptídicos o no peptídicos. Los inhibidores de 5-lipooxigenasa se consideran superiores a los antagonistas de receptor de LT, puesto que los inhibidores de 5-lipooxigenasa bloquean la acción de todo el espectro de productos de 5-LO, mientras que los antagonistas de LT producen efectos más

reducidos. Sin embargo, las realizaciones de la presente invención incluyen combinaciones de los compuestos de fórmula (1.0.0) con antagonistas de LT así como con inhibidores de 5-LO, como se describe a continuación. Se utilizan también inhibidores de 5-lipooxigenasa de estructuras químicas que se diferencian de las clases de N-hidroxiureas y ácidos hidroxámicos descritas anteriormente en combinación con los compuestos de fórmula (1.0.0) para formar realizaciones adicionales de la presente invención. Un ejemplo de dicha clase diferentes es la de N-tiofen-2-alquilsulfonamidas sustituidas en 5 de fórmula (5.2.8):




(5.2.8)

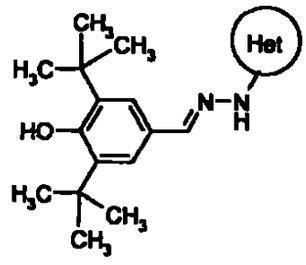
en la que X es O ó S, R' es metilo, isopropilo, n-butilo, n-octilo ó fenilo; y R es n-pentilo, ciclohexilo, fenilo, tetrahidro-1-naftilo, 1- ó 2-naftilo ó fenilo mono- o disustituido con Cl, F, Br, $CH_3$, $OCH_3$, $SCH_3$, $SO_2CH_3$, $CF_3$ ó isopropilo. Un compuesto preferido es el de fórmula (5.2.9):




(5.2.9)

Puede encontrarse una descripción adicional de estos compuestos en Beers et al., "N-(5-substituted)tiophene-2-alkylsulfonamides as potent inhibitors of 5-lipoxygenase", *Bioorganic. & Medicinal Chemistry* **5**(4), 779-786, 1997.

Otra clase distinta de inhibidores de 5-lipooxigenasa es la de 2,6-diterc-butilfenolhidrazonas descrita en 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. Los compuestos de este tipo se representan por la fórmula (5.2.10):



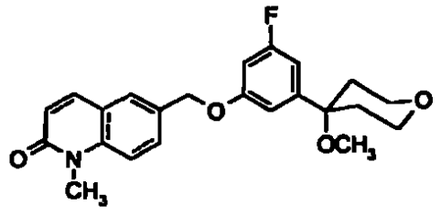

(5 2 10)

en la que "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-tiofen-2-alquilsulfonamidas sustituidas en 5 de

fórmula (5.2.8), o las 2,6-di-terc-butilfenolhidrazonas de fórmula (5.2.10), o cualquiera de los derivados anteriormentes descritos de estos, se combina con los compuestos de fórmula (1.0.0) para formar realizaciones de la presente invención.

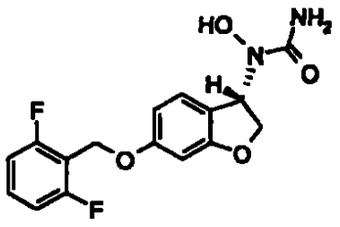
Otra clase distinta más de inhibidores de 5-lipooxigenasa es la de metoxitetrahidropiranos, a los cuales pertenece ZD-2138 de Zeneca ZD-2138 se representa por la fórmula (5.2.11):




(5.2.11)

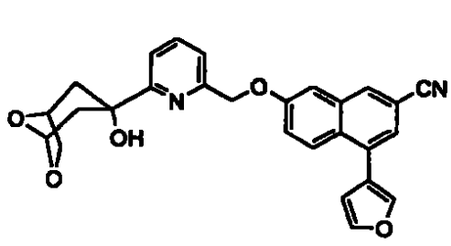
ZD-2138 es altamente selectivo y altamente activo por vía oral en una serie de especies y se ha evaluado en el tratamiento del asma y artritis reumatoide por administración oral. Se describen más detalles respecto de ZD-2138 y derivados de este en Crawley et al., *J. Med. Chem.* **35**, 2600, 1992; y Crawley et al., *J Med. Chem.* **36**, 295, 1993.

Otra clase distinta de inhibidores de 5-lipooxigenasa es aquella a la que pertenece el compuesto SB-210661 de Beecham. SB-210661 se representa por la fórmula (5.2.12):

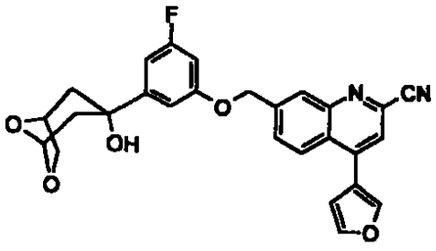


(5.2.12)

Dos clases distintas y relacionadas más de inhibidores de 5-lipooxigenasa 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-lipooxigenasa se ilustran a modo de ejemplo con 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)

Se describen detalles referentes a L-739.010 y L-746.530 en Dubé et al., "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 et al.).

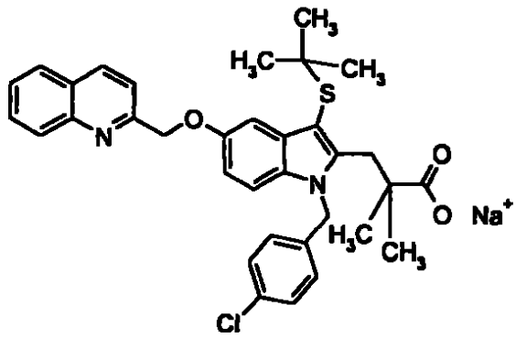
La clase de metoxitetrahidropiranos que incluye ZD-2138 de Zeneca de fórmula (5.2.11); o el compuesto principal SB-210661 de fórmula (5.2 12) y la clase a la que pertenece; o la serie de compuestos de 2-cianonaftaleno sustituidos con piridinilo a la que pertenece L-739 010, o la serie de compuestos de 2-cianoquinolina a la que pertenece L-746.530, o cualquiera de los derivados anteriormente descritos de cualquiera de las clases anteriormente citadas, se combinan con los compuestos de fórmula (1.0 0) para formar realizaciones de la presente invención.

Además de la enzima 5-lipooxigenasa, el otro agente endógeno que desempeña un papel significativo en la biosíntesis de los leucotrienos es la proteína activadora de 5-lipooxigenasa (FLAP). Este papel es indirecto, en contraposición con el papel directo de la enzima 5-lipooxigenasa Sin embargo, se emplean antagonistas de proteína activadora de 5-lipooxigenasa para inhibir la síntesis celular de leucotrienos, y como tales, se

utilizan también en combinación con los compuestos de fórmula (1.0.0) para formar realizaciones de la presente invención.

Se han sintetizado compuestos que se unen a la proteína activadora de 5-lipooxigenasa, y que por tanto bloquean la utilización del conjunto endógeno de ácido araquidónico que está presente, a partir de estructuras de indol y quinolina; véase 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**, 1436-1442, 1990; y 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**, 868-872, 1994.

MK-591, que se ha designado como quiflipón de sodio, se representa por la fórmula (5.2 15)



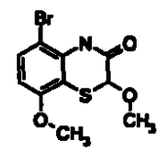

(5 2 15)

Las clases de compuestos de indol y quinolina anteriormente citadas y los compuestos específicos MK-591, MK-886 y BAY x 1005 a las que pertenecen, o cualquiera de los derivados anteriormente descritos de cualquiera de las clases anteriormente citadas, se combinan con los compuestos de fórmula (1.0.0) para formar realizaciones de la presente invención.

**9.2 Con antagonistas de receptor de los leucotrienos $LTB_4$, $LTC_4$, $LTD_4$ y $LTE_4$**

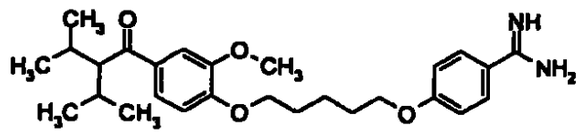
Se utiliza uno o más compuestos de fórmula (1.0.0) en combinación con antagonistas de receptor de los leucotrienos $LTB_4$, $LTC_4$, $LTD_4$ y $LTE_4$ Los más significativos de estos leucotrienos en términos de mediación de la respuesta inflamatoria son $LTB_4$ y $LTD_4$ Se describen en los párrafos siguientes las clases de antagonistas para los receptores de estos leucotrienos.

Las 4-bromo-2,7-dimetoxi-3H-fenotiazin-3-onas, incluyendo L-651.392, son potentes antagonistas de receptor de $LTB_4$ que se describen en el documento US 4 939.145 (Guindon et al.), y el documento US 4.845 083 (Lau et al.). L-651.392 se representa por la fórmula (5 2.16)



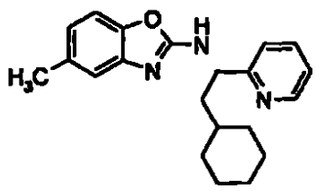
L-651 392 (5.2.16)

Se describe una clase de compuestos amidino que incluye CGS-25019c 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 receptor de $LTB_4$ se tipifican por CGS-25019c, que se representa por la fórmula (5.2.17):



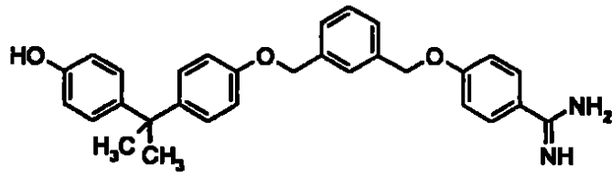
CGS-25019c (5 2 17)

Se describe el ontazolast, un miembro de una clase de benzoxaolaminas que son antagonistas de receptor de $LTB_4$, en el documento EP 535.521 (Anderskewitz et al.); y se representa por la fórmula (5 2.18):



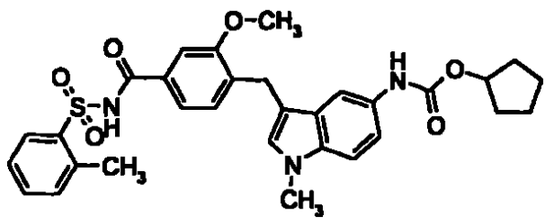
Ontazolast (5 2 18)

El mismo grupo de investigadores ha descubierto también una clase de bencenocarboximidamidas que son antagonistas de receptor de $LTB_4$, descrita en los documentos WO 97/21670 (Anderskewitz et al.); y WO 98/11119 (Anderskewitz et al.); y que se tipifican por BIIL 284/260, representado por la fórmula (5.2.19):



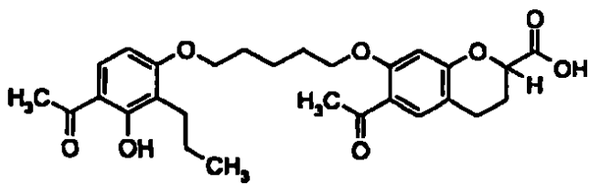

BIIL 284/260 (5.2.19)

El zafirlukast es un antagonista de receptor de $LTC_4$, $LTD_4$ y $LTE_4$ que se comercializa con el nombre de Accolate(R). Pertenece a una clase de derivados amida heterocíclicos descritos en los documentos US 4 859.692 (Bernstein et al.), US 5.319.097 (Holohan y Edwards), US 5.294.636 (Edwards y Sherwood); US 5.482.963, US 5.583 152 (Bernstein et al.) y US 5.612.367 (Timko et al.). El zafirlukast se representa por la fórmula (5.2.20).



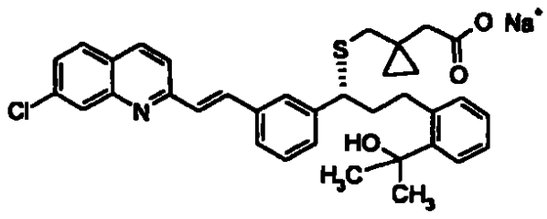
Zafirlukast (5 2 20)

El ablukast es un antagonista de receptor de $LTD_4$ que se designa como Ro 23-3544/001, y se representa por la fórmula (5 2.21)·



Ablukast (5.2.21)

El montelukast es un antagonista de receptor de $LTD_4$ que se comercializa con el nombre de Singulair(R), y se describe en el documento US 5 565 473. El montelukast se representa por la fórmula (5.2.22):



Montelukast (5.2.22)

Otros antagonistas de receptor de $LTD_4$ incluyen pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), y BAY x 7195.

La clase de compuestos fenotiazin-3-ona anteriormente citados, incluyendo L-651.392; la clase de compuestos amidino que incluye CGS-25019c, la clase de benzoxaolaminas que incluye ontazolast; la clase de bencenocarboximidamidas que está tipificada por BIIL 284/260; los derivados de amida heterocíclicos que incluyen zafirlukast; ablukast y montelukast, y las clases de compuestos a las que pertenecen; o cualquiera de los derivados anteriormente descritos de cualquiera de las clases anteriormente citadas, 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**

Se utilizan uno o más compuestos de fórmula (1.0.0) junto con otros agentes terapéuticos, así como agentes no

terapéuticos, para formar combinaciones que son realizaciones adicionales de la presente invención, y que son útiles en el tratamiento de una serie significativa de diferentes enfermedades, trastornos y afecciones descritas en la presente descripción. Las citadas 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-lipooxigenasa (5-LO); ó antagonistas de la proteína activadora de 5-lipooxigenasa (FLAP),

(c) inhibidores duales de 5-lipooxigenasa (5-LO) y antagonistas del factor de activación de plaquetas (PAF);

(d) antagonistas de leucotrieno (LTRA), incluyendo antagonistas de $LTB_4$, $LTC_4$, $LTD_4$ y $LTE_4$,

(e) antagonistas de receptor $H_1$ antihistamínico, incluyendo cetirizina, loratadina, desloratadina, fexofenadina, astemizol, azelastina y clofeniramina;

(f) antagonistas de receptor $H_2$ gastroprotectores;

(g) agentes agonistas $\alpha_1$- y $\alpha_2$-adrenoceptores simpaticomiméticos vasoconstrictores administrados oral o tópicamente para uso decongestivo, incluyendo propilhexedrina, fenilefrina, fenilpropanolamina, seudoefedrina, clorhidrato de nafazolina, clorhidrato de oximetazolina, clorhidrato de tetrahidrozolina, clorhidrato de xilometazolina, y clorhidrato de etilnorepinefrina;

(h) agonistas $\alpha_1$- y $\alpha_2$-adrenoceptores en combinación con inhibidores de 5-lipooxigenasa (5-LO),

(i) agentes anticolinérgicos, incluyendo bromuro de ipratropio;

(j) agonistas $\beta_1$- a $\beta_4$-adrenoceptores, incluyendo isoprenalina, albuterol, salbutamol, formoterol, salmeterol, terbutalina, orciprenalina, mesilato de bitolterol y pirbuterol,

(k) teofilina y aminofilina;

(l) cromoglicato de sodio;

(m) antagonistas de receptor muscarínico (M1, M2 y M3);

n) inhibidores de COX-1 (AINE); inhibidores selectivos de COX-2, incluyendo rofecoxib; y AINE de óxido nítrico;

(o) miméticos de factor del crecimiento similares a insulina de tipo I (IGF-1);

(p) ciclesonida;

(q) glucocorticoides inhalados con efectos secundarios sistémicos reducidos, incluyendo flunisolida, acetónido de triamcinolona, dipropionato de beclometasona, budesonida, propionato de fluticasona y furoato de mometasona;

(r) inhibidores de triptasa;

(s) antagonistas de factor activador de plaquetas (PAF);

(t) anticuerpos monoclonales frente a entidades inflamatorias endógenas,

(u) IPL 576;

(v) agentes anti-factor de necrosis tumoral (TNFα), incluyendo etanercept, infliximab y D2E7;

(w) DMARD, incluyendo leflunomida;

(x) péptidos TCR;

(y) inhibidores de la enzima conversora de interleuquina (ICE);

(z) inhibidores de IMPDH;

(aa) inhibidores de moléculas de adhesión, incluyendo antagonistas de VLA-4;

(bb) catepsinas;

(cc) inhibidores de MAP quinasa;

(dd) inhibidores de glucosa-6-fosfato deshidrogenasa;

(ee) antagonistas de receptor de cinina $B_1$ y $B_2$;

(ff) oro en forma de un grupo aurotion junto con diversos grupos hidrófilos;

(gg) agentes inmunosupresores, por ejemplo, ciclosporina, azatioprina y metotrexato;

(hh) agentes anti-gota, por ejemplo, colchicina;

(ii) inhibidores de xantina oxidasa, por ejemplo alopurinol;

(jj) agentes uricosúricos, por ejemplo, probenecida, sulfinpirazona y benzobromarona;

(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 metaloproteinasas de matriz (MMP), es decir, estromelisinas, colagenasas y gelatinasas, así como de agrecanasa, especialmente colagenasa-1 (MMP-1), colagenasa-2 (MMP-8), colagenasa-3 (MMP-13); estromelisina-1 (MMP-3); estromelisina-2 (MMP-10) y estromelisina-3 (MMP-11);

(nn) factor del crecimiento transformante (TGFβ);

(oo) factor del crecimiento derivado de plaquetas (PDGF);

(pp) factor del crecimiento de fibroblastos, por ejemplo, factor

del crecimiento de fibroblastos básicos (bFGF);

(qq) factor estimulante de colonia de macrófagos granulocitos (GM-CSF),

(rr) crema de capsaicina;

(ss) agentes anti-eméticos, incluyendo antagonistas de receptor NK-1 y D-4418, y

(tt) antidepresivos.

**DESCRIPCION DETALLADA DE LA INVENCION**

**10.0 Composiciones y formulaciones farmacéuticas**

La descripción siguiente se refiere a la manera en que los compuestos de fórmula (1.0.0), junto con otros agentes terapéuticos o agentes no terapéuticos, cuando se deseen estos, se combinan con lo que son en su mayor parte 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 al paciente dado.

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 éstos como se ha descrito también anteriormente, junto con un vehículo farmacéuticamente aceptable según las propiedadse y la actuación esperada de dichos vehículos, que son bien conocidos en la técnica pertinente.

La cantidad de ingrediente activo que puede combinarse con los materiales vehiculantes para producir una forma de dosificación sencilla dependerá del huésped tratado, y del modo particular de administración. Sin embargo, debe comprenderse que la dosificación y régimen de tratamiento específicos para cualquier paciente particular dependerá de una variedad de factores, incluyendo la actividad del compuesto específico empleado, la edad, el peso corporal, el estado general de salud, el sexo, la dieta, el momento de administración, la tasa de excreción, la combinación de fármacos y el juicio del médico a cargo, y la gravedad de la enfermedad particular que se esté tratando. La cantidad de ingrediente activo puede depender también del agente terapéutico o profiláctico, si lo hay, con el que se administra conjuntamente el ingrediente.

Los compuestos anteriormente descritos de la presente invención pueden utilizarse en forma de ácidos, ésteres u otras clases químicas de compuestos a los que pertenezcan los compuestos descritos. Está también dentro del alcance de la

presente invención utilizar aquellos compuestos en forma de sales farmacéuticamente aceptables derivados de diversos ácidos y bases orgánicos e inorgánicos, según procedimientos descritos con detalle anteriormente, y bien conocidos en la técnica. Se utiliza a menudo un ingrediente activo que comprende un compuesto de fórmula (1.0.0) en forma de una sal de éste, especialmente cuando dicha forma de sal confiere al citado ingrediente activo propiedades farmacocinéticas mejoradas en comparación con la forma libre del citado ingrediente activo, o alguna otra forma de sal del citado ingrediente activo utilizada anteriormente. La forma de sal farmacéuticamente aceptable del citado ingrediente activo puede conferir también inicialmente una propiedad farmacocinética deseable al citado ingrediente activo que no poseía anteriormente, y puede incluso afectar positivamente a la farmacodinámica del citado ingrediente activo con respecto a su actividad terapéutica en el cuerpo.

Las propiedades farmacocinéticas del citado ingrediente activo que pueden afectarse favorablemente incluyen, por ejemplo, la manera en que el citado ingrediente activo se transporta a través de las membranas celulares, que a su vez puede afectar directa y positivamente la absorción, distribución, biotransformación y excreción del citado 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 del citado ingrediente activo depende habitualmente del carácter de la sal particular de este que se utilice. Además, como comprende el experto, una solución acuosa del citado ingrediente activo proporcionará la absorción más rápida del citado ingrediente activo en el cuerpo de un paciente que se esté tratando, mientras que las soluciones y suspensiones lipídicas, así como las formas de dosificación sólidas, darán como resultado una absorción menos rápida del citado ingrediente activo. La ingestión oral del citado ingrediente activo es la vía de administración más preferida por razones de seguridad, conveniencia y economía, pero la absorción de dicha forma de dosificación oral puede verse afectada adversamente por características físicas, tales como polaridad, émesis causada por la irritación de la mucosa gastrointestinal, destrucción por enzimas digestivas y bajo pH, absorción irregular o propulsión en presencia de comida u otros fármacos, y metabolismo por enzimas de la mucosa, la flora intestinal o el hígado. La formulación del citado ingrediente activo en diferentes formas de sales farmacéuticamente aceptables puede ser eficaz para superar o mitigar uno o más de los problemas anteriormente enumerados hallados con la absorción de formas de dosificación oral.

Entre las sales farmacéuticas enumeradas anteriormente, las preferidas incluyen, pero sin limitación, acetato, besilato, citrato, fumarato, gluconato, hemisuccinato, hipurato, clorhidrato, bromhidrato, isetionato, mandelato, meglumina, nitrato, oleato, fosfonato, pivalato, fosfato de sodio, estearato, sulfato, sulfosalicilato, tartrato, tiomalato, tosilato y trometamina.

Están incluidas dentro del alcance de la presente invención formas de sales múltiples en las que un compuesto de la presente invención contiene más de un grupo capaz de formar dichas sales farmacéuticamente aceptables. Los ejemplos de formas de sal múltiple típios incluyen, pero sin limitación, bitartrato, diacetato, difumarato, dimeglumina, difosfato, disodio 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 éstos como se describió también anteriormente, junto con un vehículo farmacéuticamente aceptable según las propiedades y la actuación esperada de dichos vehículos que son bien conocidos en la técnica pertinente.

El término "vehículo", como se utiliza en la presente

descripción, incluye diluyentes, excipientes, coadyuvantes, vehículos, adyuvantes de solubilización, modificadores de la viscosidad, conservantes y otros agentes aceptables bien conocidos por el experto para proporcionar propiedades favorables en la composición farmacéutica final. Para ilustrar dichos vehículos, sigue una breve panorámica de los vehículos farmacéuticamente aceptables que pueden utilizarse en las composiciones farmacéuticas de la presente invención, y después una descripción más detallada de los diversos tipos de ingredientes Los vehículos típicos incluyen, pero en absoluto sin limitación, composiciones de intercambio iónico, alúmina; estearato de magnesio, lecitina, proteínas de suero, por ejemplo, albúmina de suero bovino; fosfatos; glicina, ácido sórbico; sorbato de potasio; mezclas de glicéridos parciales de ácidos grasos vegetales saturados: aceites de palma hidrogenados; agua; sales o electrolitos, por ejemplo, sulfato de prolamina, fosfato ácido de disodio, fosfato ácido de potasio, cloruro de sodio y sales de zinc, sílice coloidal; trisilicato de magnesio; polivinilpirrolidona, sustancias basadas en celulosa, por ejemplo, carboximetilcelulosa, polietilenglicol; poliacrilatos, ceras, polímeros de bloque de polietileno-polioxipropileno, y grasa de lana.

Más particularmente, los vehículos utilizados 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 aquellos enumerados en los siguientes párrafos.

Se añaden agentes acidificantes y alcalinizantes para obtener un pH deseado o predeterminado, que comprenden agentes acidificantes, por ejemplo, ácido acético, ácido acético glacial, ácido málico y ácido propiónico. Pueden utilizarse ácidos más fuertes tales como ácido clorhídrico, ácido nítrico y ácido sulfúrico, pero son menos preferidos. Los agentes alcalinizantes incluyen, por ejemplo, edetol, carbonato de potasio, hidróxido de potasio, borato de sodio, carbonato de sodio e hidróxido de sodio. Pueden utilizarse también agentes alcalinizantes que contienen grupos amina activos, tales como dietanolamina y trolamina.

Se requieren impulsores de aerosol cuando la composición farmacéutica ha de suministrarse en forma de un aerosol a presión significativa. Dichos impulsores incluyen, por ejemplo, fluoroclorohidrocarburos tales como diclorodifluorometano, diclorotetrafluoroetano y tricloromonofluorometano; nitrógeno o un hidrocarburo volátil tal como butano, propano, isobutano o mezclas de estos.

Se añade agentes antimicrobianos, que incluyen agentes antibacterianos, antifúngicos y antiprotozooarios, cuando la composición farmacéutica se administra tópicamente a áreas de la piel que es probable que hayan sufrido condiciones adversas o abrasiones sostenidas o cortes, que exponen la piel a infección por bacterias, hongos o protozoos. Los agentes antimicrobianos incluyen compuestos tales como alcohol bencílico, clorobutanol, alcohol feniletílico, acetato fenilmercúrico, sorbato de potasio y ácido sórbico. Los agentes antifúngicos incluyen compuestos tales como ácido benzoico, butilparabén, metilparabén, propilparabén y benzoato de sodio.

Se añaden conservantes antimicrobianos a las composiciones farmacéuticas de la presente invención para protegerlas frente al crecimiento de microorganismos potencialmente dañinos, que invaden habitualmente la fase acuosa, pero en algunos casos pueden crecer también en la fase oleosa de una composición Así, son deseables conservantes con solubilidad tanto acuosa como lipídica. Los conservantes antimicrobianos adecuados incluyen, por ejemplo, ésteres alquílicos de ácido p-hidroxibenzoico, sales de propionato, fenoxietanol, metilparabén de sodio, propilparabén de sodio, deshidroacetato de sodio, cloruro de benzalconio, cloruro de benzetonio, alcohol bencílico, derivados de hidantoína, compuestos de amonio cuaternario y polímeros catiónicos, imidazolizinilurea, diazolidinilurea y

etilendiaminotetraacetato de sodio (EDTA). Se emplean preferiblemente los conservantes en cantidades en el intervalo de aproximadamente el 0,01% a aproximadamente el 2,0% en peso de la composición total.

Se añaden antioxidantes para proteger todos los ingredientes de la composición farmacéutica de daño o degradación por agentes oxidantes presentes en la composición misma o en el entorno de uso, por ejemplo, anoxómero, palmitato de ascorbilo, hidroxianisol butilado, hidroxitolueno butilado, ácido hipofosforoso, metabisulfito de potasio, galato propiloctílico y dodecílico, metabisulfito de sodio, dióxido de azufre y tocoferoles.

Se utilizan agentes tamponantes para mantener un pH deseado de una composición, una vez establecido, ante los efectos de agentes externos y que desplazan el equilibrio de los componentes de la composición. Los tamponantes pueden seleccionarse entre aquellos familiares para el experto en la preparación de composiciones farmacéuticas, por ejemplo, acetato de calcio, metafosfato de potasio, fosfato de potasio monobásico, y ácido tartárico.

Los agentes quelantes se utilizan para ayudar a mantener la fuerza iónica de la composición farmacéutica y para unirse a

y retirar eficazmente los compuestos destructivos y metales, e incluyen, por ejemplo, edetato de dipotasio, edetato de disodio y ácido edético.

Se añaden agentes dermatológicamente activos a las composiciones farmacéuticas de la presente invención cuando se han de administrar tópicamente, e incluyen, por ejemplo, agentes cicatrizantes de heridas, tales como derivados peptídicos, levaduras, pantenol, hexilrresorcinol, fenol, clorhidrato de tetraciclina, lamina y cinetina; retinoides para tratar cáncer de piel; por ejemplo, retinol, tretinoína, isotretinoína, etretinato, acitretina y arotinoide; agentes antibacterianos débiles para tratar infecciones de la piel, por ejemplo, resorcinol, ácido salicílico, peróxido de benzoílo, eritromicina-peróxido de benzoílo, eritromicina y clindamicina; agentes antifúngicos para tratar tiña corporal, tiña pedicular, candidiasis y tiña tornasolada, por ejemplo, griseofulvina, azoles tales como miconazol, econazol, itraconazol, fluconazol y cetoconazol, y alilaminas tales como naftifina y terfinafina; agentes antivirales para tratar herpes simplex cutáneo, herpes zóster y varicela, por ejemplo, aciclovir, famciclovir y valaciclovir, antihistamínicos para tratar prurito, dermatitis atópica y de contacto, por ejemplo, difenhidramina, terfenadina, astemizol, loratadina, cetirizina, acrivastina y temelastina; anestésicos tópicos para aliviar el dolor, irritación y picor,

por ejemplo benzocaína, lidocaína, dibucaína y clorhidrato de pramoxina; analgésicos tópicos para aliviar el dolor e inflamación, por ejemplo salicilato de metilo, alcanfor, mentol y resorcinol; antisépticos tópicos para prevenir la infección, por ejemplo cloruro de benzalconio y povidona-yodo; y vitaminas y derivados de éstas tales como tocoferol, acetato de tocoferol, ácido retinocio y retinol.

Se utilizan agentes dispersantes y de suspensión como adyuvantes para la preparación de formulaciones estables e incluyen, por ejemplo, poligenina, povidona y dióxido de silicio.

Los emolientes son agentes, preferiblemente no oleosos y solubles en agua, que suavizan y calman la piel, especialmente piel que se ha quedado seca debido a una pérdida excesiva de agua. Se utilizan dichos agentes con composiciones farmacéuticas de la presente invención que se pretenden para administración tópica e incluyen, por ejemplo, aceites hidrocarbonados y ceras, ésteres de triglicéridos, monoglicéridos acetilados, ésteres metílicos y otros alquílicos de ácidos grasos $C_{10}$-$C_{20}$, ácidos grasos $C_{10}$-$C_{20}$, alcoholes de ácidos grasos $C_{10}$-$C_{20}$, lanolina y derivados, ésteres de alcoholes polihidroxílicos tales como polietilenglicol (200-600), ésteres de ácido graso de polioxietilensorbitán, ésteres de ceras, fosfolípidos y

esteroles; agentes emulsionadores utilizados para preparar emulsiones de aceite en agua; excipientes, por ejemplo, laurocapramo y polietilenglicolmonometiléter; humectantes, por ejemplo, sorbitol, glicerina y ácido hialurónico; bases de ungüentos, por ejemplo, vaselina, polietilenglicol, lanolina y poloxámero; potenciadores de la penetración, por ejemplo, isosorbida de dimetilo, dietilglicolmonoetiléter, 1-dodecilazacicloheptan-2-ona y dimetilsulfóxido (DMSO); conservantes, por ejemplo cloruro de benzalconio, cloruro de benzetonio, alquilésteres de ácido p-hidroxibenzoico, derivados de hidantoína, cloruro de cetilpiridinio, propilparabén, compuestos de amonio cuaternario tales como benzoato de potasio y timerosal, agentes secuestrantes que comprenden ciclodextrinas; disolventes, por ejemplo, acetona, alcohol, amileno hidratado, alcohol butílico, aceite de maíz, aceite de semilla de algodón, acetato de etilo, glicerina, hexilenglicol, alcohol isopropílico, alcohol isoestearílico, alcohol metílico, cloruro de metileno, aceite mineral, aceite de cacahuete, ácido fosfórico, polietilenglicol, polioxipropilen-15-estearíléter, propilenglicol, diacetato de propilenglicol, aceite de sésamo y agua purificada; estabilizantes, por ejemplo, sacarato de calcio y timol; tensioactivos, por ejemplo, cloruro de lapirio, laureth 4, es decir, α-dodecil-ω-hidroxipoli(oxi-1,2-etanodiilo) o polietilenglicolmonododeciléter.

Se utilizan agentes emulsionantes, incluyendo agentes emulsionantes y endurecedores y coadyuvantes de emulsión, para preparar emulsiones de aceite en agua cuando éstas forman la base de las composiciones farmacéuticas de la presente invención. Dichos agentes emulsionantes incluyen, por ejemplo, emulsionantes no iónicos, tales como alcoholes grasos $C_{10}$-$C_{20}$ y los citados 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 de ácidos grasos $C_{10}$-$C_{20}$ de etilenglicol, monoglicéridos de ácidos grasos $C_{10}$-$C_{20}$, dietilenglicol, polietilenglicoles de PM 200-6000, polipropilenglicoles de PM 200-3000, y particularmente, sorbitol, sorbitán, polioxietilensorbitol, polioxietilensorbitán, ésteres de cera hidrófila, alcohol cetoestearílico, alcohol oleico, alcoholes de lanolina, colesterol, mono- y diglicéridos, monoesterato de glicerilo, monoesterato de polietilenglicol, ésteres mono- y diesteáricos mixtos de etilenglicol y polioxietilen-glicol, monoesterato de propilenglicol e hidroxipropil-celulosa. Pueden utilizarse también agentes emulsionantes que contienen grupos amina activos, e incluyen típicamente 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 ($C_{10}$-

$C_{50}$)etoxiétersulfonatos. Otros agentes emulsionantes adecuados incluyen aceite de ricino y aceite de ricino hidrogenado; lecitina; y polímeros de ácido 2-propenoico junto con polímeros de ácido acrílico, ambos reticulados con aliléteres de sacarosa y/o pentaeritritol, con viscosidades variables e identificados por los nombres de producto carbómero 910, 934, 934P, 940, 941 y 1342. Pueden utilizarse también emulsionantes catiónicos con grupos amina activos, incluyendo aquellos basados en compuestos de amonio cuaternario, morfolinio y piridinio. De forma similar, pueden utilizarse emulsionantes anfóteros con grupos amina activos, tales como cocobetaínas, óxido de laurildimetilamina y cocoilimidazolina. Los agentes emulsionantes y endurecedores útiles incluyen también alcohol cetílico y estearato de sodio; y coadyuvantes de emulsión tales como ácido oleico, ácido esteárico y alcohol estearílico

Los excipientes incluyen, por ejemplo, laurocapramo y polietilenglicolmonometiléter.

Cuando la composición farmacéutica de la presente invención ha de administrarse tópicamente, pueden utilizarse potenciadores de la penetración que incluyen, por ejempo, isosorbida de dimetilo, dietilglicolmonoetil-éter, 1-dodecilazacicloheptan-2-ona y dimetilsulfóxido (DMSO). Dichas 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 tensioactivo o agente emulsionante.

Se utilizan conservantes para proteger las composiciones farmacéuticas de la presente invención del ataque degradativo por microorganismos ambientales, e incluyen por ejemplo, cloruro de benzalconio, cloruro de benzetonio, alquilésteres de ácido p-hidroxibenzoico, derivados de hidantoína, cloruro de cetilpiridinio, monotioglicerol, fenol, fenoxietanol, metilparagén, imidazolidinilurea, deshidroacetato de sodio, propilparabén, compuestos de amonio cuaternario, especialmente polímeros tales como cloruro de polixetonio, benzoato de potasio, formaldehídosulfoxilato de sodio, propionato de sodio y timerosal.

Se utilizan agentes secuestrantes 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 que son de tamaño de anillo variable, refiriéndose habitualmente aquellos con 6, 7 y 8 residuos de glucosa en un anillo como α-ciclodextrinas, β-ciclodextrinas y γ-ciclodextrinas,

respectivamente. Las ciclodextrinas adecuadas incluyen, por ejemplo, α-ciclodextrina, β-ciclodextrina, γ-ciclodextrina, δ-ciclodextrinas y ciclodextrinas cationizadas.

Los disolventes que pueden utilizarse en la preparación de las composiciones farmacéuticas de la presente invención incluyen, por ejemplo, acetona, alcohol, amileno hidratado, alcohol butílico, aceite de maíz, aceite de semilla de algodón, acetato de etilo, glicerina, hexilenglicol, alcohol isopropílico, alcohol isoestearílico, alcohol metílico, cloruro de metileno, aceite mineral, aceite de cacahuete, ácido fosfórico, polietilenglicol, polioxipropilen-15-estearíléter, propilenglicol, diacetato de propilenglicol, aceite de sésamo y agua purificada.

Los estabilizantes que son adecuados para uso incluyen, por ejemplo, sacarato de sodio y timol.

Se utilizan típicamente agentes endurecedores en formulaciones para administración tópica para proporcionar la viscosidad y las características de manejo deseadas e incluyen, por ejemplo, cera de ésteres de cetilo, alcohol miristílico, parafina, parafina sintética, cera emulsionante, cera microcristalina, cera blanca y cera amarilla.

Se utilizan a menudo azúcares 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 éstos.

Se emplean tensioactivos para proporcionar estabilidad a las composiciones multicomponente de la presente invención, potenciar las propiedades existentes de esas composiciones, y conferir nuevas características deseables a las citadas composiciones. Se utilizan los tensioactivos 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; laureth 4, es decir, α-dodecil-ω-hidroxipoli(oxi-1,2-etanodiilo) o polietilenglicolmonododeciléter; laureth 9, es decir, una mezcla de polietilenglicolmonododeciléteres con 9 grupos óxido de etileno de media por molécula; monoetanolamina; nonoxinol 4, 9 y 10, es decir, polietilenglicolmono(p-nonilfenil)éter; nonoxinol-15, es decir α-(p-nonilfenil)-ω-hidroxipentadeca(oxietileno); nonoxinol 30, es decir, α-(p-nonilfenil)-ω-hidroxitriaconta(oxietileno); poloxaleno, es

decir, un polímero no iónico de tipo polietilenpolipropilenglicol, PM= aproximadamente 3000; poloxámero, referido en la discusión de bases de ungüentos anteriormente; estearato de polioxilo 8, 40 y 50, es decir, α-hidro-ω-hidroxipoli(oxi-1,2-etanodiilo), octadecanoato, polioxil-10-oleiléter, es decir, α-[(E)-9-octadecenil-ω-hidroxipoli(oxi-1,2-etanodiilo); polisorbato 20, es decir, poli(oxi-1,2-etanodiil)monododecanoato de sorbitán; polisorbato 40, es decir, poli(oxi-1,2-etanodiil)monohexa-decanoato de sorbitán; polisorbato 60, es decir, poli(oxi-1,2-etanodiil)monooctadecanoato de sorbitán; polisorbato 65, es decir, poli(oxi-1,2-etanodiil)trioctadecanoato de sorbitán; polisorbato 80, es decir, poli(oxi-1,2-etanodiil)mono-9-monodecenoato de sorbitán; polisorbato 85, es decir, poli(oxi-1,2-etanodiil)tri-9-octadecenoato de sorbitán; laurilsulfato de sodio; monolaurato de sorbitán; monooleato de sorbitán; monopalmitato de sorbitán; monoesterato de sorbitán; sesquiolato de sorbitán; trioleato de sorbitán; y triesterato de sorbitán.

Las composiciones farmacéuticas de la presente invención pueden prepararse utilizando una metodología muy sencilla que es bien comprendida por el experto de conocimiento medio. Cuando las composiciones farmacéuticas de la presente invención son simples soluciones acuosas y/o en otros disolventes, se combinan los diversos componentes de la composición general en cualquier

orden práctico, que estará dictado en gran medida por consideraciones de conveniencia. Aquellos componentes con solubilidad en agua reducida, pero suficiente solubilidad en el mismo disolvente adicional con agua, pueden disolverse todos en el citado disolvente adicional, después de lo cual puede añadirse el disolvente adicional a la parte de agua del vehículo, con lo que el soluto en éste se disuelve en el agua. Para ayudar a este proceso de dispersión/solución, puede emplearse un tensioactivo.

Cuando las composiciones farmacéuticas de la presente invención van a estar en forma de emulsiones, los componentes de la composición farmacéutica se combinarán según los procedimientos generales siguientes. En primer lugar, se calienta la fase acuosa continua a una temperatura en el intervalo de aproximadamente 60°C a aproximadamente 95°C, preferiblemente de aproximadamente 70°C a aproximadamente 85°C, dependiendo la elección de la temperatura de uso de las propiedades físicas y químicas de los componentes que forman la emulsión de aceite en agua. Después de que la fase acuosa continua ha alcanzado su temperatura seleccionada, se mezclan los componentes de la composición final a añadir en esta etapa con el agua, y se dispersan en esta con agitación a alta velocidad. A continuación, se restablece la temperatura del agua aproximadamente a su nivel original, después de lo cual se

añaden los componentes de la composición que comprenden la siguiente etapa a la mezcla de composición con agitación moderada, y se continúa la mezcla durante de aproximadamente 5 a aproximadamente 60 minutos, preferiblemente de aproximadamente 10 a aproximadamente 30 minutos, dependiendo de los componentes de las dos primeras etapas. Después, se enfría pasiva o activamente la mezcla a aproximadamente 20°C a aproximadamente 55°C para la adición de cualquier otro componente de las etapas restantes, después de lo cual se añade agua en suficiente cantidad para alcanzar su concentración predeterminada original en la composición general.

Según la presente invención, las composiciones farmacéuticas pueden estar en forma de una preparación inyectable estéril, por ejemplo, una suspensión acuosa u oleaginosa inyectable estéril. Esta suspensión puede formularse según técnicas conocidas en la técnica utilizando agentes de dispersión o humectantes y agentes de suspenión adecuados. La preparación inyectable estéril puede ser también una solución o suspensión inyectable estéril en un diluyente o disolvente parenteralmente aceptable no tóxico, por ejemplo, en forma de una solución en 1,3-butanodiol. Entre los vehículos y disolventes aceptables que pueden emplearse están agua, solución de Ringer y solución isotónica de cloruro de sodio. Además, se emplean convencionalmente aceites no volátiles estériles como

disolvente o medio de suspensión. Para este fin, puede emplearse cualquier aceite no volátil suave, incluyendo mono- ó diglicéridos sintéticos. Los ácidos grasos, tales como ácido oleico y sus derivados glicéridos, son útiles en la preparación de inyectables, como lo son los aceites farmacéuticamente aceptables naturales, tales como aceite de oliva o aceite de ricino, especialmente en sus versiones polioxietiladas. Estas soluciones o suspensiones oleosas pueden contener también un diluyente o dispersante alcohol de cadena larga, tal como Rh, HClX ó alcoholes similares.

Las composiciones farmacéuticas de la presente invención pueden administrarse por vía oral en cualquier forma de dosificación aceptable oralmente, incluyendo pero sin limitación, cápsulas, comprimidos, suspensiones o soluciones acuosas. En el caso de comprimidos para uso oral, los vehículos que se utilizan habitualmente incluyen lactosa y almidón de maíz. Se añaden también típicamente agentes lubricantes, tales como estearato de magnesio. Para administración oral en forma de cápsula, los diluyentes útiles incluyen lactosa y almidón de maíz secado. Cuando se requieren suspensiones acuosas para uso oral, se combina el ingrediente activo con agentes emulsionantes y de suspensión. Si se desea, pueden añadirse también ciertos agentes edulcorantes, aromatizantes o colorantes. Como alternativa, las composiciones farmacéuticas de esta invención

pueden administrarse en forma de supositorios para administración rectal. Estos pueden prepararse mezclando el agente con un excipiente no irritante adecuado que sea sólido a temperatura ambiente pero líquido a la temperatura rectal, y por tanto se funda en el recto liberando el fármaco. Dichos 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 el objetivo de tratamiento incluye áreas u órganos fácilmente accesibles por administración tópica, incluyendo enfermedades del ojo, la piel o el tracto intestinal inferior. Las formulaciones tópicas adecuadas se preparan fácilmente para cada una de estas áreas u órganos.

La administración tópica al tracto intestinal inferior puede efecturarse con una formulación de supositorio rectal, como se describió anteriormente, o en una formulación de enema adecuada. Pueden utilizarse también parches transdérmicos tópicamente activos.

Para administración tópica, las composiciones farmacéuticas pueden formularse en un ungüento adecuado que contiene el componente activo suspendido o disuelto en uno o más

vehículos. Los vehículos para administración tópica de los compuestos de esta invención incluyen, pero sin limitación, aceite mineral, vaselina líquida, vaselina blanca, propilenglicol, polioxietileno, compuesto de polioxipropileno, cera emulsionante y agua. Como 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 sorbitán, 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 que la cantidad terapéuticamente eficaz de un ingrediente activo que comprende un compuesto de la presente invención requerido para tratar o prevenir enfermedades, trastornos y afecciones mediadas por o asociadas con la modulación de la actividad de PDE4, específicamente PDE4D, como se describe en la presente descripción, se proporciona en una forma de dosificación adecuada para administración sistémica. Dicha composición farmacéutica contendrá el citado ingrediente activo en forma líquida adecuada para suministro por. (1) inyección o infusión intraarterial, intra- o transdérmica, subcutánea, intramuscular, intraespinal, intratecal o intravenosa, estando contenido el

citado ingrediente activo: (a) en solución como un soluto; (b) en la fase discontinua de una emulsión o la fase discontinua de una emulsión inversa que se invierte por inyección o infusión, conteniendo las citadas emulsiones agentes emulsionantes adecuados; ó (c) en una suspensión en forma de sólido suspendido en forma coloidal o microparticulada, conteniendo la citada suspensión agentes de suspensión adecuados; (2) inyección o infusión en tejidos o cavidades corporales adecuadas como depósito, proporcionando la citada composición el almacenamiento del citado ingrediente activo y la liberación retardada, sostenida y/o controlada posterior del citado ingrediente activo para distribución sistémica; (3) instilación, inhalación o insuflación en tejidos o cavidades corporales adecuadas de la citada composición farmacéutica en forma sólida adecuada, estando contenido el citado ingrediente activo: (a) en una composición de implante sólido que proporciona la liberación retardada, sostenida y/o controlada del citado ingrediente activo, (b) en una composición particulada para inhalar en los pulmones; ó (c) en una composición particulada para atomizarse en tejidos o cavidades corporales adecuadas, proporcionando la citada composición opcionalmente una liberación retardada, sostenida y/o controlada del citado ingrediente activo, ó (4) ingestión de la citada composición farmacéutica en forma sólida o líquida adecuada para suministro oral del citado ingrediente activo, estando contenido el citado ingrediente activo en una

forma de dosificación sólida; ó (b) en una forma de dosificación líquida.

Las formas de dosificación particulares de las composiciones farmacéuticas anteriormentes descritas incluyen (1) supositorios como tipo especial de implante, que comprenden bases que son sólidas a temperatura ambiente pero se funden a temperatura corporal, liberando lentamente el ingrediente activo con el que están impregnados al tejido circundante del cuerpo, absorbiéndose y transportándose el ingrediente activo para efectuar una administración sistémica, (2) formas de dosificación oral sólida, seleccionadas del grupo constituido por (a) comprimidos, cápsulas, caplets, pastillas, trociscos y multipartículas orales de liberación retardada; (b) comprimidos y cápsulas con recubrimiento entérico que evita la liberación y absorción en el estómago, para facilitar el suministro distal al estómago del paciente que se esté tratando; (c) comprimidos, cápsulas y micropartículas orales de liberación sostenida, que proporcionan un suministro sistémico del ingrediente activo de manera controlada durante un periodo de hasta 24 horas; (d) comprimidos de disolución rápida, (e) soluciones encapsuladas; (f) una pasta oral; (g) una forma granular incorporada o que se ha de incorporar al alimento de un paciente que se esté tratando; y (h) formas de dosificación oral 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 eficaz de un ingrediente activo que comprende un compuesto de la presente invención requerido para tratar o prevenir enfermedades, trastornos y afecciones mediadas por o asociadas con la modulación de la actividad de PDE4, específicamente PDE4D, como se describe en la presente descripción, se proporciona en una forma de dosificación adecuada para administración local a un paciente que se esté tratando, conteniendo la citada composición farmacéutica el citado ingrediente activo en una forma líquida adecuada para el suministro del citado ingrediente activo por: (1) inyección o infusión en un sitio local intraarterial, intraarticular, intracondrial, intracostal, intraquístico, intra- o transdérmico, intrafascicular, intraligamentoso, intramedular, intramuscular, intranasal, intraneural, intraocular, es decir, administración oftálmica, intraosteal, intrapélvico, intrapericárdico, intraspinal, intrasternal, intrasinovial, intratarsiano o intratecal; incluyendo componentes que proporcionan una liberación retardada, liberación controlada y/o liberación sostenida del citado ingrediente activo en el citado sitio local; estando contenido el citado ingrediente activo: (a)

en una solución como soluto; (b) en la fase discontinua de una emulsión, o la fase discontinua de una emulsión inversa que se invierte por inyección o infusión, conteniendo las citadas emulsiones agentes emulsionantes adecuados; ó (c) en una suspensión en forma de sólido suspendido en forma coloidal o microparticulada; conteniendo la citada suspensión agentes de suspensión adecuados; ó (2) inyección o infusión en forma de depósito para suministro del citado ingrediente activo al citado sitio local; proporcionando la citada composición el almacenamiento del citado ingrediente activo y la liberación retardada, sostenida y/o controlada posterior del citado ingrediente activo al citado sitio local, e incluyendo también la citada composición componentes que aseguran que el citado ingrediente activo tiene predominantemente actividad local, con poca actividad sistémica remanente; o conteniendo la citada composición farmacéutica el citado ingrediente activo en forma sólida adecuada para suministro del citado inhibidor por: (3) instilación, inhalación o insuflación al citado sitio local, estando contenido el citado ingrediente activo: (a) en una composición de implante sólido que está instalada en el citado sitio local, proporcionando opcionalmente la citada composición la liberación retardada, sostenida y/o controlada del citado ingrediente activo al citado sitio local; (b) en una composición particulada que se inhala en un sitio local que comprende los pulmones; (c) en una composición particulada que se atomiza en

un sitio local, incluyendo la citada composición componentes que aseguran que el citado ingrediente activo tiene predominantemente actividad local, con actividad sistémica remanente insignificante, y que proporciona opcionalmente la liberación retardada, sostenida y/o controlada del citado ingrediente activo al citado sitio local. Para uso oftálmico, las composiciones farmacéuticas pueden formularse en forma de una suspensión micronizada en solución salina isotónica estéril de pH ajustado o, preferiblemente, en forma de solución salina isotónica estéril de pH ajustado con o sin un conservante tal como cloruro de benzalconio. Como alternativa, para usos oftálmicos, las composiciones farmacéuticas pueden formulares en un ungüento como vaselina.

Las composiciones farmacéuticas de la presente invención pueden administrarse también por aerosol o inhalación nasal mediante el uso de un nebulizador, un inhalador de polvo seco o un inhalador de dosis medida. Se preparan dichas composiciones según técnicas bien conocidas en la técnica de la formulación farmacéutica, y pueden prepararse en forma de soluciones en solución salina, empleando alcohol bencílico u otros conservantes, promotores de la absorción para potenciar la biodisponibilidad, hidrofluorocarburos y/o otros agentes solubilizantes o dispersantes convencionales adecuados.

Como ya se indicó, los ingredientes activos de fórmula (1.0.0) de la presente invención pueden administrarse por vía sistémica a un paciente a tratar en forma de una composición farmacéutica en forma líquida adecuada por inyección o infusión. Existe una serie de sitios y sistemas de órganos en el cuerpo del paciente que permitirán que la composición farmacéutica adecuadamente formulada, después de inyectada o infundida, permee el cuerpo entero y todo el sistema de órganos del paciente que se esté tratando. Una inyección es una dosis sencilla de la composición farmacéutica forzada, habitualmente con una jeringuilla, a entrar en el tejido implicado. Los tipos más comunes de inyecciones son intramuscular, intravenosa y subcutánea. En contraposición, una infusión es la introducción gradual de la composición farmacéutica en el tejido implicado. El tipo más común de infusión es la intravenosa. Otros tipos de inyección o infusión comprenden intraarterial, intra- ó transdérmica (incluyendo subcutánea), o intraspinal, especialmente intratecal. En estas composiciones farmacéuticas líquidas, el ingrediente activo puede estar contenido en solución en forma de soluto. Este es el tipo más común y más preferido de dicha composición, pero requiere un ingrediente activo en una forma de sal que tenga una solubilidad acuosa razonablemente buena. El agua (o solución salina) es con mucho el disolvente más preferido para dichas composiciones. Pueden utilizarse ocasionalmente soluciones supersaturadas, pero éstas

presentan problemas de estabilidad que las hacen impracticables para el uso de base diaria.

Si no es posible obtener una forma de algún compuesto de fórmula (1.0.0) que tenga el grado necesario de solubilidad acuosa, como puede ocurrir a veces, está dentro de las habilidades del experto preparar una emulsión, que es una dispersión de pequeños glóbulos de un líquido, la fase discontinua o interna, en un segundo líquido, la fase continua o externa, con el que es inmiscible. Los dos líquidos se mantienen en estado emulsionado mediante el uso de emulsionantes que sean farmacéuticamente aceptables. Así, si el ingrediente activo es un aceite insoluble en agua, puede administrarse en una emulsión de la que sea la fase discontinua. Además, cuando el ingrediente activo es insoluble en agua, pero puede disolverse en un disolvente que es inmiscible con agua, puede utilizarse una emulsión. Aunque el ingrediente activo se utilizará lo más habitualmente como fase discontinua o interna de lo que se designa como una emulsión de aceite en agua, podría utilizarse también como la fase discontinua o interna de una emulsión inversa, que se designa habitualmente como emulsión de agua en aceite. En este caso, el ingrediente activo es soluble en agua, y podría administrarse en forma de una solución acuosa sencilla. Sin embargo, las emulsiones inversas se invierten con la inyección o infusión en un medio acuoso tal como la sangre, y

ofrecen la ventaja de proporcionar una dispersión más rápida y eficaz del ingrediente activo en ese medio acuoso de la que puede obtenerse utilizando una solución acuosa. Las emulsiones inversas se preparan utilizando agentes emulsionantes farmacéuticamente aceptables adecuados bien conocidos en la técnica. Cuando el ingrediente activo tiene una solubilidad en agua limitada, puede administrarse también en forma de un sólido suspendido en forma coloidal o microparticulada en una suspensión preparada utilizando agentes de suspensión farmacéuticamente aceptables adecuados. Los sólidos suspendidos que contienen el ingrediente activo pueden formularse también en forma de composiciones de liberación retardada, sostenida y/o controlada.

Aunque la administración sistémica se llevará a cabo lo más frecuentemente mediante inyección o infusión de un líquido, existen muchas situaciones en las que será ventajoso o incluso necesario suministrar el ingrediente activo en forma de un sólido. La administración sistémica de sólidos se lleva a cabo por instilación, inhalación o insuflación de una composición farmacéutica en una forma sólida adecuada que contiene el ingrediente activo. La instilación del ingrediente activo puede implicar la instalación de una composición de implante sólido en tejidos o cavidades corporales adecuadas. El implante puede comprender una matriz de materiales biocompatibles y

bioerosionables en la que están dispersadas las partículas de un ingrediente activo sólido, o en la que, posiblemente, están atrapados los glóbulos o células aisladas de un ingrediente activo líquido. Convenientemente, la matriz se disgregará y será completamente absorbida por el cuerpo. La composición de la matriz se selecciona también preferiblemente para proporcionar una liberación controlada, sostenida y/o retardada del ingrediente activo durante periodos extendidos de tiempo, incluso tanto como varios meses.

El término "implante" indica la mayoría de las veces una composición farmacéutica sólida que contiene el ingrediente activo, mientras que el término "depósito" implica habitualmente una composición farmacéutica líquida que contiene el ingrediente activo que se deposita en cualquier tejido o cavidad corporal adecuada formando un reservorio o acúmulo que migra lentamente a los tejidos y órganos circundantes, y en su caso se distribuye sistémicamente. Sin embargo, estas distinciones no se realizan siempre estrictamente en la técnica, y consiguientemente, se contempla que estén incluidos dentro del alcance de la presente invención implantes líquidos y depósitos sólidos, e incluso formas sólidas y líquidas mezcladas para cada uno. Los supositorios pueden considerarse como un tipo de implante, ya que comprenden bases que son sólidas a temperatura ambiente pero se funden a la temperatura corporal de un paciente, liberando

lentamente el ingrediente activo con el que están impregnados al tejido circundante del cuerpo del paciente, absorbiéndose y transportándose el ingrediente activo para efectuar una administración sistémica.

La administración sistémica puede realizarse también mediante inhalación o insuflación de un polvo, es decir, una composición particulada que contiene el ingrediente activo. Por ejemplo, el ingrediente activo en forma de polvo puede inhalarse en los pulmones utilizando dispositivos convencionales para formar aerosoles de formulaciones particuladas. El ingrediente activo como formulación particulada puede administrarse también por insuflación, es decir, atomizarse o dispersarse de otra manera en tejidos o cavidades corporales adecuadas mediante pulverización simple o utilizando dispositivos convencionales para la formación de aerosoles de formulaciones particuladas. Estas composiciones particuladas pueden formularse también para proporcionar la liberación retardada, sostenida y/o controlada del ingrediente activo según principios bien entendidos y materiales conocidos.

Otros medios de administración sistémica que pueden utilizar los ingredientes activos de la presente invención en forma líquida o sólida incluyen las vías transdérmica, intranasal y oftálmica. En particular, los parches transdérmicos

preparados según tecnología de suministro de fármacos bien conocida pueden prepararse y aplicarse a la piel de un paciente a tratar, después de lo cual, el ingrediente activo migra a través de la epidermis, a causa de sus características de solubilidad formuladas, a las capas dérmicas de la piel del paciente, en las que se incorpora como parte de la circulación general del paciente, proporcionando finalmente la distribución sistémica del ingrediente activo durante un periodo extendido deseado de tiempo. Se incluyen también implantes que se colocan debajo la capa epidérmica de la piel, es decir, entre la epidermis y la dermis de la piel del paciente que se esté tratando. Dicho implante se formulará según principios bien conocidos y materiales utilizados habitualmente en esta tecnología de suministro, y puede prepararse de tal manera que proporcione una liberación controlada, sostenida y/o retardada del ingrediente activo en la circulación sistémica del paciente. Dichos implantes subepidérmicos (subcuticulares) proporcionan la misma facilidad de instalación y eficacia de suministro que los parches transdérmicos, pero sin la limitación de estar sujetos a degradación, daño o retirada accidental como consecuencia de estar expuestos en 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), las expresiones equivalentes: "administración", "administración de",

"administrar", "administrar un", se han utilizado con respecto de las citadas composiciones farmacéuticas. Empleadas así, estas expresiones se pretende que signifiquen proporcionar a un paciente necesitado de tratamiento una composición farmacéutica de la presente invención por cualquiera de las vías de administración descritas en la presente descripción, siendo el ingrediente activo un compuesto de fórmula (1.0.0) o un profármaco, derivado o metabolito de éste que es útil en el tratamiento de una enfermedad, trastorno o afección mediada por o asociada con la modulación de la actividad de PDE4, especialmente PDE4D, en el citado paciente. Consiguientemente, se incluye dentro del alcance de la presente invención cualquier otro compuesto que, tras administración a un paciente, sea capaz de proporcionar directa o indirectamente un compuesto de fórmula (1.0.0). Dichos compuestos se reconocen como profármacos, y están disponibles una serie de procedimientos establecidos para preparar dichas formas de los compuestos de fórmula (1.0.0).

La dosificación y velocidad de dosificación de los compuestos de fórmula (1.0.0) eficaz para tratar o prevenir una enfermedad, trastorno o afección mediada por o asociada con la modulación de la actividad de PDE4, especialmente PDE4D, dependerá de una serie de factores, tales como la naturaleza del inhibidor, el peso del paciente, el objetivo del tratamiento, la naturaleza de la patología a tratar, la composición específica

utilizada, y las observaciones y conclusiones del médico a cargo.

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 lo más preferiblemente entre aproximadamente 20,0 µg/kg y aproximadamente 0,5 mg/kg de peso corporal al día de ingrediente activo.

Cuando se administra la forma de dosificación por vía tópica 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 lo más preferiblemente, entre aproximadamente 2,0 µg/kg y

aproximadamente 0,05 mg/kg de peso corporal al día de ingrediente activo.

Utilizando pesos corporales representativos de 10 kg y 100 kg para ilustrar el intervalo de dosificaciones tópicas en forma de aerosol que podrían utilizarse como se describió anteriormente, los niveles de dosificación adecuados de los compuestos de fórmula (1.0.0) estarán entre aproximadamente 1,0-10,0 µg y 500,0-5.000,0 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 lo 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 cantidades de dosificación totales de 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 tasa de catabolismo y eliminación, así como de los niveles mínimos y óptimos en plasma sanguíneo u otros fluidos corporales del citado ingrediente activo alcanzados en el paciente que se requieren para eficacia terapéutica.

Deben considerarse también numerosos otros factores en la decisión del número de dosis por día y de la cantidad de ingrediente activo por dosis que se administrará. No es el menos importante de dichos otros factores la respuesta individual del paciente que se esté tratando. Así, por ejemplo, cuando se utiliza el ingrediente activo para tratar o prevenir asma, y se administra por vía tópica mediante inhalación de aerosol en los pulmones, se administrará cada día de una a cuatro dosis constituidas por accionamientos de un dispositivo dispensador, es decir, "ráfagas" de un inhalador, conteniendo cada dosis de aproximadamente 50,0 µg a aproximadamente 10,0 mg de ingrediente activo.

**DESCRIPCION DETALLADA DE LA INVENCION**

**11.0 Preparaciones y ejemplos de trabajo**

A continuación sigue una descripción de numerosas preparaciones mediante las cuales se prepararon los intermedios utilizados en la preparación de compuestos específicos de fórmula (1.0.0). También siguen a continuación numerosos ejemplos que muestran la preparación de compuestos específicos de fórmula (1.0.0). Estas preparaciones y ejemplos se pretende que ilustren adicionalmente los compuestos de la presente invención y los procedimientos según los cuales pueden prepararse fácilmente por el experto. El experto será consciente

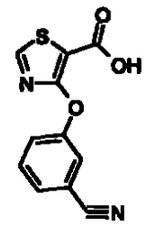
de muchos otros procedimientos adecuados que son también asequibles, así como de variaciones aceptables de los procedimientos descritos a continuación.

La descripción siguiente es para fines de ilustración de la presente invención, y no se pretende que cree limitaciones en modo alguno, expresadas o implícitas, sobre el alcance de la presente invención. Las reivindicaciones adjuntas a ésta son para fines de enumeración de la presente invención, de expresión del alcance contemplado de ésta y de indicación de particulares de ésta.

En las siguientes preparaciones, las caracterizaciones analíticas de los compuestos preparados se realizaron por análisis de espectros de masas determinados por procedimientos GCMS, AMPI, APCI o de termopulverización. Se tomaron todos los espectros RMN-$^1$H con un instrumento a 400 MHz.

**Preparación 1**

Acido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (9.0.1):



(9.0.1)

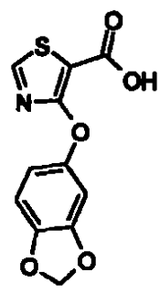
Se agitó una mezcla de 375 mg (1,4 mmol) de éster etílico del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico, 1,4 ml de LiOH y 10 ml de THF durante 18 horas a temperatura ambiente. Se concentró la mezcla con rotavapor, proporcionando un aceite amarillo. Se diluyó el aceite con HCl 1 N (30 ml), precipitando un sólido blanco. Se filtró el sólido y después se secó en pistola de secado, proporcionando 265 mg de polvo blanco.

APCI MS (m/z $M^+$-1): 245.

Se prepararon los compuestos de las preparaciones 1a-1b según el procedimiento de la preparación 1, sustituyendo el correspondiente éster etílico del ácido oxitiazol-5-carboxílico. La duración de la reacción fue de entre 1 y 24 horas.

**Preparación 1a**

Acido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (9.0.2).

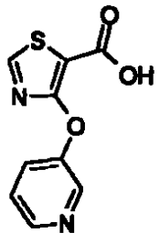


(902)

APCI MS (m/z $M^+$+1): 266.

**Preparación 1b**

Acido 4-(piridin-3-iloxi)tiazol-5-carboxílico de fórmula (9.0.3)

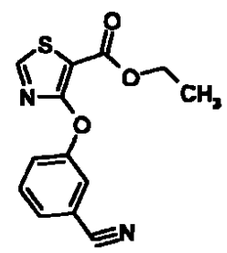


(903)

APCI MS (m/z $M^+$+1): 221.

**Preparación 2**

Ester etílico del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (9.0.4)



(9.0.4)

Se calentó a 80°C una mezcla agitada de 665 mg (3,5 mmol) de éster etílico del ácido 4-clorotiazol-5-carboxílico, 416 mg (3,5 mmol) de 3-cianofenol, 2,4 g (7,3 mmol) de $Cs_2CO_3$ y 60 ml de dimetilformamida en un baño de aceite durante 72 horas. Se enfrió entonces la mezcla, se vertió sobre 70 ml de agua, y se extrajo con acetato de etilo (3 x 40 ml). Se lavaron los extractos reunidos con agua (2 x 50 ml), salmuera (1 x 50 ml), se secaron sobre $Na_2SO_4$, y se concentraron por rotavapor. Se

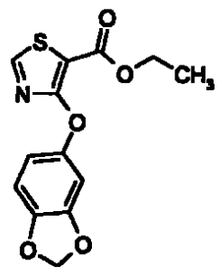
cromatografió el aceite resultante en una columna de sílice Biotage Flash 40S(R), cargada con cloruro de metileno y eluida con acetato de etilo al 20%/hexanos al 80%, proporcionando 375 mg de un aceite amarillo claro.

APCI MS (m/z $M^+$+1): 275.

Se prepararon los compuestos de las preparaciones 2a-2b según el procedimiento de la preparación 1, sustituyendo el correspondiente fenol. La duración de la reacción fue de entre 1 y 24 horas.

**Preparación 2a**

Ester etílico del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (9.0.5):

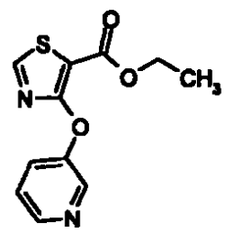


(905)

Se continuó con el material bruto.

**Preparación 2b**

Ester etílico del ácido 4-(pirıdın-3-ıloxı)tıazol-5-carboxílico de fórmula (9.0.6):

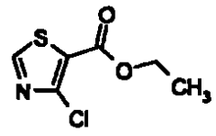


(906)

APCI MS (m/z $M^+$+1) 251.

**Preparación 3**

Ester etílıco del ácido 4-clorotıazol-5-carboxílıco de fórmula (9.0.7)·



(907)

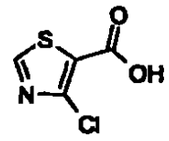
Se agıtó a reflujo durante 2 horas una mezcla de 2,0 g (12,2 mmol) de ácido 4-clorotıazol-5-carboxílıco y 6,24 ml (85,6 mmol) de $SOCl_2$. Se concentró después la mezcla por rotavapor y se sometıó a alto vacío con bomba durante 2 horas. A contınuación, se dıluyó el materıal con etanol y se calentó a reflujo durante 18 horas. Se concentró la mezcla por rotavapor y se dıluyó con cloruro de metıleno. Se eluyó a través de una capa de sılıce con

cloruro de metileno y se concentró por rotavapor, proporcionando 1,49 g de un sólido amarillo claro.

PF: 43-45°C.

**Preparación 4**

Acido 4-clorotiazol-5-carboxílico de fórmula (9.0.8):



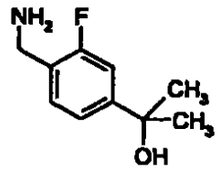
(908)

Se añadió gota a gota a una mezcla agitada de 10,3 g (69,8 mmol) de 4-clorotiazol-5-carbaldehído (*Journal of the Chemical Society, Perkins Transactions*, **1992**, 973-978), 296 ml (2792 mmol) de 2-metil-2-buteno y 200 ml de butanol terciario, una solución de 50,5 g (558 mmol) de $NaClO_2$ y 50,2 g (419 mmol) de $NaH_2PO_4$ en 300 ml de agua durante 20 minutos. Se agitó la reacción durante 1 hora, después se concentró a 1/3 de volumen por rotavapor. Se acidificó la solución restante con HCl 6 N con agitación rápida Se filtró el sólido precipitado y se secó al aire a alto vacío durante la noche, proporcionando 10,6 g de sólido blanco.

PF: 235-240°C (descomposición).

**Preparación 5**

2-(4-Aminometil-3-fluorofenil)propan-2-ol de fórmula (9.0.9):



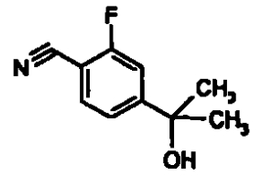

(909)

Se añadieron gota a gota a una solución agitada de 1,95 g (0,011 mmol) de 2-fluoro-4-(1-hidroxi-1-metiletil)-benzonitrilo en 30 ml de THF anhidro a 0°C, 34 ml (0,034 mmol) de $LiAlH_4$ 1,0 M. Se calentó la mezcla a temperatura ambiente, después se calentó a reflujo durante 30 minutos. Se enfrió entonces la mezcla hasta 0°C y se inactivó con 20 ml de MeOH añadido gota a gota. A continuación, se diluyó con 700 ml de $CHCl_3$ y se lavó con 100 ml de agua. Se filtró la suspensión resultante a través de Celite, se secó la capa orgánica sobre $MgSO_4$ y se concentró, proporcionando 1,6 g de un aceite ámbar.

APCI MS (m/z $M^+$+1): 183.

**Preparación 6**

2-Fluoro-4-(1-hidroxi-1-metiletil)benzonitrilo de fórmula (9.0.10):



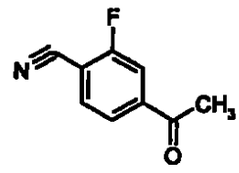
(9.0.10)

Se añadieron gota a gota a una suspensión agitada de 4,7 g (0,019 mmol) de $CeCl_3$ anhidro en 30 ml de THF anhidro a 0°C, 6 ml de $CH_3MgCl$ 3,0 M. Se agitó a 0°C durante 45 minutos. A continuación, se añadió gota a gota una solución de 2,5 g (0,015 mol) de 4-acetil-2-fluorobenzonitrilo en 200 ml de THF anhidro. Se agitó a 0°C durante 1 hora, después se inactivó con ácido acético 2 N añadido gota a gota. Se vertió la mezcla sobre 200 ml de agua y se acidificó a pH 2 con ácido acético 2 N. Se extrajo la capa acuosa con acetato de etilo (2 x 200 ml) Se reunieron los extractos de acetato de etilo, se lavaron con agua (2 x 40 ml), salmuera (1 x 40 ml), se secaron sobre $MgSO_4$ y se concentraron, proporcionando un aceite que se cromatografió sobre gel de sílice eluyendo con acetato de etilo al 50%/hexanos al 50%, proporcionando 1,95 g de un aceite ámbar.

APCI MS (m/z $M^+$+1): 179

**Preparación 7**

4-Acetil-2-fluorobenzonitrilo de fórmula (9.0.11):



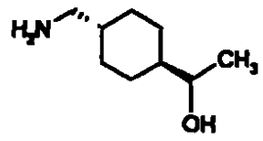
(9011)

Se desgasificó una mezcla de 5,0 g (0,02 mol) de 4-bromo-2-fluorobenzonitrilo, 6 ml de TEA, 906 mg (0,0022 mmol) de dppp, 5,8 g (0,04 mmol) de TlOAc, y 448 mg (0,002 mmol) de $Pd(OAc)_2$ en 50 ml de DMF en corriente de $N_2$. Se calentó la mezcla a 90°C durante 7 horas. Se enfrió la reacción hasta temperatura ambiente, se añadieron 25 ml de HCl 2 N y se agitó durante 30 minutos. Se vertió la mezcla sobre 300 ml de agua y se extrajo con $Et_2O$ (2 x 300 ml). Se lavaron los extractos orgánicos reunidos con agua (2 x 80 ml), salmuera (1 x 80 ml), se secaron sobre $MgSO_4$ y se concentraron, proporcionando un aceite, que se cromatografió después sobre gel de sílice eluido con acetato de etilo al 30%/hexanos al 70%, proporcionando 2,5 g de un aceite amarillo/naranja,

APCI MS (m/z $M^+$+1): 164.

**Preparación 8**

Trans-(-)-1-(-4-aminometilciclohexil)etanol de fórmula (9.0.12):



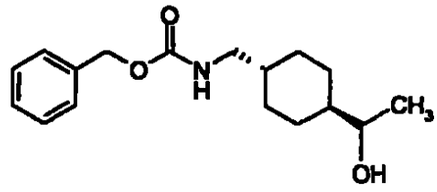
(9012)

Se cargó un frasco Parr de 500 ml con 400 mg de $Pd(OH)_2$, 7,0 g (24,1 mol) de éster bencílico del ácido trans-(-)-[4-(1-hidroxietil)ciclohexilmetil]carbámico, 125 ml de acetato de etilo y 125 ml de MeOH. Se colocó al frasco a 50 psi (345 kPa) de $H_2$ y se agitó durante 2 horas. Se filtró entonces la suspensión a través de Celite y se concentró, proporcionando 3,6 g de un sólido blanco.

APCI MS (m/z $M^+$+1): 158.

**Preparación 9**

Ester bencílico del ácido trans-(-)-[4-(1-hidroxietil)-ciclohexilmetil]carbámico de fórmula (9.0.13):



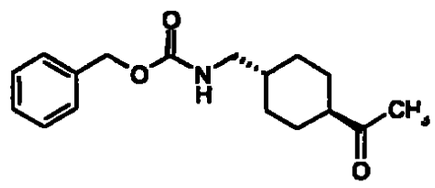
(9013)

Se cargó un matraz de 250 ml secado a la llama con 7,95 g (27,5 mmol) de éster bencílico del ácido trans-(4-acetil-ciclohexilmetil)carbámico, 60 ml de THF anhidro y 2,7 ml (2,7 mmol) de (S)-2-metil-CBS-oxazoborolidina 1 M. Se calentó la mezcla a 50°C, después se añadieron gota a gota 11 ml (22 mmol) de $BH_3$ DMS 2 M durante 10 minutos, se agitó la mezcla de reacción durante 30 minutos adicionales a 50°C, y después se enfrió. Se inactivó la reacción con 25 ml de MeOH y se concentró, proporcionando un aceite. Se diluyó el material con agua y se extrajo con acetato de etilo (3 x 100 ml). Se lavaron los extractos orgánicos reunidos con agua (1 x 100 ml), salmuera (1 x 100 ml), se secaron sobre $Na_2SO_4$ y se concentraron, proporcionando un sólido blanco que se cromatografió sobre gel de sílice eluido con acetato de etilo al 50%/hexanos al 50%, proporcionando 7,0 g de un sólido blanco.

PF: 83-84°C.

**Preparación 10**

Ester bencílico del ácido trans-(4-acetilciclohexilmetil)-carbámico de fórmula (9.0.14):



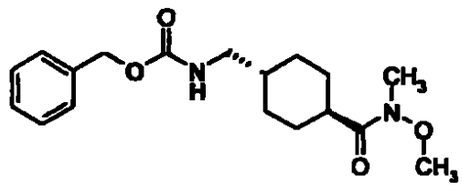
(9.0.14)

Se cargó un matraz de 500 ml con 15,2 g (45,4 mmol) de éster bencílico del ácido trans-[4-(metoximetilcarbamoil)-ciclohexilmetil]carbámico y 350 ml de THF andhidro. Se enfrió la solución hasta 0°C, después se añadieron gota a gota 33,3 ml (99,9 mmol) de $CH_3MgCl$ 3 M durante 10 minutos. Se agitó entonces la mezcla de reacción durante 1 hora a 0°C, después se inactivó con 20 ml de ácido acético 2 N y se vertió sobre 300 ml de agua. Se extrajo la fase acuosa con acetato de etilo (3 x 200 ml), y se lavaron los extractos orgánicos reunidos con HCl 0,5 M (1 x 100 ml), agua (1 x 100 ml), salmuera (1 x 100 ml), se secaron sobre $Na_2SO_4$ y se concentraron hasta un sólido. Se recristalizó el sólido con IPE y se filtró, proporcionando 5,5 g de un sólido blanco.

PF. 66-67°C.

**Preparación 11**

Ester bencílico del ácido trans-[4-(metoximetilcarbamoil)-ciclohexilmetil]carbámico de fórmula (9.0.15):



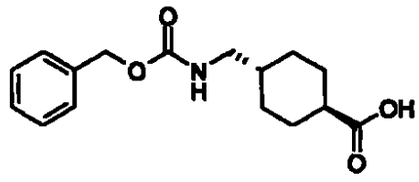
(9 0 15)

Se cargó una matraz de 1 l con 25,02 g (85,9 mmol) de ácido trans-4-(benciloxicarbonilaminometil)ciclohexano-carboxílico), 9,21 g (94,5 mmol) de HCl de O,N-dimetil-hidroxilamina, 41,8 g (94,5 mmol) de BOP, 750 ml de cloruro de metileno y 75 ml de diisopropilamina. Se agitó entonces la mezcla de reacción en atmósfera de nitrógeno durante la noche. Se lavó después la solución con agua, ácido cítrico al 5% (2 x 300 ml), bicarbonato de sodio saturado (2 x 300 ml), salmuera (1 x 300 ml), se secó sobre $Na_2SO_4$ y se concentró hasta un aceite. Se cromatografió el aceite sobre gel de sílice eluido con acetato de etilo al 50%/hexanos al 50%, proporcionando 27,2 g de un aceite transparente que solidificó en reposo.

PBMS (m/z $M^+$+1) 335

**Preparación 12**

Acido trans-4-(benciloxicarbonilaminometil)ciclohexano-carboxílico de fórmula (9.0.16):



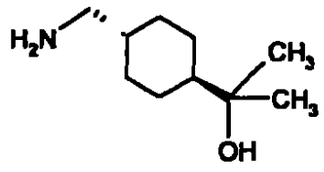
(9 0 16)

Se cargó un matraz de 3 bocas de 1 l con 25,09 g (160 mmol) de ácido trans-4-aminometilciclohexanocarboxílico, 77,4 mg (560 mmol) de $K_2CO_3$, 250 ml de dioxano y 250 ml de agua. Se agitó la suspensión, y se añadieron después gota a gota 28,5 ml (200 mmol) de cloroformiato de bencilo. Se agitó entonces la mezcla de reacción a temperatura ambiente durante 6,5 horas y después se vertió sobre 800 ml de agua y se acidificó (lentamente) con HCl 1 N. Se filtró el precipitado blanco resultante y se secó - 45,6 g.

PBMS (m/z $M^+$+1) 292.

**Preparación 13**

Trans-2-(4-aminometilciclohexil)propan-2-ol de fórmula (9.0.17)



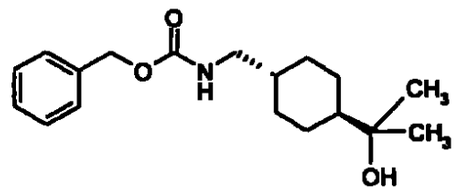
(9 0 17)

Se cargó un frasco Parr de 500 ml con 150 mg de $Pd(OH)_2$, 3,3 g (10,7 mmol) de éster bencílico del ácido trans-[4-(1-hidroxi-1-metiletil)ciclohexilmetil]carbámico, 100 ml de acetato de etilo y 100 ml de MeOH. Se coloco el frasco a 50 psi (345 kPa) de $H_2$ y se agitó durante 1 hora. Se filtró el material a través de Celite y se concentró, proporcionando 1,57 g de un sólido blanco.

PBMS (m/z $M^+$+1): 172.

**Preparación 14**

Ester bencílico del ácido trans-[4-(1-hidroxi-1-metiletil)-ciclohexilmetil]carbámico de fórmula (9.0.18):



(9.0.18)

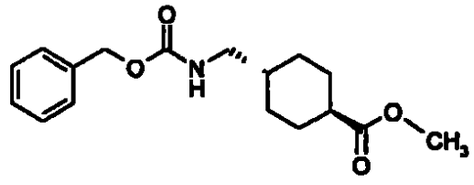
Se cargó un matraz de 3 bocas de 1 l con 7,2 g (29,2 mmol) de $CeCl_3$ y 100 ml de THF anhidro. Se calentó la suspensión a reflujo durante 15 minutos, después se enfrió hasta 0°C y se añadió una solución de 8,10 g (26,5 mmol) de éster metílico del ácido trans-(benciloxicarbonilaminometil)-ciclohexanocarboxílico

en 200 ml de THF anhidro. A continuación, se añadieron gota a gota 29 ml (87,5 mmol) de $CH_3MgCl$ 3 M durante 30 minutos. Se agitó la mezcla de reacción durante 2 horas adicionales a 0°C, después se inactivó y se diluyó con ácido acético 2 N a pH 2. Se extrajo el material con acetato de etilo (3 x 100 ml). Se lavaron los extractos reunidos con bicarbonato de sodio saturado (1 x 100 ml), salmuera (1 x 100 ml), se secaron sobre $Na_2SO_4$ y se concentraron hasta un aceite ámbar. Se cromatografió el aceite sobre una columna de sílice Biotage Flash 40S(R) + SIM eluida con acetato de etilo al 40%/hexanos al 60%, proporcionando 3,3 g de un sólido amarillo claro.

PBMS (m/z $M^+$+1): 306.

**Preparación 15**

Ester metílico del ácido trans-(benciloxicarbonilamino-metil)ciclohexanocarboxílico de fórmula (9.0.19):



(9.0.19)

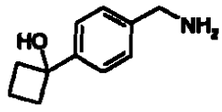
Se cargó un matraz de 500 ml con 7,0 g (24,1 mmol) de ácido trans-4-(benciloxicarbonilaminometil)ciclohexano-carboxílico,

8,32 g (60,2 mmol) de $K_2CO_3$, 200 ml de DMF y 1,95 ml (31,3 mmol) de yoduro de metilo. Se agitó la mezcla de reacción a temperatura ambiente durante la noche, después se diluyó con agua y se extrajo con acetato de etilo (3 x 60 ml). Se lavaron los extractos reunidos de acetato de etilo con agua (1 x 100 ml), salmuera (1 x 100 ml), se secaron sobre $Na_2SO_4$ y se concentraron hasta 8,1 g de un aceite amarillo claro que solidificó en reposo.

PBMS (m/z $M^+$+1) 306.

**Preparación 16**

1-(4-Aminometilfenil)ciclobutanol de fórmula (9.0.20):




(9.0.20)

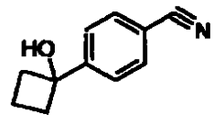
Se cargó un matraz de 250 ml con 4,1 g (23,5 mmol) de 4-(1-hidroxiciclobutil)benzonitrilo y 100 ml de THF anhidro, y después se enfrió a 0°C. A continuación, se añadieron gota a gota 70,5 ml (70,5 mmol) de $LiAlH_4$ 1 M. Se agitó la mezcla de reacción a 0°C durante 10 minutos, después se calentó a reflujo durante 30 minutos, se enfrió hasta 0°C y se inactivó con MeOH.

Se diluyó con cloruro de metileno y se lavó con agua (2 x 100 ml). Se filtró la fase orgánica a través de Celite y se concentró, proporcionando 2 g de un sólido amarillo.

GC/MS (m/z): 177.

**Preparación 17**

4-(1-Hidroxiciclobutil)benzonitrilo de fórmula (9.0.21):




(9.0.21)

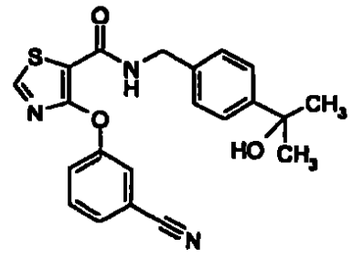
Se cargó un matraz de 500 ml con 10,8 g (59,4 mmol) de 4-bromobenzonitrilo y 150 ml de THF anhidro. Se enfrió la solución hasta -78°C y se añadieron gota a gota 26,1 ml (65,3 mmol) de n-butil-litio 2,5 M. Se agitó la mezcla de reacción a -78°C durante 10 minutos adicionales, después se añadieron gota a gota 5,0 g (71,3 mmol) de ciclobutanona. Se agitó la mezcla de reacción durante 10 minutos adicionales a -78°C, después se retiró el baño y se agitó la reacción durante 1 hora adicional. Se vertió el material sobre 300 ml de agua y se extrajo con acetato de etilo (3 x 100 ml). Se lavaron los extractos orgánicos reunidos con agua (2 x 100 ml), salmuera (1 x 100 ml), se secaron sobre $Na_2SO_4$ y se concentraron hasta un aceite marrón

claro. Se cromatografió el aceite sobre una columna Biotage Flash 40S(R) + SIM, eluida con acetato de etilo al 10%/hexanos al 90%, proporcionando 4,1 g de un aceite amarillo claro.

APMS (m/z $M^+$-1): 172.

**Ejemplo 1**

4-(1-Hidroxi-1-metiletil)bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.1)



(851)

Se agitó una mezcla de 93,8 mg (0,38 mmol) de ácido 4-(3-cianofenoxi)tiazol-5-carboxílico 5, 63,0 mg (0,40 mmol) de 2-(4-aminometilfenil)propan-2-ol, 56,6 mg (0,42 mmol) de HOBT y 87,6 mg (0,46 mmol) de EDCl en 15 ml de dimetilformamida a temperatura ambiente durante 18 horas. Se vertió entonces la mezcla sobre agua y se extrajo con acetato de etilo (3 x 50 ml). Se reunieron los extractos orgánicos y se lavaron con NaOH 1 N (1 x 30 ml), agua (1 x 30 ml), salmuera (1 x 30 ml), se secaron sobre $Na_2SO_4$ y se concentraron, proporcionando un aceite

amarillo. La cromatografía sobre columna de sílice Biotage Flash 12S(R), cargada con cloruro de metileno y eluida con acetato de etilo al 40%/hexanos al 60%, proporcionó 10,8 mg de un aceite transparente que solidificó en reposo.

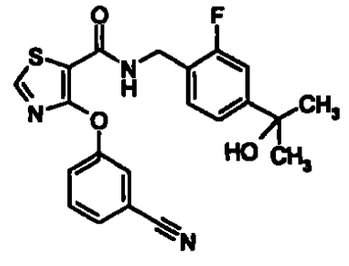
APCI MS (m/z $M^+$-1). 392.

RMN-$^1$H (400 MHz, $CDCl_3$) δ 1,53 (6H, s), δ 4,6 (2H, d), δ 7,2-7,5 (8H, m), δ 8,6 (1H, s).

Se prepararon los compuestos de los ejemplos 2-8 según el procedimiento del ejemplo 1, sustituyendo el 2-(4-aminometilfenil)propan-2-ol por la correspondiente amina. La duración de la reacción fue entre 1 y 24 horas.

**Ejemplo 2**

2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.2):



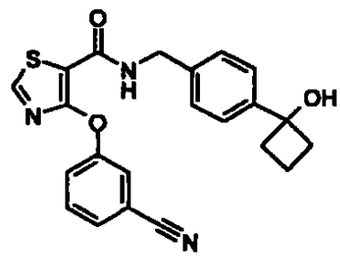

(852)

APCI MS (m/z $M^+$-1): 410.

RMN-$^1$H (400 MHz, $CDCl_3$) δ 1,53 (6H, s), δ 4,6 (2H, d), δ 7,1-7,6 (7H, m), δ 8,6 (1H, s).

**Ejemplo 3**

4-(1-Hidroxiciclobutil)bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.3):



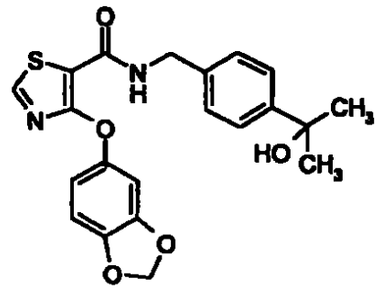
(853)

APCI MS (m/z $M^+$-1): 404.

RMN-$^1$H (400 MHz, $CDCl_3$) δ 1,95 (2H, m), δ 2,3 (2H, m), δ 2,5 (2H, m), δ 4,6 (2H, d), δ 7,2-7,6 (8H, m), δ 8,6 (1H, s).

**Ejemplo 4**

4-(1-Hidroxi-1-metiletil)bencilamida del ácido 4-(benzo-[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.4):



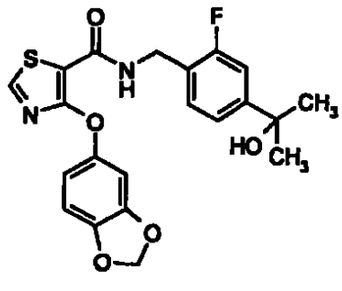
(8.5.4)

APCI MS (m/z $M^+$+1): 413.

RMN-$^1$H (400 MHz, $CDCl_3$) δ 1,53 (6H, s), δ 4,6 (2H, d), δ 5,9 (2H, s), δ 6,6 (1H, d), δ 6,63 (1H, s), δ 6,75 (1H, d), δ 7,3 (2H, d), δ 7,42 (2H, d), δ 8,6 (1H, s).

**Ejemplo 5**

2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.5).



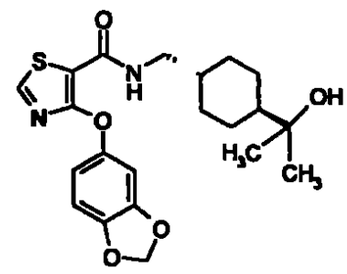
(8.5.5)

APCI MS (m/z $M^+$+1): 431.

PF· 117-118°C.

**Ejemplo 6**

[4-(1-Hıdroxı-1-metıletıl)cıclohexılmetil]amıda del ácıdo trans-4-(benzo[1,3]dıoxol-5-ıloxı)tıazol-5-carboxílıco de fórmula (8.5.6):



(856)

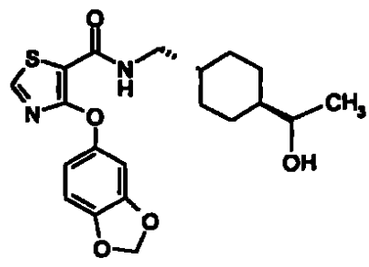
APCI MS (m/z $M^+$+1-$H_2O$): 401.

RMN-$^1$H (400 MHz, $CDCl_3$) δ 1,0 (6H, m), δ 1,9 (6H, s), δ 1,5 (2H, m), δ 1,9 (2H, d), δ 3,4 (2H, t), δ 6,0 (2H, s), δ 6,8 (3H, m), δ 7,2 (1H, a), δ 8,6 (1H, s).

**Ejemplo 7**

[4-(1-Hıdroxıetıl)cıclohexılmetıl]amıda del ácıdo trans-4-(benzo[1,3]dıoxol-5-ıloxı)tıazol-5-carboxílıco de fórmula

(8.5.7):



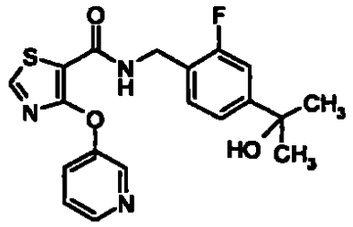
(8.5.7)

APCI MS (m/z $M^+$+1): 405.

RMN-$^1$H (400 MHz, $CDCl_3$) δ 1,0-1,9 (12H, m), δ 3,3 (2H, t), δ 3,5 (1H, m), δ 6,0 (2H, s), δ 6,6 (1H, dd), δ 6,7 (1H, s), δ 6,8 (1H, dd), δ 7,1 (1H, a), δ 8,55 (1H, s).

**Ejemplo 8**

2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(piridin-3-iloxi)tiazol-5-carboxílico de fórmula (8.5.8):



(8.5.8)

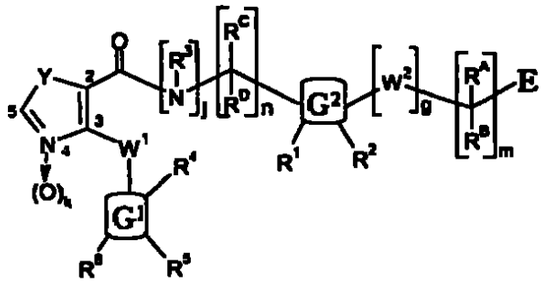
APCI MS (m/z $M^+$+1). 388.

RMN-$^1$H (400 MHz, $CDCl_3$) δ 1,5 (6H, s), δ 4,6 (2H, d), δ 7,3 (7H, m), δ 8,6 (1H, s).

Habiéndose descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

**REIVINDICACIONES**

1. Un compuesto de fórmula (1.0.0):



(100)

en la 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, 2 ó 3;

-n es 1 ó 2,

$-W^1$ es -O-; ó $-S(=O)_t-$, siendo t 0, 1 ó 2, ó $-N(R^3)-$, teniendo $R^3$ el mismo significado que se define a continuación;

$-W^2$ es -O-, $-S(=O)_t$, siendo t 0, 1 ó 2; $-N(R^3)-$, teniendo $R^3$ el mismo significado que se define a continuación; ó $-CR^{29}R^{39}-$;en la que

-$R^{29}$ 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 piridinilo, estando cada uno de los citados restos alquilo, cicloalquilo, fenilo, bencilo y piridilo sustituidos independientemente cada uno con 0 a 3 sustituyentes $R^{10}$, teniendo $R^{10}$ el mismo significado que se define a continuación;

-Y es $-S(=O)_t-$, siendo t 0, 1 ó 2, -O-; $-[N->(O)_k]-$ ó $-N(R^3)-$, siendo k 0 ó 1, y teniendo $R^3$ el mismo significado que se define a continuación, ó $-CH(R^1{}_a)-$, teniendo $R^1{}_a$ el mismo significado que se define a continuación; en la que

$-R^1{}_a$ es un miembro seleccionado del grupo constituido por -H; -F; -Cl; -CN; $-NO_2$; -alquilo ($C_1$-$C_4$); -alquinilo ($C_2$-$C_4$); alquil ($C_1$-$C_3$) fluorado; alcoxi ($C_1$-$C_3$) fluorado; $-OR^{16}$, y $-C(=O)NR^{22}{}_aR^{22}{}_b$; en la que

$-R^{22}{}_a$ 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; ó ciclopentilo;

$-R^A$ y $R^B$ son cada uno un miembro seleccionado independientemente del grupo constituido por -H, -F; $-CF_3$; -

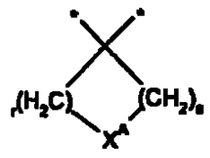
alquilo ($C_1$-$C_4$); -cicloalquilo ($C_3$-$C_7$); fenilo; y bencilo; estando los citados restos cicloalquilo, fenilo y bencilo sustituidos cada uno independientemente con 0 a 3 sustituyentes $R^{10}$; siendo

-$R^{10}$ un miembro seleccionado del grupo constituido por fenilo; piridilo; -F; -Cl, -$CF_3$; oxo (=O); -$OR^{16}$; -$NO_2$; -CN; -C(=O)$R^{16}$; -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)$_2NR^{16}R^{17}$; estando el citado fenilo o piridilo sustituido con 0 a 3 $R^{11}$; siendo

-$R^{11}$ -F; -Cl; -$CF_3$; -CN; -$NO_2$; -OH; -alcoxi ($C_1$-$C_3$); -alquilo ($C_1$-$C_3$); ó -$NR^{16}R^{17}$; y

-$R^{16}$ y $R^{17}$ son cada uno 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, estando sustituidos los citados alquilo, alquenilo, cicloalquilo, fenilo, bencilo, o piridilo con 0 a 3 sustituyentes seleccionados del grupo constituido por -F, -Cl, -$CF_3$, -CN y -alquilo ($C_1$-$C_3$); ó

-$R^A$ y $R^B$ se toman conjuntamente, pero sólo en el caso en que m sea 1, para formar un resto espiro de fórmula (1.2.0)·



(120)

en la que

-r y s son independientemente 0 a 4, con la condición de que la suma de r + s sea al menos 1, pero no superior a 5; y

-$X^A$ se selecciona de $-CH_2-$, $-CH(R^{11})-$ ó $C(R^{11})_2-$, seleccionándose cada $R^{11}$ independientemente del otro, y teniendo cada uno el mismo significado que se definió anteriormente; $-NR^{15}-$, teniendo $R^{15}$ el mismo significado que se define a continuación; -O-; y $-S(=O)_t-$, siendo t 0, 1 ó 2; y

el citado resto espiro de fórmula parcial (1.2.0) está sustituido en uno o más de los átomos de carbono de éste, distintos del que define $X^A$, con 0 a 3 sustituyentes $R^{14}$, teniendo $R^{14}$ el mismo significado que se define a continuación; en un átomo de nitrógeno de éste con 0 ó 1 sustituyentes $R^{15}$; teniendo $R^{15}$ el mismo significado que se define a continuación; y en un átomo de azufre de éste con 0 ó 2 átomos de oxígeno;

-$R^C$ y $R^D$ tienen el mismo significado que se definió

anteriormente para $R^A$ y $R^B$, excepto que uno de ellos debe ser -H, y se seleccionan independientemente entre sí y de $R^A$ y $R^B$;

$-R^1$ y $R^2$ pueden aparecer individual o conjuntamente sobre cualquier anillo o anillos que comprenda un significado del resto $G^2$ como se define a continuación; 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 $-C(=O)NR^{22}{}_aR^{22}{}_b$, teniendo $R^{16}$, $R^{22}{}_a$ y $R^{22}{}_b$ los mismos significados que se definieron anteriormente,

$-R^3$ es -H, -alquilo ($C_1$-$C_3$); fenilo, bencilo ó $-OR^{16}$; teniendo $R^{16}$ el mismo significado que se definió anteriormente;

$-R^4$, $-R^5$ y $-R^6$ pueden aparecer individual o conjuntamente en cualquier anillo o anillos que comprenda un significado del resto $G^1$ como se define a continuación; 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 -

$CH_2C(=NR^{22}_a)NR^{16}R^{17}$; en las que

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

-(b) -alquilo ($C_1$-$C_4$); y -alcoxi ($C_1$-$C_4$) en el caso en que uno o más de $R^4$, $R^5$ ó $R^6$ tenga el significado de $-OR^{16}$ en (a) anterior, y $R^{16}$ se defina como -alquilo ($C_1$-$C_6$); estando el citado alquilo y alcoxi sustituido independientemente cada uno con 0 a 3 sustituyentes -F ó -Cl; ó 0 ó 1 sustituyentes alcoxi ($C_1$-$C_2$)carbonilo-; alquil ($C_1$-$C_2$)carbonilo-; ó 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; imidazolinilo, 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: quinazolilinilo; quinoxalinilo y purinilo; estando cada uno de los citados restos arilo y heterociclilo independientemente sustituidos con 0 a 2 sustituyentes $R^{14}$ siendo

$-R^{14}$ un miembro seleccionado del grupo constituido por -alquilo ($C_1$-$C_4$); -cicloalquilo ($C_3$-$C_7$); fenilo; bencilo; piridinilo y quinolilo; estando sustituidos los citados alquilo, cicloalquilo, fenilo, bencilo, piridilo o quinolinilo con 0, 1 ó 2 sustituyentes -F, -Cl, $-CH_3$, $-OR^{16}$, $-NO_2$, -CN ó $-NR^{16}R^{17}$; estando constituido el citado grupo $R^{14}$ adicionalmente por -F; -Cl; $-CF_3$; oxo (=O); $-OR^{16}$; $-NO_2$; -CN; $-C(=O)OR^{16}$, $-O-C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$; $-O-C(=O)NR^{16}R^{17}$; $-NR^{16}R^{17}$; $-NR^{16}C(=O)R^{17}$; $-NR^{16}C(=O)OR^{17}$; $-NR^{16}S(=O)_2R^{17}$, ó $-S(=O)_2NR^{16}R^{17}$; teniendo $R^{16}$ y $R^{17}$ los mismos significados que se definieron anteriormente; y siendo además

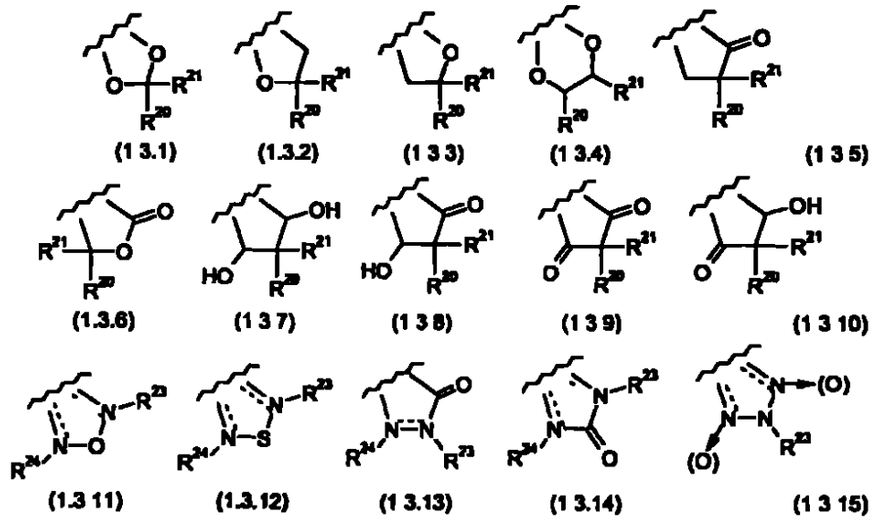
$-R^{15}$ un miembro seleccionado independientemente del grupo constituido por -H; $-C(=O)R^{16}$; $-OR^{16}$; -alquilo ($C_1$-$C_4$)-$OR^{16}$; $-C(=O)OR^{16}$; -alquilo ($C_1$-$C_2$)-$C(=O)OR^{16}$; $-C(=O)NR^{16}R^{17}$; -alquilo ($C_1$-$C_4$); -alquenilo ($C_2$-$C_4$); $-(CH_2)_u$-cicloalquilo ($C_3$-$C_7$), siendo u 0, 1 ó 2; fenilo; bencilo; piridilo; y quinolinilo; estando los citados alquilo, alquenilo, alcoxi, cicloalquilo, fenilo, bencilo, piridilo o quinolinilo

sustituidos con 0 a 3 sustituyentes $R^{12}$, teniendo $R^{16}$ y $R^{17}$ los mismos significados que se definieron anteriormente; y siendo

$-R^{12}$ un miembro seleccionado independientemente del grupo constituido por -F; -Cl; $-CO_2R^{18}$; $-OR^{16}$; -CN; $-C(=O)NR^{18}R^{19}$; $-NR^{18}R^{19}$; $-NR^{18}C(=O)R^{19}$; $-NR^{18}C(=O)OR^{19}$; $-NR^{18}S(=O)_pR^{19}$; $-S(=O)_pNR^{18}R^{19}$, siendo p 1 ó 2; -alquilo ($C_1$-$C_4$); y -alcoxi ($C_1$-$C_4$) en el caso en que $R^{12}$ tenga el significado de $-OR^{16}$ anterior y $R^{16}$ se defina como alquilo ($C_1$-$C_4$); estando el citado alquilo y alcoxi sustituidos independientemente 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; teniendo $R^{16}$ el mismo significado que se definió anteriormente; y en las que

$-R^{18}$ y $R^{19}$ se seleccionan independientemente del grupo constituido por -H; -alquilo ($C_1$-$C_4$); y fenilo; estando el citado alquilo o fenilo sustituido con 0-3 de -F; ó -Cl; o en el caso en que $G^1$ sea 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):




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 $-OCF_3$;

$-R^{23}$ 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 de trazos ---- representa un doble enlace;

$-G^1$ es un resto que comprende un sistema carbocíclico saturado o insaturado que es monocíclico de 3 a 7 miembros, o policíclico condensado de 7 a 12 miembros; con la condición de que $G^1$ no es un resto biarilo discontinuo o limitado como se define en $G^2$ a continuación; y en el que opcionalmente un

carbono del citado sistema carbocíclico puede estar reemplazado por un heteroátomo seleccionado de N, O y S; pudiendo estar reemplazado opcionalmente un segundo carbono de éste, y además opcionalmente un tercer carbono de éste, por un N, estando

el citado resto que se define como $G^1$ sustituido en cualquier anillo o anillos de éste con $R^4$, $R^5$ y $R^6$, que tienen el mismo significado que se definió anteriormente;

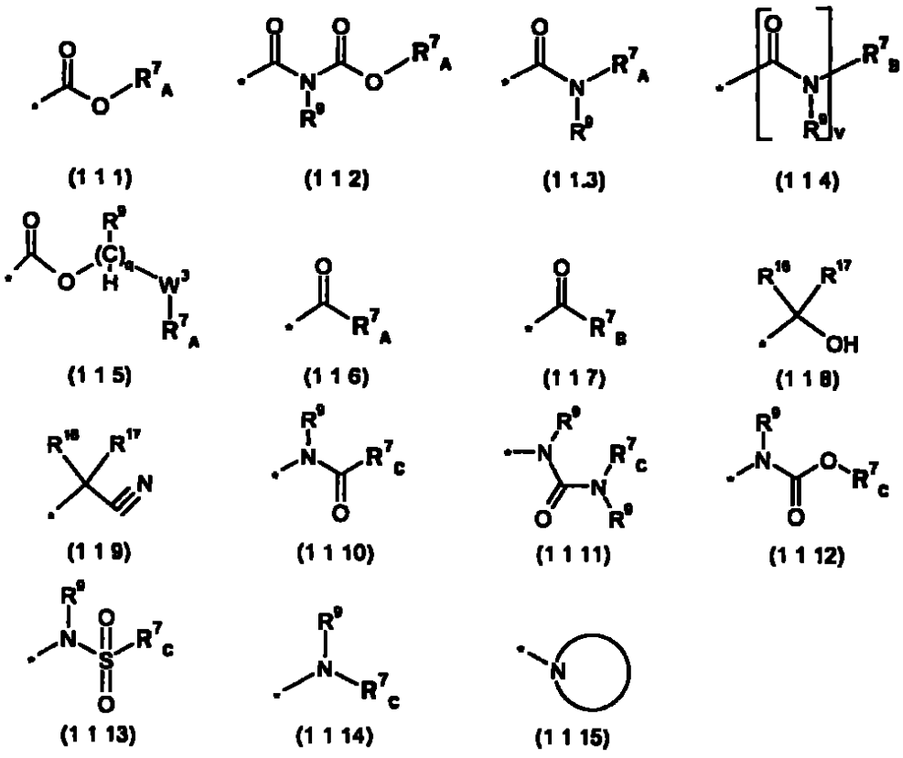
-$G^2$ es un sistema carbocíclico saturado o insaturado que es monocicclo de 3 a 7 miembros; o que es policíclico condensado de 7 a 12 miembros; o que es un resto biarilo discontinuo o limitado de 7 a 18 miembros, pudiendo estar reemplazado opcionalmente, para cada uno de los sistemas carbocíclicos citados, un átomo de carbono del citado sistema carbocíclico por un heteroátomo seleccionado de N, O y S; pudiendo estar opcionalmente reemplazado un segundo átomo de carbono de éste, y además opcionalmente un tercer átomo de carbono de éste, por un N; estando

el citado resto definido como $G^2$ sustituido en cualquier anillo o anillos de éste con $R^1$ y $R^2$, que tienen los mismos significados que se definieron anteriormente;

-E 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).




en las que

cuando $R^{16}$ y $R^{17}$ tienen el mismo significado que se definió anteriormente; y $R^9$ tiene el mismo significado que se define a continuación;

-"*" indica el punto de unión de cada fórmula parcial

(1.1.1) a (1.1.15) a la parte restante de fórmula (1.0.0);

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

-v 0 ó 1;

-$W^3$ es -O-; -N($R^9$)-, teniendo $R^9$ el mismo significado que se definió anteriormente; ó -CO(=O)-;

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

-(1) -H;

-(2) -alquilo ($C_1$-$C_6$); -alquenilo ($C_2$-$C_6$); ó -alquinilo ($C_2$-$C_6$); estando sustituidos el citado alquilo, alquenilo o alquinilo con 0 a 3 sustituyentes, teniendo $R^{10}$ el mismo significado que se definió anteriormente;

-(3) -$(CH_2)_u$-cicloalquilo ($C_3$-$C_7$), siendo u 0, 1 ó 2; y estando sustituido además el citado cicloalquilo ($C_3$-$C_7$) con 0 a 3 sustituyentes $R^{10}$, teniendo $R^{10}$ el mismo significado que se definió anteriormente; y

-(4) fenilo, bencilo o piridilo, estando opcionalmente sustituidos los citados fenilo, bencilo o piridilo con 0 a 3 sustituyentes $R^{10}$, teniendo $R^{10}$ el mismo significado que se definió anteriormente;

$-R^7_s$ 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; 2H-1-benzopiranilo; 2-H-cromenilo; cromanilo; benzotienilo; 1H-indazolilo; bencimidazolilo; benzoxazolilo; benzoisoxazolilo; benzotiazolilo;

benzotriazolilo; benzotriazinilo; ftalazinilo; 1,8-naftiridinilo; quinolinilo; isoquinolinilo; quinazolinilo; quinoxalinilo; pirazolo[3,4-d]pirimidinilo; pirimido[4,5-d]pirimidinilo; imidazo[1,2-a]piridinilo; piridopiridinilo; pteradinilo; y 1H-purinilo; estando

cualquier resto enumerado anteriormente en (1) ó (2) opcionalmente sustituido con respecto a (i) uno cualquiera o más de los átomos de carbono de éste, opcionalmente con un sustituyente $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió anteriormente; (ii) uno cualquiera o más átomos de nitrógeno de éste que no sean un punto de unión del citado resto, opcionalmente con un sustituyente $R^{15}$, teniendo $R^{15}$ el mismo significado que se definió anteriormente, y todas las formas tautoméricas de éste; y (iii) cualquier átomo de azufre de éste que no sea un punto de unión del citado resto, con 0, 1, ó 2 átomos de oxígeno;

$-R^9$ es un miembro seleccionao 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 ($C_1$-$C_2$)-$C(=O)OR^{16}$; teniendo $R^{16}$ el mismo significado que se definió 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 además en las que



(1.1.15)

comprende un sistema de anillo carbocíclico monocíclico saturado o insaturado 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); pudiendo estar opcionalmente reemplazados de 1 a 3 átomos de carbono individualmente del citado sistema de anillo carbocíclico por un heteroátomo de nitrógeno; o pudiendo estar opcionalmente reemplazado 1 átomo de carbono de éste por un heteroátomo de oxígeno o por un heteroátomo de azufre; o pudiendo estar opcionalmente reemplazados 2 átomos de carbono individualmente por un heteroátomo de nitrógeno y un heteroátomo de oxígeno, o por un heteroátomo de nitrógeno y un heteroátomo de azufre;
estando
cualquier resto de fórmula parcial (1.1.15) citado anteriormente opcionalmente sustituido con respecto a (1) uno cualquiera o más átomos de carbono de éste, con un sustituyente $R^{14}$, teniendo $R^{14}$ el mismo significado que se definió anteriormente, (2) uno

cualquiera o más átomos de nitrógeno de éste, con un sustituyente $R^{15}$, teniendo $R^{15}$ el mismo significado que se definió anteriormente, y todas las formas tautoméricas, y opcionalmente formas N-óxido de éste; ó (3) cualquier átomo de azufre de éste con 0, 1 ó 2 átomos de oxígeno;

y E se selecciona adicionalmente de:

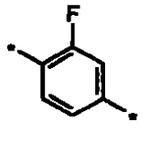
-(b) un resto que comprende un miembro seleccionado del grupo constituido por $-O-P(=O)(OH)_2$ (fosfórico); $-PH(=O)OH$ (fosfínico), $-P(=O)(OH)_2$ (fosfónico); $-[P(=O)(OH)-O-$alquilo $(C_1-C_4)]$ (alquilfosfono); $-P(=O)(OH)-O-$alquilo $(C_1-C_4)$ (alquilfosfinilo); $-P(=O)(OH)NH_2$ (fosforamido); $-P(=O)(OH)NH-$alquilo $(C_1-C_4)$ y $-P(=O)(OH)NHR^{25}$ (fosforamido sustituido), $-O-S(=O)_2OH$ (sulfúrico); $-S(=O)_2OH$ (sulfónico); $-S(=O)_2NHR^{26}$ ó $-NHS(=O_2)R^{26}$ (sulfonamido), siendo $R^{26}$ $-CH_3$, $-CF_3$ ó 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 $(C_1-C_4)$, $-C(=O)NHS(=O)_2NH-$alquilo $(C_1-C_4)$; $-C(=O)NHS(=O)_2N[$alquilo $(C_1-C_4)]_2$, $-S(=O)_2NHC(=O)$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=O)NH_2$; $-S(=O)_2NHC(=O)NH-$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=O)N[$alquilo $(C_1-C_4)]_2$, $-S(=O)_2NHC(=O)R^{25}$; $-S(=O)_2NHCN$; $-S(=O)_2NHC(=S)NH_2$; $-S(=O)_2NHC(=S)NH-$alquilo $(C_1-C_4)$; $-S(=O)_2NHC(=S)N[$alquilo $(C_1-C_4)]_2$; y $-S(=O)_2NHS(=O)_2R^{25}$;

en las que

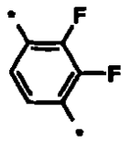
$-R^{25}$ es -H; -alquilo ($C_1$-$C_4$); fenilo; ó $-OR^{18}$, teniendo $R^{18}$ el mismo significado que se definió anteriormente;

ó una sal farmacéuticamente aceptable de éste.

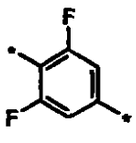
2. Un compuesto según la reivindicación 1, en el que el grupo $G^2$ y los sustituyentes $R^1$ y $R^2$ unidos a éste se seleccionan de tal manera que la parte resultante de un compuesto de fórmula (1.0.0) se representa por las fórmulas parciales (2.5.1) a (2.5.50):



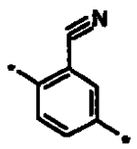
(2.5.1)



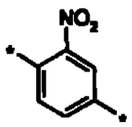
(2.5.2)



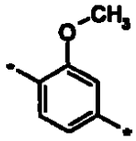
(2.5.3)



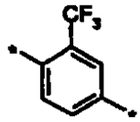
(2.5.4)



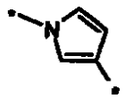
(2 5 5)



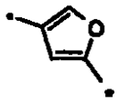
(2 5 6)



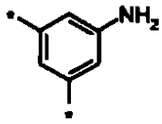
(2 5 7)



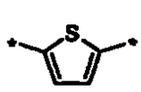
(2 5.8)



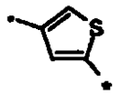
(2.5 9)



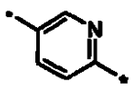
(2.5 10)



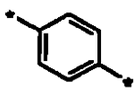
(2 5 11)



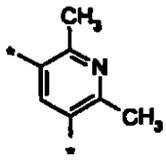
(2 5 12)



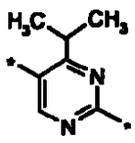
(2 5.13)



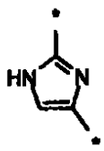
(2 5 14)



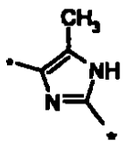
(2 5 15)



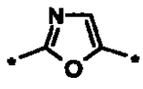
(2 5 16)



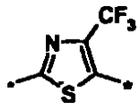
(2 5 17)



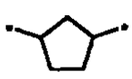
(2 5 18)



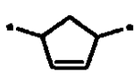
(2 5 19)



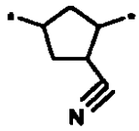
(2 5.20)



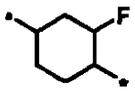
(2 5.21)



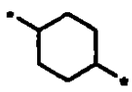
(2 5.22)



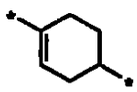
(2 5 23)



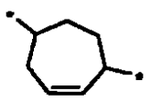
(2 5.24)



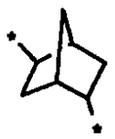
(2 5 25)



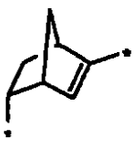
(2 5.26)



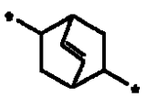
(2 5 27)



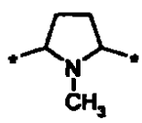
(2 5 28)



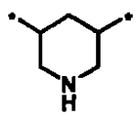
(2 5 29)



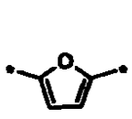
(2 5 30)



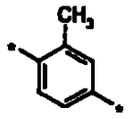
(2 5 31)



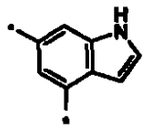
(2 5.32)



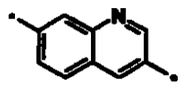
(2.5.33)



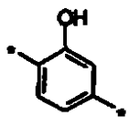
(2.5.34)



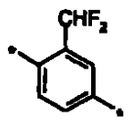
(2 5.35)



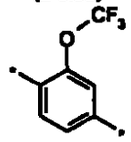
(2.5 36)



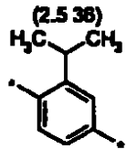
(2 5 37)



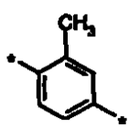
(2 5 38)



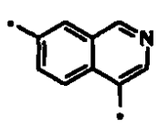
(2 5.39)



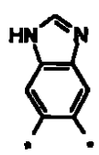
(2 5.40)



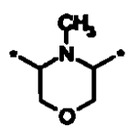
(2 5 41)



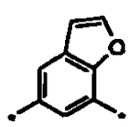
(2 5.42)



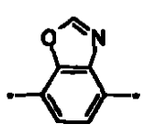
(2 5.43)



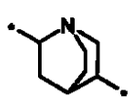
(2 5.44)



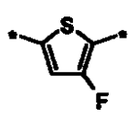
(2 5.45)



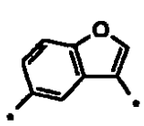
(2 5 46)



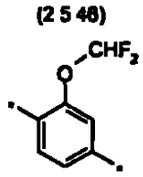
(2 5.47)



(2 5.48)



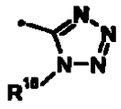
(2 5.49)



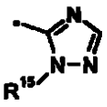
(2.5 50)

5

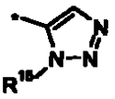
3. Un compuesto según la reivindicación 1, en el que E comprende las fórmulas parciales (1.1.4) y (1.1.10) a (1.1.14), y el significado de $R^7_B$ de la fórmula parcial (1.1.4), en la que v es 0 ó 1, o el significado de $R^7_C$ de las fórmulas parciales (1.1.10) a (1.1.14) se define como un miembro seleccionado del grupo constituido por las fórmulas parciales (1.4.1) a (1.4.32):



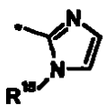
tetrazol-5-ilo
(1 4 1)



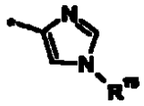
1,2,4-triazol-3-ilo
(1 4.2)



1 2,3-triazol-5-ilo
(1.4 3)

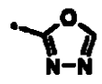


imidazol-2-ilo
(1 4.4)



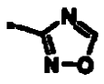
imidazol-4-ilo

(1.4.5)



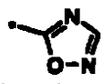
1,3,4-ossadiazolilo

(1.4.6)



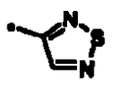
1,2,4-ossadiazol-3-ilo

(1.4.7)



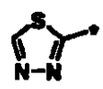
1,2,4-ossadiazol-5-ilo

(1.4.8)



1,2,5-tiadiazol-2-ilo

(1.4.9)



1,3,4-tiadiazolilo

(1.4.10)



ossazolilo

(1.4.11)



isossazolilo

(1.4.12)



tiazolilo

(1.4.13)



isotiazolilo

(1.4.14)



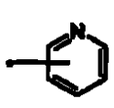
pirrolilo

(1.4.15)



pirazolilo

(1.4.16)



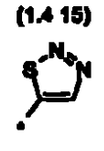
piridilo

(1.4.17)



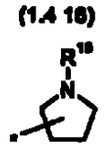
pirazinilo

(1.4.18)



1,2,3-tiadiazol-5-ilo

(1.4.19)



pirrolidinilo

(1.4.20)



furanilo

(1.4.21)



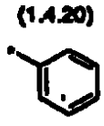
tetraidrofuranilo

(1.4.22)



tienilo

(1.4.23)



fenile

(1.4.24)



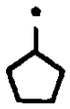
ciclopropilo

(1.4.25)



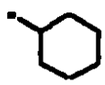
ciclobutilo

(1.4.26)



ciclopentilo

(1.4.27)



cicloesilo

(1.4.28)



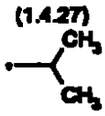
metile

(1.4.29)



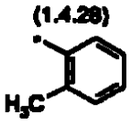
trifluorometile

(1.4.30)



isopropile

(1.4.31)

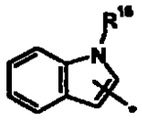


o-tolile

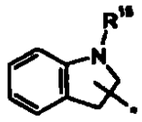
(1.4.32)

en las que "*" indica el punto de unión a la parte restante de fórmula (1.0.0); y en las que cada átomo de carbono está opcionalmente sustituido con un sustituyente $R^{14}$; y en las que $R^{14}$ y $R^{15}$ tienen el mismo significado que el definido en la reivindicación 1; y todas las formas tautoméricas, y opcionalmente formas N-óxido, de éste.

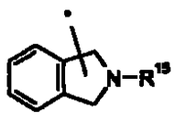
4. Un compuesto según la reivindicación 1, en el que E comprende las fórmulas parciales (1.1.4) y (1.1.9) a (1.1.13), y los significados de $R^7_B$ y $R^7_C$ de las citadas fórmulas parciales son cada uno independientemente un miembro seleccionado del grupo constituido por las fórmulas parciales (1.5.1) a (1.5.29).



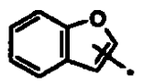
indolilo
(1.5 1)



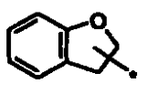
indolinilo
(1 5 2)



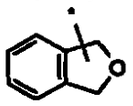
isoindolinilo
(1 5.3)



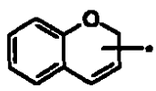
benzo[b]furanilo
(1 5.4)



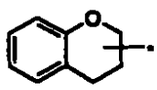
2,3-dihidro-benzofuranilo
(1 5.5)



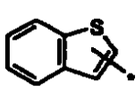
1 3-dihidroisobenzo-furanilo, ftalanilo
(1 5 6)



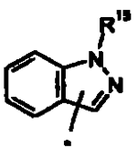
2H-1-benzopiranilo
(1 5 7)



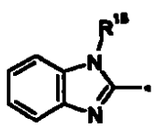
cromanilo
(1.5.8)



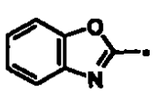
benzotienilo
(1 5 9)



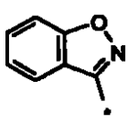
1H-indazolilo
(1 5 10)



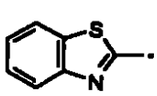
bencimidazolilo
(1 5 11)



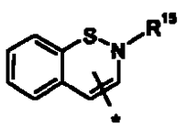
benzoxazolilo
(1.5 12)



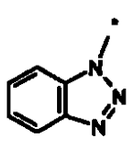
benzoisoxazolilo
(1 5 13)



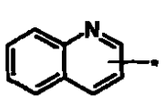
benzotiazolilo
(1 5 14)



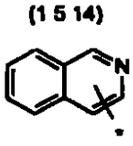
2H-1,2-benzotiazinilo
(1 5 15)



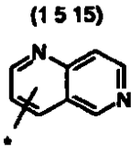
benzotriazolilo
(1 5.16)



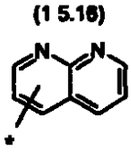
quinolinilo
(1 5 17)



isoquinolinilo
(1 5 18)



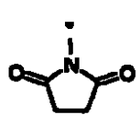
1,6-naftindinilo
(1 5 19)



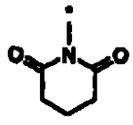
1,8-naftiridinilo
(1 5.20)

en las que "*" indica el punto de unión a la parte restante de fórmula (1.0.0); y en las que cada átomo de carbono está opcionalmente sustituido con un sustituyente $R^{14}$, y en las que $R^{14}$ y $R^{15}$ tienen el mismo significado que el definido en la reivindicación 1; y todas las formas tautoméricas, y opcionalmente formas N-óxido, de éste.

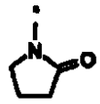
5. Un compuesto según la reivindicación 1, en el que E comprende la fórmula parcial (1.1.15) y es un miembro seleccionado del grupo constituido por las fórmulas parciales (1.7.1) a (1.7.46).



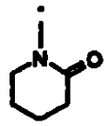
succinimid-1-ilo
(1.7.1)



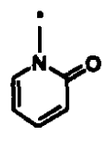
glutarimid-1-ilo
(1.7.2)



pirrolidin-2-on-1-ilo
(1.7.3)

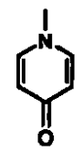


piperid-2-on-1-ilo
(1.7.4)



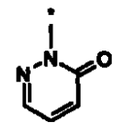
pirid-2-on-1-ilo

(1 7 5)



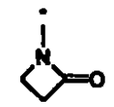
pirid-4-on-1ilo

(1 7 6)



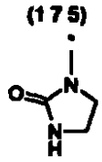
piridazin-3-on-2-ilo

(1 7 7)



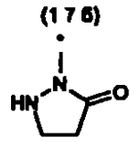
azetidin-2-on-1-ilo

(1 7.8)



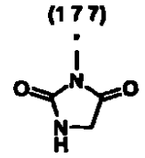
imidazolidin-2-on-1-ilo

(1 7 9)



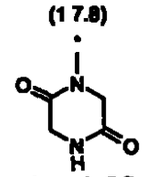
pirazol-5-on-1-ilo

(1 7 10)



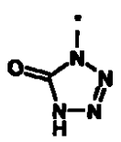
imidazolidin-2,4-dion-1-ilo

(1 7 11)



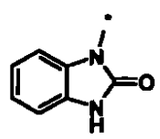
piperazin-2,5-dion-1-ilo

(1 7 12)



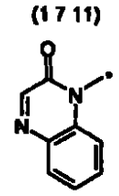
4 5-dihidro-5-oxo-1H-tetrazol-1-ilo

(1 7 13)



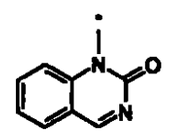
bencimidazolin-2-on-1-ilo

(1 7 14)



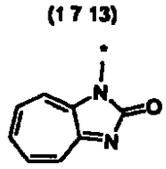
1H-quinoxalin-2-on-1-ilo

(1 7 15)



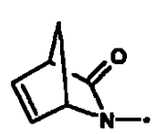
1H-quinozalin-2-on-1-ilo

(1 7 16)



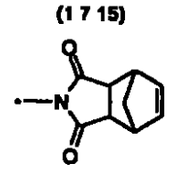
1H-ciclohептimidazol-2-on-1-ilo

(1 7 17)



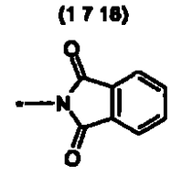
2-azabiciclo[2 2 1]-hept-5-en-3-on-1-ilo

(1 7 18)



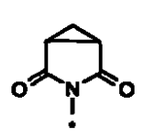
norborn-5-en-2 3-dicarboximid-1-ilo

(1 7 19)



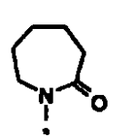
ftalimid-1-ilo 1H-isoindol-1,3(2H)-dion-1-ilo

(1 7 20)



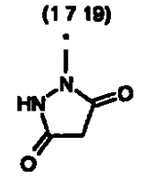
3-azabiciclo[3.1 0]-hexano-2,4-dion-3-ilo

(1 7 21)



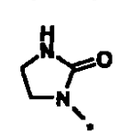
2H-azepin-2-on-1-ilo

(1 7.22)



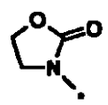
pirazolidin-3,5-dion-1-ilo

(1 7.23)



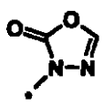
imidazolidin-2-on-1-ilo

(1 7.24)



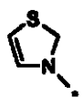
oxazolidin-2-on-1-ile

(1 7.25)



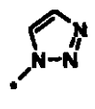
1,3,4-oxadiazol-2(3H)-on-3-ile

(1 7 26)



tiazol-3-ile

(1 7.27)



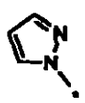
1H-1,2 3-triazol-1-ile

(1 7 28)



imidazol-1-ile

(1 7.29)



pirazol-1-ile

(1 7.30)



1H-1,2,4-triazol-1-ile

(1 7 31)



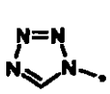
azetidin-1-ile

(1 7.32)



pirrolidin-1-ile

(1 7.33)



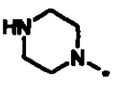
tetrazol-1-ile

(1 7 34)



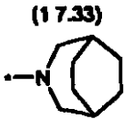
piperidin-1-ile

(1 7 35)



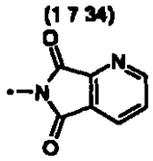
piperazin-1-ile

(1 7 36)



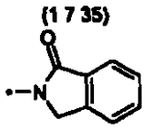
3-azabiciclo[3.2 2]-non-3-ile

(1 7.37)



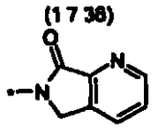
pirrolo[3,4-b]piridin-5,7-dion-6-ile

(1 7.38)



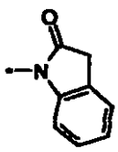
2 3-dihidroisoindol-1-on-2-ile

(1 7 39)



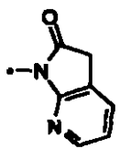
pirrolo[3,4-b]piridin-7-on-6-ile

(1 7.40)



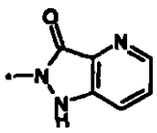
1 3-dihidroindol-2-on-1-ile

(1 7 41)



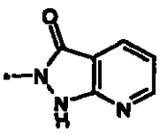
pirrolo[4,5-b]-piridin-3-on-2-ile

(1 7.42)



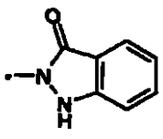
1H-pirazolo[4 5-e] piridin-7-on-2-ile

(1 7 43)



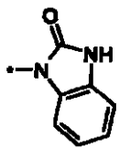
1H-pirazolo[4,5-b] piridin-4-on-2-ile

(1 7.44)



1H-indazol-3-on-2-ile

(1 7 45)

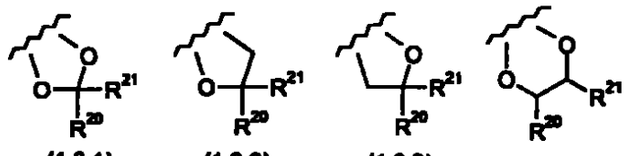


1H-bencimidazol-2-on-3-ile

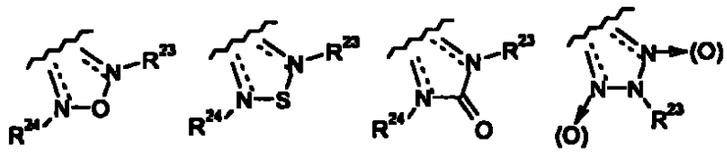
(1 7 46)

en las que "*" indica el punto de unión a la parte restante de fórmula (1.0.0); y en las que cada átomo de carbono está opcionalmente sustituido con un sustituyente $R^{14}$; y en las que cada átomo de nitrógeno está opcionalmente sustituido con un sustituyente $R^{15}$; y en las que $R^{14}$ y $R^{15}$ tienen el mismo significado que el definido en la reivindicación 1; y todas las formas tautoméricas, y opcionalmente formas N-óxido, de éste.

6. Un compuesto según la reivindicación 1, en el que m es 1; n es 1; $W^1$ es -O-, $W^2$ está ausente; Y es $=C(R^1_a)-$; $R^1_a$ es -H, -F, -Cl, $-CH_3$, $-CF_3$ ó $-OCH_3$; $R^A$ y $R_B$ son independientemente -H ó $-CH_3$; ó $R^A$ y $R^B$ se toman conjuntamente para formar un resto -cicloalquilespiro ($C_3$-$C_7$), $R^C$ y $R^D$ son ambos -H; y $R^5$ y $R^6$ se toman conjuntamente para formar un resto seleccionado del grupo constituido por las fórmulas parciales (1.3.1) a (1.3.4), (1.3.11), (1.3.12), (1.3.14) y (1.3.15):



(1.3.1) (1.3.2) (1.3.3) (1.3.4)



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

en las que $R^{20}$ y $R^{21}$ son cada uno independientemente -H; -F; $-CH_3$ ó $-OCH_3$; y $R^{23}$ y $R^{24}$ son cada uno independientemente -H; $-CH_3$; $-OCH_3$; o están ausentes, en cuyo caso la línea de trazos --- representa un doble enlace.

7. Un compuesto según la reivindicación 1, siendo el citado compuesto un miembro seleccionado del grupo constituido por los siguientes:

4-(1-Hidroxi-1-metiletil)bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.1),

2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.2.),

4-(1-Hidroxiciclobutil)bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.3),

4-(1-Hidroxi-1-metiletil)bencilamida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.4),

2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.5);

[4-(1-Hidroxi-1-metiletil)ciclohexilmetil]amida del ácido *trans*-4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.6);

[4-(1-Hidroxietil)ciclohexilmetil]amida del ácido *trans*-4-

(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.7);

2-Fluoro-4-(1-hidroxi-1-metiletil)bencilamida del ácido 4-(piridin-3-iloxi)tiazol-5-carboxílico de fórmula (8.5.8);

Acido 4-({[4-(4-fluorofen-4-iloxi)[1,3]tiazol-5-carbonil]amino}metil)benzoico de fórmula (8.5.9);

Acido 4-{[(4-benzo[1,3]dioxol-5-iloxi)[1,3]tiazol-5-carbonil]amino]metil}benzoico de fórmula (8.5.10);

Acido 4-({[4-(benzo[1,3]dioxol-5-iloxi)[1,3]tiazol-5-carbonil]amino}metil)-3-fluorobenzoico de fórmula (8.5.11);

Acido [4-({[4-(benzo[2,1,3]tiadiazol-5-iloxi)[1,3]-tiazol-5-carbonil]amino}metil)fen-4-iloxi]acético de fórmula (8.5.12);

Acido [4-({[4-(benzo[2,1,3]oxadiazol-5-iloxi)[1,3]-tiazol-5-carbonil]amino}metil)fenil-4-iloxi]acético de fórmula (8.5.13);

Acido (±)-2-[4-({[4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)-3-fluorofenoxi]propiónico de fórmula (8.5.14),

Acido (±)-2-[4-({[4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)ciclohexiloxi]propiónico de fórmula (8.5.15);

2-Fluoro-4-(piridin-2-ilmetoxi)bencilamida del ácido 4-(3-metoxifenoxi)tiazol-5-carboxílico de fórmula (8.5.16);

2-Fluoro-4-[1-(1H-tetrazol-5-il)etoxi]bencilamida del ácido (±)-4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de

fórmula (8.5.17);

4-(1-Carbamoiletoxi)-2-fluorobencilamida del ácido (±)-4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.18);

Acido (±)-2-[3-fluoro-4-({[4-(3-nitrofenoxi)tiazol-5-carbonil]amino}metil)fenoxi]propiónico de fórmula (8.5.19);

4-[1-(5-Metil-4H-[1,2,4]triazol-3-il)etoxi]bencilamida del ácido (±)-4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.20;

Acido [4-({[4-(3-cianofenoxi)tiazol-5-carbonil]amino}-metil)-3-fluorofenil]acético de fórmula (8.5.21);

Acido 2-[4-({[4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)-3-fluorofenil]-2-metilpropiónico de fórmula (8.5.22);

4-Carbamoilmetil-2-fluorobencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.23),

4-[1-Metil-1-(1H-tetrazol-5-il)etil]bencilamida del ácido 4-(3-metoxifenoxi)tiazol-5-carboxílico de fórmula (8.5.24);

4-[(2-Cianobenzoilamino)metil]bencilamida del ácido 4-(3-nitrofenoxi)tiazol-5-carboxílico de fórmula (8.5.25);

4-({[4-(Benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]-amino}metil)-3-fluorobencilamida del ácido piridin-2-carboxílico de fórmula (8.5.26);

3-Fluoro-4-({[4-(3-metoxifenoxi)tiazol-5-carbonil]-amino}metil)bencilamida del ácido 4H-[1,2,4]triazol-3-carboxílico de fórmula (8.5.27);

2-Fluoro-4-[(2-metoxibenzoilamino)metil]bencilamida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.28);

4-{[(3H-Imidazol-4-carbonil)amino]metil}bencilamida del ácido 4-(4-fluorofenoxi)tiazol-5-carboxílico de fórmula (8.5.29);

4-(1,3-Dioxo-1,3-dihidroisoindol-2-ilmetil)-2-fluoro-bencilamida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.30);

Acido (±)-2-[4-({[4-(benzo[2,1,3]tiadiazol-5-iloxi)-tiazol-5-carbonil]amino}metil)fenoxi]propiónico de fórmula (8.5.31);

Acido 4'-({[4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)-3'-fluorobifenil-3-carboxílico de fórmula (8.5.32),

Acido 4'-({[4-(3-cianofenoxi)tiazol-5-carbonil]amino}-metil)-3'-fluorobifenil-4-carboxílico de fórmula (8.5.33);

Acido (±)-2-[4'-({[4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil)-2-fluorobifenil-4-iloxi]propiónico de fórmula (8.5.34);

Acido [2-fluoro-4'-({[4-(4-fluorofenoxi)tiazol-5-carbonil]amino}metil)bifenil-4-il]acético de fórmula (8.5.35);

Acido 2-[3'-fluoro-4'-({[4-(3-metoxifenoxi)tiazol-5-carbonil]amino}metil)bifenil-4-il]-2-metilpropiónico de fórmula (8.5.36);

{3,2'-Difluoro-4'-[1-(1H-tetrazol-5-il)etoxi]bifenil-4-

ilmetil}amida del ácido (±)-4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.37);

{4'-[(2-Cianobenzoilamino)metil]-3-fluorobifenil-4-ilmetil}amida del ácido 4-(4-fluorofenoxi)tiazol-5-carboxílico de fórmula (8.5.38);

[4'-({[4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carbonil]amino}metil-3'-fluorobifenil-4-ilmeil]amida del ácido piridin-2-carboxílico de fórmula (8.5.39);

[4'-(1,3-Dioxo-1,3-dihidroisoindol-2-ilmetil)-2'-fluorobifenil-4-ilmetil]amida del ácido 4-(4-fluorofenoxi)-tiazol-5-carboxílico de fórmula (8.5.40);

{3-Fluoro-4'-[(2-metoxibenzoilamino)metil]bifenil-4-ilmetil}amida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.41),

{2'-Fluoro-4'-[1-metil-1-(1H-tetrazol-5-il)etil]-bifenil-4-ilmetil}amida del ácido 4-(3-cianofenoxi)tiazol-5-carboxílico de fórmula (8.5.42);

(4'-Carbamoilmetil-3-fluorobifenil-4-ilmetil)amida del ácido 4-(3-cloro-4-fluorofenoxi)tiazol-5-carboxílico de fórmula (8.5.43); y

(3-Fluoro-4'-{[(3H-imidazol-4-carbonil)amino]metil}-bifenil-4-ilmetil)amida del ácido 4-(benzo[1,3]dioxol-5-iloxi)tiazol-5-carboxílico de fórmula (8.5.44).

8. Una composición farmacéutica para uso en el

tratamiento de un sujeto que sufre una enfermedad, trastorno o afección mediada por la isozima PDE4, incluyendo el subtipo D de ésta, con la cual se regula la activación y desgranulación de eosinófilos, que comprende una cantidad terapéuticamente eficaz de un compuesto de fórmula (1.0.0) como se definió en la reivindicación 1, junto con un vehículo farmacéuticamente aceptable para éste.

9. Un procedimiento de tratamiento de un sujeto que sufre una enfermedad, trastorno o afección mediada por la isozima PDE4, incluyendo el subtipo D de ésta, con la cual se regula la activación y desgranulación de eosinófilos, que comprende administrar al citado sujeto necesitado de dicho tratamiento una cantidad terapéuticamente eficaz de un compuesto de fórmula (1.0.0) como se definió en la reivindicación 1, caracterizado porque la citada 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 selecionado del grupo constituido por asma atópica; asma no atópica; asma alérgica; asma mediada por IgE bronquial atópica; asma bronquial, asma esencial; asma verdadera; asma intrínseca causada por perturbaciones patofisiológicas; asma extrínseca causada por factores

medioambientales; asma esencial de causa desconocida o no evidente; asma no atópica; asma bronquítica; asma enfisematosa; asma inducida por ejercicio, asma ocupacional; asma infecciosa causada por infección bacteriana, fúngica, protozooaria o viral; asma no alérgica; asma incipiente; síndrome de jadeos en infantes;

- broncoconstricción crónica o aguda; bronquitis crónica; obstrucción de las vías aéreas pequeñas; y enfisema;

- enfermedades obstructivas o inflamatorias de las vías aéreas de cualquier tipo, etiología o patogénesis; o una enfermedad inflamatoria u obstructiva de las vías aéreas que es un miembro seleccionado del grupo constituido por asma; neumoconiosis; neumonía eosinófila crónica; enfermedad pulmonar obstructiva crónica (EPOC), EPOC que incluye bronquitis crónica, enfisema pulmonar o disnea asociadas con ésta; EPOC que se caracteriza por una obstrucción irreversible progresiva de las vías aéreas; síndrome del distrés respiratorio en adultos (SDRA) y exacerbación de la hiperreactividad de las vías aéreas posterior a otra terapia de fármacos;

- neumoconiosis de cualquier tipo, etiología o patogénesis; o neumoconiosis que es un miembro seleccionado del grupo constituido por aluminosis o enfermedad de los

trabajadores con bauxita; antracosis o asma de los mineros; asbestosis o asma de los montadores de calderas; calicosis o enfermedad del sílex; ptilosis causada por la inhalación de polvo de plumas de avestruz; siderosis causada por la inhalación de partículas de hierro; silicosis o enfermedad de los molineros; bisinosis o asma de polvo de algodón y neumoconiosis de 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 de crup; bronquitis seca; bronquitis asmática infecciosa; bronquitis productiva; bronquitis por estafilococo o estreptococo; y bronquítis vesicular;

- bronquiectasis de cualquier tipo, etiología o patogénesis; o bronquiectasis que es un miembro seleccionado del grupo constituido por bronquiectasis cilíndrica; bronquiectasis de sáculos; bronquiectasis fusiforme; bronquiectasis capilar; bronquiectasis quística; bronquiectasis seca; y bronquiectasis 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 etmoidea, frontal, maxilar o esfenoide;

- 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 psoriática y artritis vertebral:

- gota, y fiebre y dolor asociados con inflamación,

- un trastorno relacionado con eosinófilos de cualquier tipo, etiología o patogénesis; o un trastorno relacionado con eosinófilos que es un miembro seleccionado del grupo constituido por eosinofilia, eosinofilia de 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 nodular (PAN), y vasculitis necrotizante 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 mediada por sistema inmune; urticaria mediada por complemento; urticaria inducida por material urticariogénico; urticaria inducida por un agente físico; urticaria inducida por el estrés; urticaria idiopática; urticaria aguda; urticaria crónica; angioedema; urticaria colinérgica; urticaria por el frío en la forma autosómica dominante o en la forma adquirida; urticaria de contacto, urticaria gigante; 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, conjuntitivitis contagiosa aguda; conjuntivitis alérgica; conjuntivitis atópica, conjuntivitis catarral crónica; conjuntivitis purulenta; y conjuntitivitis primaveral:

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

- psoriasis;

- 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 de remisión recurrente;

- enfermedades autoinmunes/inflamatorias de cualquier tipo, etiología o patogénesis; o una enfermedad autoinmune/ inflamatoria que es un miembro seleccionado del grupo constituido por trastornos hematológicos autoinmunes; anemia hemolítica; anemia aplásica; anemia pura de glóbulos rojos, púrpura trombocitopénica idiopática, lupus sistémico eritematoso; policondritis, escleroderma; granulomatosis de Wegner; dermatomiositis; hepatitis activa crónica; miastenia grave; síndrome de Stevens-Johnson; esprúe idiopático; enfermedad inflamatoria intestinal autoinmune; colitis ulcerosa, enfermedad de Crohn; oftamopatía endocrina; enfermedad de Grave; sarcoidosis, alveolitis; neumonitis de hipersensibilidad crónica; cirrosis biliar primaria; diabetes juvenil o diabetes mellitus tipo I; uveitis anterior; uveitis granulomatosa o posterior; queratoconjuntivitis seca, queratoconjuntivitis epidérmica; fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial; fibrosis pulmonar idiopática; fibrosis

quística; artritis psoriática; glomerulonefritis; con y sin síndrome nefrótico; glomerulonefritis aguda; síndrome nefrótico idiopático; nefropatía con cambios mínimos; enfermedades dérmicas inflamatorias/hiperproliferativas, psoriasis; dermatitis atópica; dermatitis de contacto; dermatitis de contacto alérgico; pénfigo familiar benigno; pénfigo eritematoso; pénfigo foliáceo y pénfigo vulgar;

- prevención de rechazo de injertos alogénicos después de un trasplante de órganos;

- enfermedad inflamatoria del intestino (EII) de cualquier tipo, etiología o patogénesis; o enfermedad inflamatoria del intestino que es un miembro del grupo constituido por colitis ulcerosa (CU), colitis colágena; colitis poliposa; colitis transmural; y enfermedad de Crohn (EC);

- 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 de 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 la inmunodeficiencia humana (VIH):

- daño hepático;

- 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 de aprendizaje y memoria; discinesia tardía, dependencia de drogas; demencia arteriosclerótica y demencias que acompañan a la corea de Huntigton, enfermedad de Wilson, parálisis agitante y atrofias talámicas;

- infección, especialmente infección por virus en la que dichos virus aumentan la producción de TNF-α en su huésped, o en la que dichos virus son sensibles a la sobrerregulación de TNF-α en su huésped de modo que su replicación u otras actividades vitales se ven afectadas adversamente, incluyendo un virus que es un miembro seleccionado del grupo constituido por VIH-1, VIH-2 y VIH-3; citomegalovirus, CMV; gripe; adenovirus; y

herpesvirus, incluyendo *Herpes zoster* y *Herpes simplex*;

- infecciones por levaduras y hongos en las que las citadas levaduras y hongos son sensibles a la sobrerregulación por TNF-α o desencadenan la producción de TNF-α en su huésped, cuando se administra en combinación con otros fármacos de elección para el tratamiento de infecciones sistémicas por levaduras y hongos, incluyendo pero sin limitación, polimixinas, polimicina B; imidazoles, clotrimazol, econazol, miconazol y cetoconazol; triazoles, fluconazol e itranazol; y anfotericinas, anfotericina B y anfotericina B liposómica; y

- daños de reperfusión por isquemia; diabetes autoinmune; autoinmunidad retinal; leucemia linfocítica crónica; infecciones por VIH; lupus eritematoso; enfermedades renales y de uréter; trastornos urogenitales y gastrointestinales; y enfermedades de próstata.

10. La combinación de un compuesto de fórmula (1.0.0) como se definió 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-lipooxigenasa (5-LO) y antagonistas de proteína activadora de 5-lipooxigenasa (FLAP) seleccionados del

grupo constituido por zileutón; ABT-761; fenleutón; tepoxalina; Abbot-79175; Abbott-85761; N-tiofen-2-alquilsulfonamidas sustituidas en 5 de fórmula (5.2.8); 2,6-diterc-butilfenolhidrazonas de fórmula (5.2.10); la clase de metoxitetrahidro-piranos que incluye ZD-2138 de Zeneca 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 sustituidos con piridinilo 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 las que pertenecen MK-591, MK-886 y BAY x 1005.

(b) Antagonistas de receptor de leucotrienos $LTB_4$, $LTC_4$, $LTD_4$ y $LTE_4$ seleccionados del grupo constituido por la clase fenotiazin-3-ona de compuestos 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 el ontazolast; la clase de bencenocarboximidamidas a la que pertenece BIIL 284/260; y las clases de compuestos a las que pertenecen 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-lipooxigenasa (5-LO); ó antagonistas de la proteína activadora de 5-lipooxigenasa (FLAP);

(e) inhibidores duales de 5-lipooxigenasa (5-LO) y antagonistas del factor de activación de plaquetas (PAF);

(f) antagonistas de leucotrieno (LTRA), incluyendo antagonistas de $LTB_4$, $LTC_4$, $LTD_4$ y $LTE_4$;

(g) antagonistas de receptor $H_1$ antihistamínico, incluyendo cetirizina, loratadina, desloratadina, fexofenadina, astemizol, azelastina y clofeniramina;

(h) antagonistas de receptor $H_2$ gastroprotectores;

(i) agentes agonistas $\alpha_1$- y $\alpha_2$-adrenoceptores simpaticomiméticos vasoconstrictores administrados oral o tópicamente para uso decongestivo, incluyendo propilhexedrina, fenilefrina, fenilpropanolamina, seudoefedrina, clorhidrato de nafazolina, clorhidrato de oximetazolina, clorhidrato de tetrahidrozolina, clorhidrato de xilometazolina, y clorhidrato de etilnorepinefrina;

(j) agonistas $\alpha_1$- y $\alpha_2$-adrenoceptores en combinación con inhibidores de 5-lipooxigenasa (5-LO);

(k) agentes anticolinérgicos, incluyendo bromuro de ipratropio;

(l) agonistas $\beta_1$- a $\beta_4$-adrenoceptores, incluyendo isoprenalina, albuterol, salbutamol, formoterol, salmeterol, terbutalina, orciprenalina, mesilato de bitolterol y pirbuterol;

(m) teofilina y aminofilina;

(n) cromoglicato de sodio;

(o) antagonistas de receptor muscarínico (M1, M2 y M3);

(p) inhibidores de COX-1 (AINE); inhibidores selectivos de COX-2, incluyendo rofecoxib; y AINE de óxido nítrico;

(q) miméticos de factor del crecimiento similar a insulina de tipo I (IGF-1);

(r) ciclesonida;

(s) glucocorticoides inhalados con efectos secundarios sistémicos

reducidos, incluyendo flunisolida, acetónido de triamcinolona, dipropionato de beclometasona, budesonida, propionato de fluticasona y furoato de mometasona;

(t) inhibidores de triptasa;

(u) antagonistas de factor activador de plaquetas (PAF);

(v) anticuerpos monoclonales frente a entidades inflamatorias endógenas;

(w) IPL 576;

(x) agentes anti-factor de necrosis tumoral (TNFα), incluyendo etanercept, infliximab y D2E7,

(y) DMARD, incluyendo leflunomida;

(z) péptidos TCR,

(aa) inhibidores de la enzima conversora de interleuquina (ICE),

(bb) inhibidores de IMPDH,

(cc) inhubidores de moléculas de adhesión, incluyendo

antagonistas de VLA-4;

(dd) catepsinas,

(ee) inhibidores de MAP quinasa,

(ff) inhibidores de glucosa-6-fosfato deshidrogenasa;

(gg) antagonistas de receptor de cinina $B_1$ y $B_2$;

(hh) oro en forma de un grupo aurotio junto con diversos grupos hidrófilos;

(ii) agentes inmunosupresores, por ejemplo, ciclosporina, azatioprina y metotrexato;

(jj) agentes anti-gota, por ejemplo, colchicina;

(kk) inhibidores de xantina oxidasa, por ejemplo alopurinol;

(ll) agentes uricosúricos, por ejemplo, probenecida, 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 metaloproteinasas de matriz (MMP), es decir, estromelisinas, colagenasas y gelatinasas, así como agrecanasa, especialmente colagenasa-1 (MMP-1), colagenasa-2 (MMP-8), colagenasa-3 (MMP-13); estromelisina-1 (MMP-3); estromelisina-2 (MMP-10) y estromelisina-3 (MMP-11);

(pp) factor del crecimiento transformante (TGFβ);

(qq) factor del crecimiento derivado de plaquetas (PDGF);

(rr) factor del crecimiento de fibroblastos, por ejemplo, factor del crecimiento de fibroblastos básicos (bFGF);

(ss) factor estimulante de colonia de macrófagos granulocitos (GM-CSF);

(tt) crema de capsaicina;

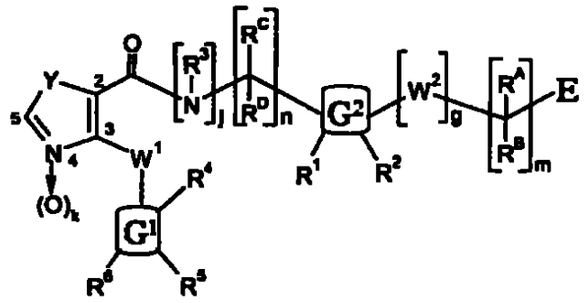
(uu) agentes anti-eméticos, incluyendo antagonistas de receptor NK-1 y D-4418; y

(vv) antidepresivos.

# DERIVADOS AMIDA DE ACIDO TIAZOLILICO, OXAZOLILICO, PIRROLILICO E IMIDAZOLILICO UTILES COMO INHIBIDORES DE LAS ISOZIMAS PDE4

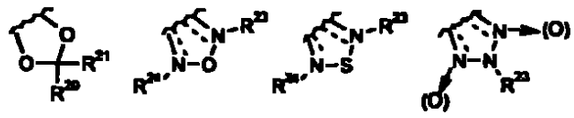
## Resumen de la Invención

Compuestos útiles como inhibidores de PDE4 en el tratamiento de enfermedades reguladas por la activación y la desgranulación de eosinófilos, especialmente asma, bronquitis crónica y enfermedad pulmonar obstructiva crónica, de fórmula:



en la que j es 0 ó 1, con la condición de que cuando j es 0, n debe ser 2; k es 0 ó 1; m es 0, 1, 2 ó 3; n es 1 ó 2; $W^1$ es -O-; ó $-S(=O)_t-$, siendo t 0, 1 ó 2; ó $-N(R^3)-$; $W^2$ es $-O-CR^AR^B-$ ó está ausente; Y es $=C(R^1{}_a)-$ ó $-[N->(O)_k]-$, siendo k 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 $R^{10}$, ó $R^A$ y $R^B$ se toman conjuntamente, pero sólo en el caso en que m sea 1, para formar un resto espiro; $R^C$ y $R^D$ tienen el mismo significado que $R^A$ y $R^B$, excepto que uno de ellos debe ser -H, $R^1$ y $R^2$ son -H;

-F; -Cl; -CN; -$NO_2$; -alquilo ($C_1$-$C_4$); -alquinilo ($C_2$-$C_4$); -alquilo ($C_1$-$C_3$) fluorado; -$OR^{16}$; y -$C(=O)NR^{22}{}_aR^{22}{}_b$; $R^3$ es -H; -alquilo ($C_1$-$C_3$); fenilo; bencilo; ó -$OR^{16}$; $R^4$, $R^5$ y $R^6$, además de otros significados, pueden tomarse conjuntamente para formar, por ejemplo

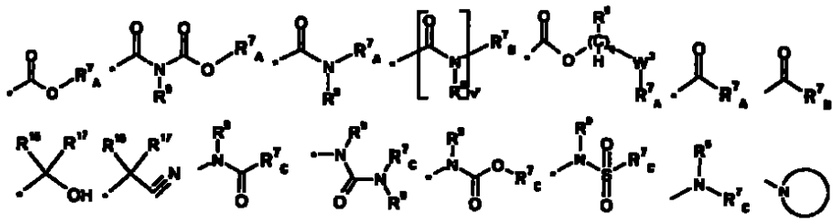


$G^1$ es un sistema carbocíclico saturado o insaturado monocíclico de 3 a 7 miembros, o policíclico condensado de 7 a 12 miembros; con la condición de que $G^1$ no es un resto biarilo discontinuo o limitado como se define en $G^2$; pudiendo estar opcionalmente reemplazado un átomo de carbono por un heteroátomo seleccionado de N, O y S; pudiendo estar reemplazado opcionalmente un segundo átomo de carbono de éste, y opcionalmente además un tercer átomo de carbono de éste, por N; -$G^2$ es un sistema carbocíclico saturado o insaturado monocíclico de 3 a 7 miembros, o policíclico condensado de 7 a 12 miembros; o es un resto biarilo discontinuo o limitado de 7 a 18 miembros; pudiendo estar opcionalmente reemplazado, para cada uno de los sistemas carbocíclicos enumerados, un átomo de carbono del citado sistema carbocíclico por un heteroátomo seleccionado de N, O y S, pudiendo estar opcionalmente reemplazado un segundo átomo de carbono del mismo, y opcionalmente un tercer átomo de carbono del mismo, por N; y E se selecciona de.

600 A

~~00604~~





PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| PC11894ARMS | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/IB 01/02728 | 24/12/2001 | 31/01/2001 |
| International Patent Classification (IPC) or national classification and IPC | | |
| C07D417/12 | | |
| Applicant | | |
| PFIZER PRODUCTS INC. et al. | | |

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

2 This REPORT consists of a total of 2 sheets, including this cover sheet.

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

These annexes consists of a total of _____ sheets.

3 This report contains indications relating to the following items:

I ☒ Basis of the report

II ☐ Priority

III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

IV ☐ Lack of unity of invention

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

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 18/03/2002 | 05/09/2002 |
| Name and mailing address of the IPEA/ | Authorized officer |
| European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0, Tx. 523656 epmu d<br>Fax: (+49-89) 2399-4465 | BARTHL-WAGNER J C R<br><br>Tel. (+49-89) 2399 2828 |

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

## I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

## V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i e it appears to be novel, to involve an inventive step and to be industrially applicable

# INTERNATI NAL SEARCH REP RT

Int ernal Application No PCT/IB 01/02728 603

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61P11/06 A61P29/00 C07D277/56 A61K31/427

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,A | 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,A | WO 01 57025 A (CHAMBERS ROBERT JAMES ,MAGEE THOMAS VICTOR (US); MARFAT ANTHONY (U) 9 August 2001 (2001-08-09) claim 1 | 1-10 |
| A | GB 2 327 675 A (EISAI CO LTD) 3 February 1999 (1999-02-03) claims 1,5 | 1-10 |
| A | WO 98 45628 A (NEVREKAR VENKATESH R) 15 October 1998 (1998-10-15) cited in the application claim 1 | 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 | 06/06/2002 |

| 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. |
|---|---|---|
| A | VINICK F J ET AL: "NICOTINAMIDE ETHERS: NOVEL INHIBITORS OF CALCIUM-INDEPENDENT PHOSPHODIESTERASE AND [3H]ROLIPRAM 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 |
| A | 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

Int nal Application No
PCT/IB 01/02728 604

| 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 | |

605

CD611

# REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

| | USUARIO | RADICADOR |
|---|---|---|
| PATENTE DE INVENCIÓN X MODELO DE UTILIDAD | ( ) | ( ) |
| - Indicación de que se solicita la concesión de una patente | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que se presenta la solicitud | ( ) | ( ) |
| - Descripcion de la invención | ( ) | ( ) |
| - Dibujos de ser estos pertinentes | ( ) | ( ) |
| - Comprobante de Pago de las tasas establecidas | | |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |
| DISEÑO INDUSTRIAL ( ) | | |
| - Indicación de que se solicita el registro de Diseño Industrial | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta | ( ) | ( ) |
| - la solicitud | | |
| - Representación grafica y fotografica del Diseño Industrial o muestra del Material que incorpora el diseño | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |
| ESQUEMA DE TRAZADO ( ) | | |
| - Indicacion de que solicita el registro de un Esquema de trazado | ( ) | ( ) |
| - Datos de identificación del solicitante o de la persona que presenta La solicitud | ( ) | ( ) |
| Representación grafica del esquema de trazado | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| COMPLETA ( ) INCOMPLETA | ( ) | ( ) |

Firma Responsable

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03065412 00000000 Folios: 432

Fecha Fecha (AMD): 2003-07-31 16:54:27

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

606

Folio 842

2020
Bogotá DC

Doctor(a)
CARLOS R. OLARTE
Apoderado(a)
PFIZER PRODUCTS INC.

| | | |
|---|---|---|
| **REFERENCIA:** | Radicación No. | 03 65412 |
| | Solicitud Internacional | PCT/IB2001/02728 |
| | Fecha inicio fase nacional | 31/08/2003 |
| | Trámite | 011 |
| | Evento | 379 |
| | Actuación | 416 |
| | Oficio No | 1335 |
| | Folios | 001 |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

**Cúmplase**
Dado en Bogotá DC, 31 OCT. 2003

**ALIX CARMENZA CÉSPEDES DE VERGEL**
Jefe de la División de Nuevas Creaciones

202057