# Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

# PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 04-78332

54 **TÍTULO** Derivados de Nicotinamida útiles como inhibidores de PDE 4

51 **CLASIFICACIÓN INTERNACIONAL** A61K31/455

71 **SOLICITANTE** Pfizer Inc

**DOMICILIO** 235 East 42nd Street, New York, NY 10017 EUA

74 **APODERADO** Carlos Zolorio

22 **BOGOTÁ, D. C.,** Agosto 11 2004

(FORMA P-10)

04/101

# OLARTE RAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04078322 0000000 Folios: 435
Fecha (AMD): 2004-08-11 17:01:05
Tramite : 011 PCT-PATENT. 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL**

**SOLICITUD DE:**

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

**Nombre:** PFIZER INC
**Dirección:** 235 East 42nd Street, New York, NY 10017 E.U.A.
**Nacionalidad o Domicilio:** ESTADOUNIDENSE
**Lugar de Constitución:** Delaware, Estados Unidos de América.
**Teléfono:** _____ **Fax:** _____
**E-mail:** _____

**IDENTIFICACIÓN**
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

**REPRESENTANTE O APODERADO**

**Nombre:** CARLOS R. OLARTE
**Dirección:** Wold Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
**Teléfono:** 601-7700 **Fax:** 601-7799
**E-mail:** office@olarteraisbeck.com

**IDENTIFICACIÓN**
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79782747Bta
TP 74.295

**INVENTOR (ES) (72)**

**Nombre:** VER PAGINA ADJUNTA.
**Dirección:** VER PAGINA ADJUNTA
**Nacionalidad o Domicilio:** VER PAGINA ADJUNTA

(3) **PCT (86)**

Solicitud Internacional No. PCT/IB03/00439 Fecha Febrero 3, 2003

Publicación Internacional No. WO 03/068235 Fecha Agosto 21, 2003

(6) **Título (54)** DERIVADOS DE NICOTINAMIDA UTILES COMO INHIBIDORES DE PDE4.

**Clasificación Internacional (51)** A61K31/455

| Prioridad | (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|---|
| SI [X] N [ ] | GB | Febrero 11, 2002 | 0203196.1 |
| | GB | Septiembre 10,2002 | 0220999.7 |
| | GB | Octubre 21, 2002 | 0224453.1 |
| | GB | Noviembre 20, 2002 | 0227139.3 |

(9) **Comprobante de pago No.** 60,567 **Fecha** Agosto 3, 2004

**(0) 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. Ver expediente No.04.025.929
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

**(1) FIGURA CARACTERÍSTICA:**

**(2)** Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES

1. SIMON BAILEY
10770 Science Center Driva,
La Jolla, California 92121,
Estados Unidos de América
Nacionalidad: Británica

2. ELISABETH COLETTE LOUISE GAUTIER
Ramsgate Road,
Sandwich, Kent, CT13 9NJ
Reino Unido
Nacionalidad: Francesa

3. ALAN JOHN HENDERSON
Ramsgate Road,
Sandwich, Kent, CT13 9NJ
Reino Unido
Nacionalidad: Británica

4. THOMAS VICTOR MAGEE
Eastern Point Road,
Groton, Connecticut 06340,
Estados Unidos de América
Nacionalidad: Estadounidense

5. ANTHONY MARFAT
Eastern Point Road,
Groton, Connecticut 06340,
Estados Unidos de América
Nacionalidad: Estadounidense

6. JOHN PAUL MATHIAS
Ramsgate Road,
Sandwich, Kent, CT13 9NJ
Reino Unido
Nacionalidad: Británica

7. DALE GORDON MCLEOD
Eastern Point Road,
Groton, Connecticut 06340,
Estados Unidos de América
Nacionalidad: Canada

8. SANDRA MARINA MONAGHAN
Ramsgate Road,
Sandwich, Kent, CT13 9NJ
Reino Unido
Nacionalidad: Británica

9. BLANDA LUZIA CHRISTA STAMMEN
Ramsgate Road,
Sandwich, Kent, CT13 9NJ
Reino Unido
Nacionalidad: Alemana

1

NIT : 900176089-2

SUPERINTENDENCIA Y COMERCIO
Radicacion : 04070332
Fecha (AMD): 2004-08-11 17:01:05
Tramite : 011 PCT-PATENT 379 FARE MACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

Folios: 435

RECIBO OFICIAL DE CAJA : 04 - 60,357
FECHA : AGOSTO 3 DE 2004

##### C O N S I G N A C I O N #####

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| FREDERICK TORRES | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 23290408 | 02/08/2004 | 4,607,000.00 |

##### C O N C E P T O #####

| CANT. | REMTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 422,000.00 |
| | | TOTAL : $ | 422,000.00 |

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

S

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# CESION

Por contraprestación valiosa pagada a nosotros por PFIZER INC, sociedad constituida en virtud de las leyes del Estado de Delaware, Estados Unidos de América, cuya dirección postal completa es 235 East 42nd Street, NewYork, New Cork 10017, Estados Unidos de América, por el presente vendemos y traspasamos a la citada PFIZER INC, todo nuestro derecho, titulo e interés en y sobre nuestro invento de una nueva y útil mejora en DERIVADOS DE NICOTINAMIDA UTILES COMO INHIBIDORES DE PDE4, en cuanto respecta a la República de Colombia, tal como se indica y describe plenamente en la especificación y por el presente autorizamos y solicitamos al Comisionado de Patentes de Colombia expedir dicha patente a nombre de la citada PFIZER INC, de conformidad con esta Cesión.

En fe de lo cual, firmamos de nuestro puño y letra,

PFIZER LIMITED

30 de enero de 2003 (Fdo) Keith S. Ruddock .
Sándwich, Kent, England - Keith S. Ruddock Abogado Autorizado

Certificado, verificado y autenticado
En la ciudad de Egham en Surrey

A los 13 días del mes de julio de 2004

(Fdo) Kenneth Greenwood

KENNETH GREENWOOD
NOTARIO PUBLICO
HORNE ENGALL AND FREEMAN

(Adherido, sello notarial)

6

# APOSTILLA

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

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

   Este es documento público

2. Ha sido firmado por **K. Greenwood**

3. Actuando en calidad de **Notario Público**

4. Lleva el sello/estampilla de **El antedicho Notario Público**

   Certificado

5. En Londres

6. El **14 de julio de 2004**

7. Por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Mancomunidad.

8. Número **G464075**

9. Sello/Estampilla

10. Firma

(Sello de la Oficina de Asuntos Exteriores y de la Mancomunidad

(Fdo) S. Gardiner
Por el secretario de Estado.

7

PC22066A

# CESION

Por contraprestación valiosa pagada a nosotros por PFIZER LIMITED., sociedad constituida en virtud de las leyes del Inglaterra cuya dirección postal completa es Ramsgate Road, Sándwich, Kent CT13 9NJ, Reino Unido, por el presente vendemos y traspasamos a la citada PFIZER LIMITED, todo nuestro derecho, titulo e interés en y sobre nuestro invento de una nueva y útil mejora en DERIVADOS DE NICOTINAMIDA UTILES COMO INHIBIDORES DE PDE4, en cuanto respecta a la República de Colombia, tal como se indica y describe plenamente en la especificación y por el presente autorizamos y solicitamos al Comisionado de Patentes de Colombia expedir dicha patente a nombre de la citada PFIZER LIMITED, de conformidad con esta Cesión.

En fe de lo cual, firmamos de nuestro puño y letra,

La Jolla, California, USA - Simon BAILEY

Melbourn, Australia 17-01-2003 (Fdo) Elisabeth Colette Louise Gautier
Lugar, fecha y firma - Elisabeth Colette Louise GAUTIER

Lugar, fecha y firma - Alan John HENDERSON

Groton, Connecticut, USA - Thomas Victor MAGEE

Groton, Connecticut, USA - Anthony MARFAT

Sandwich, Kent, England - Diciembre 2002 John Paul MATHIAS

Groton, Connecticut, USA - Dale Gordon MCLEOD

Sandwich, Kent, England - Diciembre 2002 Sandra Marina MONAGHAN

Sandwich, Kent, England - Diciembre 2002 Blanda Luzia Christa STAMMEN

8

Certificado, verificado y autenticado
En la ciudad de Egham en Surrey

A los 13 días del mes de julio de 2004

(Fdo) Kenneth Greenwood

KENNETH GREENWOOD
NOTARIO PUBLICO
HORNE ENGALL AND FREEMAN

(Adherido, sello notarial)

## APOSTILLA

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

2. País: Reino Unido de Gran Bretaña e Irlanda del Norte

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2. Ha sido firmado por — K. Greenwood

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4. Lleva el sello/estampilla de — El antedicho Notario Público

5. En Londres — Certificado
6. El 14 de julio de 2004

7. Por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Mancomunidad.

8. Número G464083

9. Sello/Estampilla — 10. Firma

(Sello de la Oficina de Asuntos Exteriores y de la Mancomunidad

(Fdo) S. Gardiner
Por el secretario de Estado.

9

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# CESION

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En fe de lo cual, firmamos de nuestro puño y letra,

(Fdo) Simon Bailey 16/12/02

La Jolla, California, USA - Simon BAILEY

Lugar, fecha y firma - Elisabeth Colette Louise GAUTIER

Lugar, fecha y firma - Alan John HENDERSON

Groton, Connecticut, USA - Thomas Victor MAGEE

Groton, Connecticut, USA - Anthony MARFAT

Sandwich, Kent, England - Diciembre 2002 John Paul MATHIAS

Groton, Connecticut, USA - Dale Gordon MCLEOD

Sandwich, Kent, England - Diciembre 2002 Sandra Marina MONAGHAN

Sandwich, Kent, England - Diciembre 2002 Blanda Luzia Christa STAMMEN

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En fe de lo cual, firmamos de nuestro puño y letra,

La Jolla, California, USA - Simon BAILEY

Lugar, fecha y firma

Albano, NY, USA 23/12/02 (Fdo)Alan John Henderson

Lugar, fecha y firma - Alan John HENDERSON

Groton, Connecticut, USA - Thomas Victor MAGEE

Groton, Connecticut, USA - Anthony MARFAT

Sandwich, Kent, England - Diciembre 2002 John Paul MATHIAS

Groton, Connecticut, USA - Dale Gordon MCLEOD

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En fe de lo cual, firmamos de nuestro puño y letra,

La Jolla, California, USA - Simon BAILEY

Lugar, fecha y firma - Elisabeth Colette Louise GAUTIER

Lugar, fecha y firma - Alan John HENDERSON

18 de diciembre de 2002 (Fdo) Thomas Victor Magee

Groton, Connecticut, USA - Thomas Victor MAGEE

18 de diciembre de 2002 (Fdo) Anthony Marfat

Groton, Connecticut, USA - Anthony MARFAT

(Fdo) John Paul Mathias

Sandwich, Kent, England - 16 de diciembre 2002 John Paul MATHIAS

18 de diciembre de 2002 (Fdo) Dale Gordon Mcleod

Groton, Connecticut, USA - Dale Gordon MCLEOD

(Fdo) Sandra Marina Monaghan

Sandwich, Kent, England - 16 de diciembre 2002 Sandra Marina MONAGHAN

(Fdo) Blanda Luzia Christa Stammen

Sandwich, Kent, England- 16 diciembre 2002 Blanda Luzia Christa STAMMEN

PC22066A

CO-1X

# ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER INC., a corporation organized under the laws of the State of Delaware, United States of America of 235 East 42nd Street, New York, New York 10017, United States of America**, I (we) do hereby sell and assign to the said **PFIZER INC.**, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in

**NICOTINAMIDE DERIVATIVES USEFUL AS PDE4 INHIBITORS**

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 INC.** in accordance with this assignment.

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

**PFIZER LIMITED**

30 January 2003
Sandwich, Kent, England. - **KEITH S. RUDDOCK, AUTHORISED ATTORNEY**

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 13th Day Of July 2004
KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

3198

**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 **14 July 2004**

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 **G464075**

9. Stamp:
   timbre:

10. Signature: **S. Gardiner**

*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.

PC22066A

CO-1

# ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER LIMITED** a corporation organized under the laws of **England** whose full post office address is **Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom,** I (we) do hereby sell and assign to the said **PFIZER LIMITED,** all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in **NICOTINAMIDE DERIVATIVES USEFUL AS PDE4 INHIBITORS** 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 LIMITED** in accordance with this assignment.

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

La Jolla, California, USA - Simon BAILEY

Melbourne, Australia 17-01-2003 Elisabeth Colette Louise Gautier

Place, date and signature - Elisabeth Colette Louise GAUTIER

Place, date and signature - Alan John HENDERSON

Groton, Connecticut, USA - Thomas Victor MAGEE

Groton, Connecticut, USA - Anthony MARFAT

Sandwich, Kent, England. December 2002 - John Paul MATHIAS

Groton, Connecticut, USA - Dale Gordon MCLEOD

Sandwich, Kent, England. December 2002 - Sandra Marina MONAGHAN

Sandwich, Kent, England. December 2002 - Blanda Luzia Christa STAMMEN

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 13th day of July 2004

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

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   a été signé par

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

5. at London/à Londres

Certified/Attesté

6. the/le 14 July 2004

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 **G464083**

9. Stamp:
   timbre:

10. Signature: S. Gardiner

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

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Simon Bailey 16/12/02

La Jolla, California, USA - Simon BAILEY

Place, date and signature - Elisabeth Colette Louise GAUTIER

Place, date and signature - Alan John HENDERSON

Groton, Connecticut, USA - Thomas Victor MAGEE

Groton, Connecticut, USA - Anthony MARFAT

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La Jolla, California, USA - Simon BAILEY

Place, date and signature - Elisabeth Colette Louise GAUTIER

Albany, NY, USA 23/12/02 A. Henderson

Place, date and signature - Alan John HENDERSON

Groton, Connecticut, USA - Thomas Victor MAGEE

Groton, Connecticut, USA - Anthony MARFAT

Sandwich, Kent, England. December 2002 - John Paul MATHIAS

Groton, Connecticut, USA - Dale Gordon MCLEOD

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Place, date and signature - Elisabeth Colette Louise GAUTIER

Place, date and signature - Alan John HENDERSON

18 December 2002
Groton, Connecticut, USA - Thomas Victor MAGEE

18 December 2002
Groton, Connecticut, USA - Anthony MARFAT

Sandwich, Kent, England. 16 December 2002 - John Paul MATHIAS

18 December 2002
Groton, Connecticut, USA - Dale Gordon MCLEOD

Sandwich, Kent, England. 16 December 2002 - Sandra Marina MONAGHAN

Sandwich, Kent, England. 16 December 2002 - Blanda Luzia Christa STAMMEN

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2003 (21.08.2003)

PCT

(10) International Publication Number
WO 03/068235 A1

(51) International Patent Classification⁷: A61K 31/455, A61P 29/00, 11/00, C07D 405/12, 213/82, 401/12, 451/04

(21) International Application Number: PCT/IB03/00439

(22) International Filing Date: 3 February 2003 (03.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 0203196.1 | 11 February 2002 (11.02.2002) | GB |
| 0220999.7 | 10 September 2002 (10.09.2002) | GB |
| 0224453.1 | 21 October 2002 (21.10.2002) | GB |
| 0227139.3 | 20 November 2002 (20.11.2002) | GB |

(71) Applicant (*for GB only*): PFIZER LIMITED [GB/GB]; Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(71) Applicant (*for all designated States except GB, US*): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BAILEY, Simon [GB/US]; Pfizer Global Research and Development, 10770 Science Center Drive, La Jolla, CA 92121 (US). GAUTIER, Elisabeth, Colette, Louise [FR/AU]; UK Patent Department, Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). HENDERSON, Alan, John [GB/US]; UK Patent Department, Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MAGEE, Thomas, Victor [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). MARFAT, Anthony [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). MATHIAS, John, Paul [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). MCLEOD, Dale, Gordon [CA/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US). MONAGHAN, Sandra, Marina [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). STAMMEN, Blanda, Luzia, Christa [DE/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: WOOD, David, J. et al.; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

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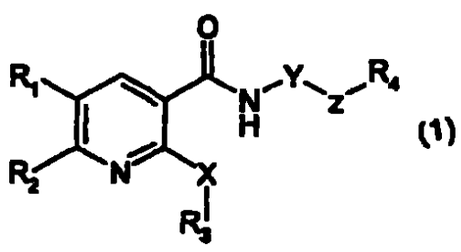
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WO 03/068235 A1

(54) Title: NICOTINAMIDE DERIVATIVES USEFUL AS PDE4 INHIBITORS

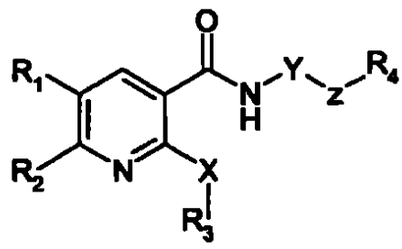


(1)

(57) Abstract: The invention relates to nicotinamide derivatives of formula (I) and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives. The nicotinamide derivatives according to the present invention are phosphodiesterase-4 inhibitors and are useful in numerous diseases, disorders and ( conditions, in particular inflammatory, allergic, respiratory diseases, disorders and conditions, as well as wounds.

# NICOTINAMIDE DERIVATIVES USEFUL AS PDE4 INHIBITORS

This invention relates to nicotinamide derivatives of general formula :



in which $R_1$, $R_2$, $R_3$, $R_4$, X, Y, and Z have the meanings indicated below,

and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

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.

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.* ,1994, 102 Suppl. 10, p. 79-84 ; Duplantier *et al.*, *J. Med. Chem.*, 1996, 39, p. 120-125 ; Schneider *et al.*, *Pharmacol. Biochem. Behav.*, 1995, 50,

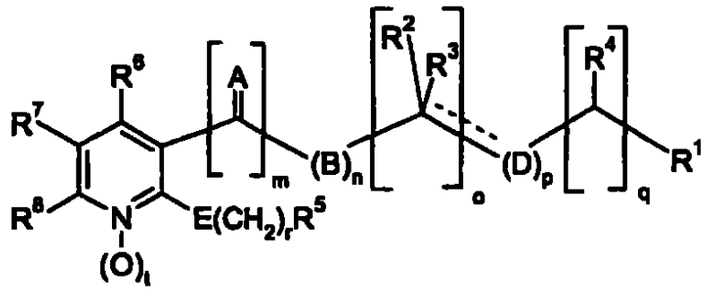
p. 211-217 ; Banner and Page, *Br. J. Pharmacol.*, 1995, 114, p. 93-98 ; Barnette *et al.*, *J. Pharmacol. Exp. Ther.*, 1995, 273, p. 674-679 ; Wright *et al.*, *Can. J. Physiol. Pharmacol.*, 1997, 75, p. 1001-1008 ; Manabe *et al.*, *Eur. J. Pharmacol.*, 1997, 332, p. 97-107 and Ukita *et al.*, *J. Med. Chem.*, 1999, 42, p. 1088-1099). Accordingly, there continues to be considerable interest in the art with regard to the discovery of further selective inhibitors of PDE4s.

Successful results have already 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, $CD4^+$ T-lymphocytes, eosinophils and neutrophils. PDE4 inhibitors also reduce vascular smooth muscle mitogenesis 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. Therefore, PDE4 inhibitors are particularly useful for the treatment of a great number of inflammatory, respiratory and allergic diseases, disorders or conditions and for wounds and some of them are in clinical development mainly for tretament of asthma, COPD, bronchitis and emphysema.

The effects of PDE4 inhibitors on various inflammatory cell responses can be used as a basis for profiling and selecting inhibitors for further study.

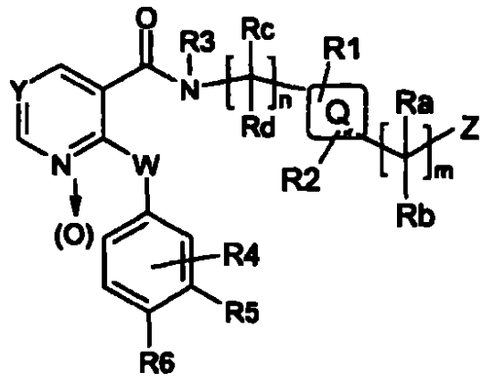
These effects include elevation of cAMP and inhibition of superoxide production, degranulation, chemotaxis, and tumor necrosis factor alpha (TNFα) release in eosinophils, neutrophils and monocytes.

Some nicotinamide derivatives having a PDE4 inhibitory activity have already been synthetized. For example, the patent application N° WO 98/45268 discloses nicotinamide derivatives having activity as selective inhibitors of PDE4D isozyme. These selective PDE4D inhibitors are represented by the following formula :



wherein r may be equal to 0, $(A)_m$ may be oxygen and $(B)_n$ may be NH, o may be equal to 0 or 1, $R^2$ and $R^3$ may be taken together with the carbon to which they are attached to form a $(C_3\text{-}C_7)$cycloalkyl ring, $(D)_p$ may be absent or may be –NH- or –N$(C_1\text{-}C_6)$alkyl-, q may be equal to 0 or 1, $R^4$ may be absent or may represent a carboxy, $R^1$ may be choosen from numerous substituents among which a $(C_1\text{-}C_6)$alkyl, a $(C_3\text{-}C_7)$cycloalkyl, a $(C_6\text{-}C_{10})$aryl or an (un)saturated $(C_3\text{-}C_7)$heterocyclic group, wherein each of said cycloalkyl, aryl or heterocycle may be optionally substituted by one to three substitutents.

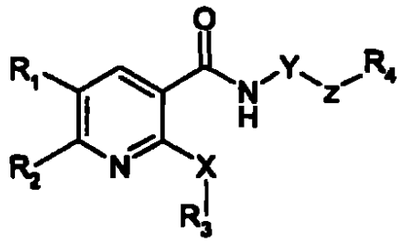
The patent application N° WO 01/57036 also discloses nicotinamide derivatives which are PDE4 inhibitors useful in the treatment of various inflammatory allergic and respiratory diseases and conditions, of formula :



wherein in particular : n is 1 or 2, m is 0 to 2, Y is $=C(R^E)-$ or $-[N\rightarrow(O)]-$, W is –O-, $-S(=O)_r-$ or $-N(R_3)-$, Q represents various rings among which the monocyclic $(C_5-C_7)$cycloalkyl moieties, Z is $-OR_{12}$, $-C(=O)R_{12}$ or CN and $R_{12}$ is choosen from alkyl, alkenyl, cycloalkyl, phenyl, benzyl and monocyclic heterocyclic moieties.

However, there is still a huge need for additional PDE4 inhibitors showing improved therapeutic index with possibly less adverse effects such as for example emesis.

Thus, the present invention concerns new nicotinamide derivatives of general formula (1) :



(1)

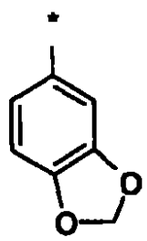
in which :

- $R_1$ and $R_2$ are each a member independently selected from the group consisting of hydrogen atom, halo, cyano, $(C_1-C_4)$alkyl and $(C_1-C_4)$alkoxy,
- X is -O-, -S- or -NH-,
- $R_3$ is a member selected from the groups consisting of :

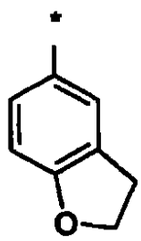
(a) phenyl, naphthyl, heteroaryl and $(C_3-C_8)$cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group

consisting of halo, cyano, trifluoromethyl, trifluoroethyl, trifluoromethoxy, trifluoroethyloxy, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)thioalkyl, –C(=O)$NH_2$, –C(=O)NH(($C_1$-$C_4$)alkyl), hydroxy, -O-C(=O)($C_1$-$C_4$)alkyl, -C(=O)-O-($C_1$-$C_4$)alkyl, hydroxy($C_1$-$C_4$)alkyl, ($C_3$-$C_8$)cycloalkyl and ($C_3$-$C_8$)cycloalkyloxy, or

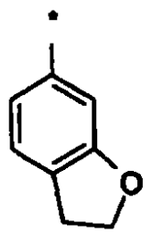
(b) the bicyclic groups conforming to one of the following structures (1.1) to (1.4):



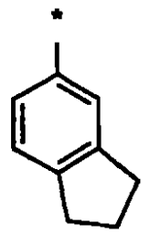
(1.1)



(1.2)



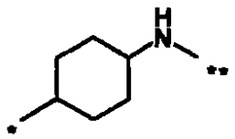
(1.3)



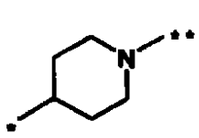
(1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1) through (1.4) to the remaining portion of formula (1),

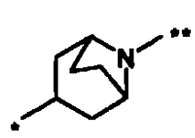
❖ Y is a member selected from the group consisting of partial formulas (1.5) through (1.8):



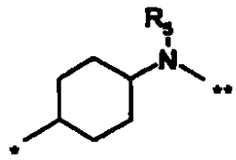
(1.5)



(1.6)



(1.7)

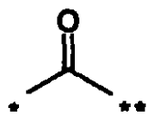


(1.8)

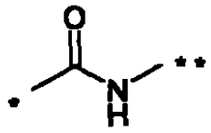
where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a member selected from the groups consisting of ($C_1$-$C_4$)alkyl and phenyl($C_1$-$C_4$)alkyl, where said phenyl group is optionally substituted with 1 to 3 substituents each independently selected from the group consisting of halo, cyano, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, hydroxy, hydroxy($C_1$-$C_4$)alkyl, carboxylic acid (-COOH), -C(=O)-O-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)haloalkyl and C(=O)$NH_2$,

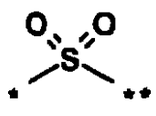
❖ Z is a member selected from the group consisting of partial formulas (1.9) through (1.15) :



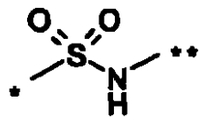
(1.9)



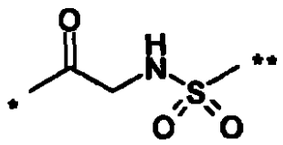
(1.10)



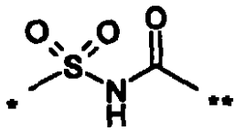
(1.11)



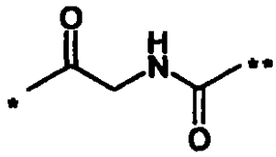
(1.12)



(1.13)



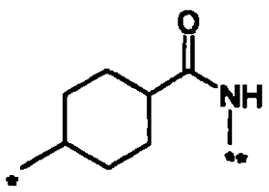
(1.14)



(1.15)

where the symbol "*" indicates the point of attachment of each partial formula (1.9) through (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.15) to the remaining portions $R_4$ of formula (1),

❖ or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

❖ and $R_4$ is a member selected from the groups consisting of :

(a) phenyl, naphthyl heteroaryl and ($C_3$-$C_8$)cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (-COOH), -C(=O)-O-($C_1$-$C_4$)alkyl, -($C_1$-$C_4$)alkyl-COOH, -($C_1$-$C_4$)alkyl-C(=O)-O-($C_1$-$C_4$)alkyl, halo, cyano, -C(=O)$NH_2$, -($C_1$-$C_4$)alkyl, -($C_1$-$C_4$)alkoxy, -($C_1$-$C_4$)haloalkyl, hydroxy and hydroxy($C_1$-$C_4$)alkyl, or

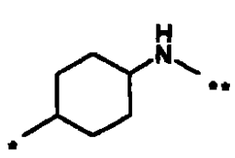
(b) ($C_1$-$C_6$)alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, -C(=O)-O-($C_1$-$C_4$)alkyl, phenyl, naphthyl, heteroaryl or ($C_3$-$C_8$)cycloalkyl group, where said phenyl, naphthyl, heteroaryl and ($C_3$-$C_8$)cycloalkyl groups are each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (-COOH), C(=O)O($C_1$-$C_4$)alkyl, halo, cyano, -C(=O)$NH_2$, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)haloalkyl, hydroxy and hydroxy($C_1$-$C_4$)alkyl,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

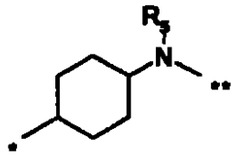
with the proviso that :

1) when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy,
- Y is a partial formula (1.5) or (1.8) :



(1.5)



(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1),

and wherein $R_5$ is a member selected from the groups consisting of ($C_1$-$C_4$)alkyl and phenyl($C_1$-$C_4$)alkyl, where said phenyl group is optionally substituted by halo, ($C_1$-$C_3$)alkyl, ($C_1$-$C_3$)alkoxy or hydroxy, and

- Z is a radical –C(=O)-

then $R_4$ cannot be :

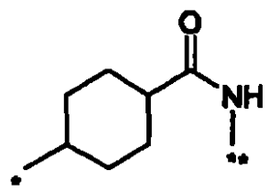
a) a ($C_3$-$C_8$)cycloalkyl optionally substituted by ($C_1$-$C_3$)alkyl,

b) a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy, or

c) a ($C_1$-$C_6$)alkyl optionally substituted with a hydroxy, or with a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy.

2) and when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy, and
- Y-Z represents a partial formula (1.16) :




(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions –$R_4$ of formula (1),

then $R_4$ cannot be :

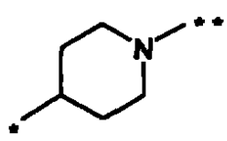
a) a ($C_3$-$C_8$)cycloalkyl or

b) a ($C_1$-$C_6$)alkyl optionally substituted by a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected

from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 or 2 substituent(s) each independently selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy, and
- Y is a partial formula (1.6) :



(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and

- Z is a radical –C(=O)-,

then $R_4$ cannot be a ($C_1$-$C_6$)alkyl optionally substituted by a hydroxy, or by a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S.

It has been found that these nicotinamide derivatives are inhibitors of PDE4 isoenzymes, particularly useful for the treatment of inflammatory, respiratory and allergic diseases and conditions or for wounds by showing excellent therapeutic utility and therapeutic index.

In the here above general formula (1), halo denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo in particular fluoro or chloro.

($C_1$-$C_4$)alkyl or ($C_1$-$C_6$)alkyl radicals denote a straight-chain or branched group containing respectively 1 to 4 and 1 to 6 carbon atoms. This also applies if they carry substituents or occur as substituents of other radicals, for example in ($C_1$-$C_4$)alkoxy radicals, ($C_1$-$C_4$)thioalkyl radicals, ($C_1$-$C_4$)haloalkyl radicals, hydroxy($C_1$-$C_4$)alkyl radicals, C(=O)O($C_1$-$C_4$)alkyl radicals etc... . Examples of suitable ($C_1$-$C_4$)alkyl and ($C_1$-$C_6$)alkyl radicals are methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pentyl and hexyl. Examples of suitable ($C_1$-$C_4$)alkoxy radicals are methoxy, ethoxy, *n*-propyloxy, *iso*-propyloxy, *n*-butyloxy, *iso*-butyloxy, *sec*-butyloxy and *tert*-butyloxy. Examples of suitable ($C_1$-$C_4$)thioalkyl radicals are thiomethyl, thioethyl, thio-*n*-propyl, thio-*iso*-propyl, thio-*n*-butyl, thio-*iso*-butyl, thio-*sec*-butyl and thio-*tert*-butyl. ($C_1$-$C_4$)haloalkyl radicals are alkyl radicals substituted by halo. They can contain 1, 2, 3, 4, 5, 6 or 7 halogen atoms, if not stated otherwise. Said halo is preferably a fluoro, a chloro, a bromo or a iodo, in particular fluoro or chloro. For example in a fluoro-substituted alkyl radical, a methyl group can be present as a trifluoromethyl group. The same applies to hydroxy(C1-C4)alkyl radicals except that they are alkyl radicals substituted by a hydroxy group (-OH). According to a preferred embodiment of said invention, such radicals contain one hydroxy substituent. Examples of suitable hydroxy($C_1$-$C_4$)alkyl radicals are hydroxymethyl, 1-hydroxyethyl or 2-hydroxyethyl.

($C_3$-$C_8$)cycloalkyl radicals represent 3-membered to 8-membered saturated monocyclic rings. Examples of suitable ($C_3$-$C_8$)cycloalkyl radicals are in particular cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. These radical can be optionally substituted as indicated in the definition of $R_3$. Examples of substituted ($C_3$-$C_8$)cycloalkyl radicals are for example 2-methylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, 5-methylcyclohexyl, 6-methylcyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, 5-hydroxycyclohexyl, 6-

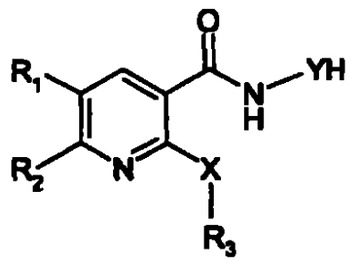
hydroxycyclohexyl, 2-fluorocyclohexyl, 3-fluorocyclohexyl, 4-fluorocyclohexyl, 5-fluorocyclohexyl, 6-fluorocyclohexyl 2-methyl-3-hydroxycyclohexyl, 2-methyl-4-hydroxycyclohexyl, 2-hydroxy-4-methylcyclohexyl, etc.... .

In the hereabove general formula (1), heteroaryl is a radical of a monocyclic or polycyclic aromatic system having 5 to 14 ring members, which contains 1, 2, 3, 4 or 5 heteroatom(s) depending in number and quality of the total number of ring members. Examples of heteroatoms are nitrogen (N), oxygen (O) and sulphur (S). If several heteroatoms are contained, these can be identical or different. Heteroaryl radicals can also be unsubstituted, monosubstituted or polysubstituted, as indicated in the definition of $R_3$ and $R_4$ hereabove for general formula (1) according to the present invention. Preferably heteroaryl is a monocyclic or bicyclic aromatic radical which contains 1, 2, 3 or 4, in particular 1, 2 or 3, identical or different heteroatoms selected from the group consisting of N, O and S. Particularly preferably, heteroaryl is a monocyclic or bicyclic aromatic radical having 5 to 10 ring members, in particular a 5-membered to 6-membered monocyclic aromatic radical which contains (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen heteroatom or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s). Examples of suitable heteroaryl radicals are the radicals derivated from pyrrole, furan, furazan, thiophene, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, tetrazole, triazine, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, indole, isoindole, indazole, purine, naphthyridine, phthalazine, quinoline, isoquinoline, quinoxaline, quinazoline, cinnoline, and benzo-fused derivatives of these heteroaryls, such as for example benzofuran, benzothiophene, benzoxazole, and benzothiazole. Particularly preferred are the heteroaryl radicals selected from pyrrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furanyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl. Nitrogen heteroaryl radicals can also be present as N-oxides or as quaternary salts.

In the general formula (1) according to the present invention, when a radical is mono- or poly-substituted, said substituent(s) can be located at any desired position(s). Also, when a radical is polysubstituted, said substituents can be identical or different, unless otherwise stated.

The nicotinamide derivatives of the formula (1) can be prepared using conventional procedures such as by the following illustrative methods in which $R_1$, $R_2$, $R_3$, $R_4$, X, Y, and Z are as previously defined for the nicotinamide derivatives of the formula (1) unless otherwise stated.

Where Z in the general formula (1) represents a group of partial formula (1.9) through (1.15), the nicotinamide derivatives of the formula (1) may be prepared starting from a compound of formula (2.1) :




(2.1)

where $R_1$, $R_2$, X, $R_3$ and Y are as previously described for the nicotinamide derivatives of formula (1).

Where Z represents a group of partial formula (1.11), (1.12) or (1.14), the compounds of formula (2.1) may be reacted with the corresponding $R_4$-sulfonyl chloride derivative ($R_4SO_2Cl$ or $R_4NHSO_2Cl$ or $R_4C(=O)NHSO_2Cl$) in a suitable solvent (e.g. dichloromethane) and in the presence of an organic base (e.g. triethylamine) at a temperature ranging from 0°C to room temperature (about 20°C).

Where Z represents a group of partial formula (1.9), (1.13) or (1.15), the compounds of formula (2.1) may be reacted with the corresponding $R_4$-carboxylic acid derivative ($R_4COOH$ or $R_4SO_2NH$-$CH_2$-COOH or $R_4C(=O)NH$-$CH_2$-COOH) using an activating agent in the presence of a suitable solvent (e.g.

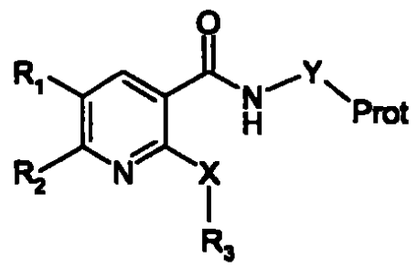
dimethylformamide) and organic base (e.g. N-methylmorpholine) at room temperature. Activation of the acid may be achieved by using for example :

a) 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, or
b) carbonyldiimidazole, or
c) oxalyl chloride and dimethylformamide (with dichloromethane as the solvent), or
d) o-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU reagent).

Where Z represents a group of partial formula (1.10), the compounds of formula (2.1) may be reacted with carbonyldiimidazole in a suitable solvent (such as dichloromethane) or with a phosgene equivalent (such as triphosgene) and the obtained intermediate is reacted with an amine bearing the substituent $R_4$.

It must be emphasized that when $R_3$ and $R_4$ in the nicotinamide derivatives of formula (1) represent alkoxy substituted phenyl rings, these structures can be converted to the hydroxy analogue using certain deprotection conditions well-known by the one skilled in the art. Similarly when $R_4$ contains an ester functionality, these structures can be easily converted to the carboxylic acid by simple saponification using alkali metal hydroxides well-known by the one skilled in the art.

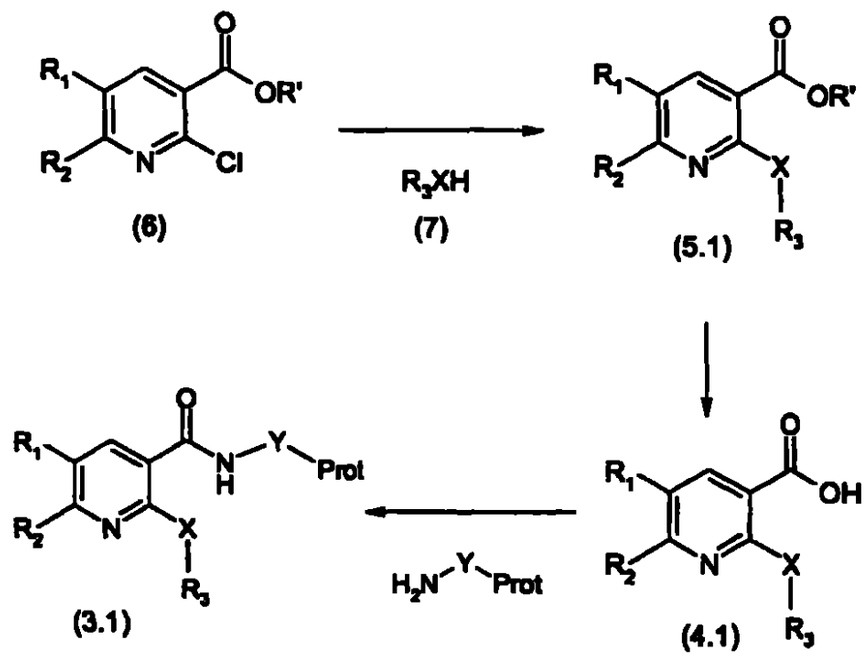
The compounds of general formula (2.1) may be prepared by removal of the protecting group "Prot" from the compounds of general formula (3.1) :




(3.1)

wherein $R_1$, $R_2$, X, $R_3$ and Y are as previously described for the nicotinamide derivatives of formula (1) and Prot is a suitable protecting group, which includes but is not limited to benzyl or a carbamate (e.g. butoxycarbonyl), by methods well known to those skilled in the art.

The compounds of formula (3.1) may be prepared according to two synthetic routes. The first synthetic route is shown in scheme 1 :



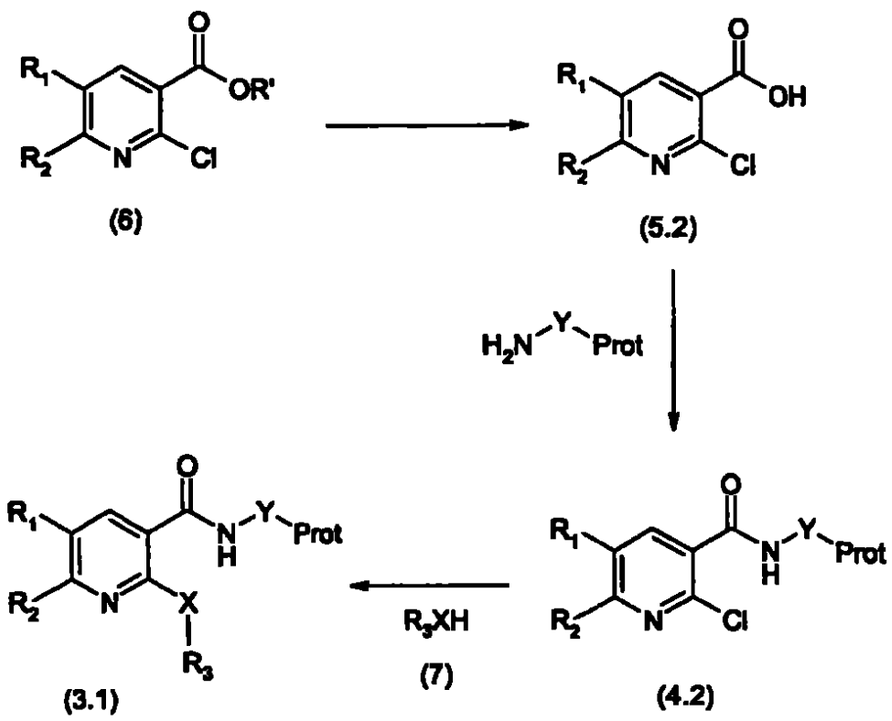

Scheme 1

wherein $R_1$, $R_2$, X, $R_3$, Y and Prot are as previously described and R' represents a ($C_1$-$C_4$)alkyl radical.

In a typical procedure the nicotinate ester of the formula (6) may be reacted with the appropriate alcohol, thiol or amine of formula $R_3XH$ (7) in the appropriate solvent (for example dimethylformamide or dioxan) containing a base, such as cesium carbonate, at temperatures ranging from room temperature to 100°C to give a compound of the formula (5.1). This can be saponified with an alkali-hydroxide to give an acid of the formula (4.1) which is then converted to a compound of the formula (3) by reaction with a

monoprotected diamine of the formula $NH_2$-Y-Prot, using an activating agent such as those described in one of the activation methods outlined before (i.e. a) 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimid hydrochloride or b) carbonyldiimidazole or c) oxalyl chloride and dimethylformamide or d) HATU reagent with dichloromethane as the solvent).

According to another alternative, the compounds of formula (3.1) may be prepared as shown in scheme 2 :




Scheme 2

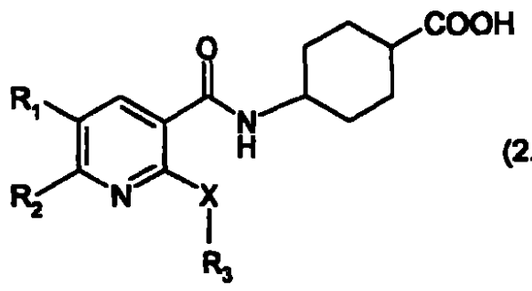
wherein $R_1$, $R_2$, X, $R_3$, Y, R' and Prot are as previously described.

In a typical procedure the nicotinate ester of the formula (6) may be hydrolysed using an alkaline metal hydroxide to a nicotinic acid of the formula (5.2), which is reacted with a monoprotected diamine of the formula $NH_2$-Y-Prot, using one of the activation methods outlined before. The chloropyridine of the formula (4.2) obtained at the preceding step may then be reacted with the appropriate alcohol, thiol or amine of formula $R_3XH$ (7) in the appropriate

solvent (for example dimethylformamide or dioxan) containing a base, such as cesium carbonate, at temperatures ranging from room temperature (about 20°C) to 100°C.

The compounds of formula (6) and (7), as well as the monoprotected diamine of the formula $NH_2$-Y-Prot, are either commercial or they can be prepared by conventional procedures well known to the one skilled in the art.

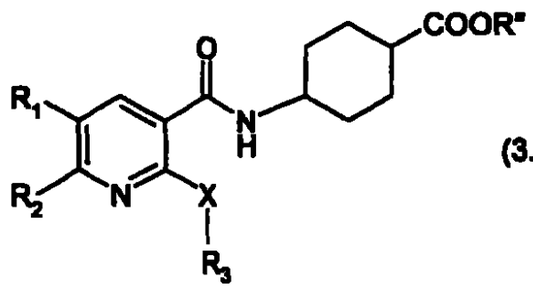
Where Y-Z in the general formula (1) represents together a group of partial formula (1.16), the nicotinamide derivatives of the formula (1) may be prepared starting from a compound of formula (2.2) :




(2.2)

where $R_1$, $R_2$, X, and $R_3$ are as previously described for the nicotinamide derivatives of formula (1), by reaction of an amine bearing a $R_4$ substituent and using one of the activation methods outlined before.

The compounds of formula (2.2) may be prepared starting from the corresponding ester of formula (3.2) :

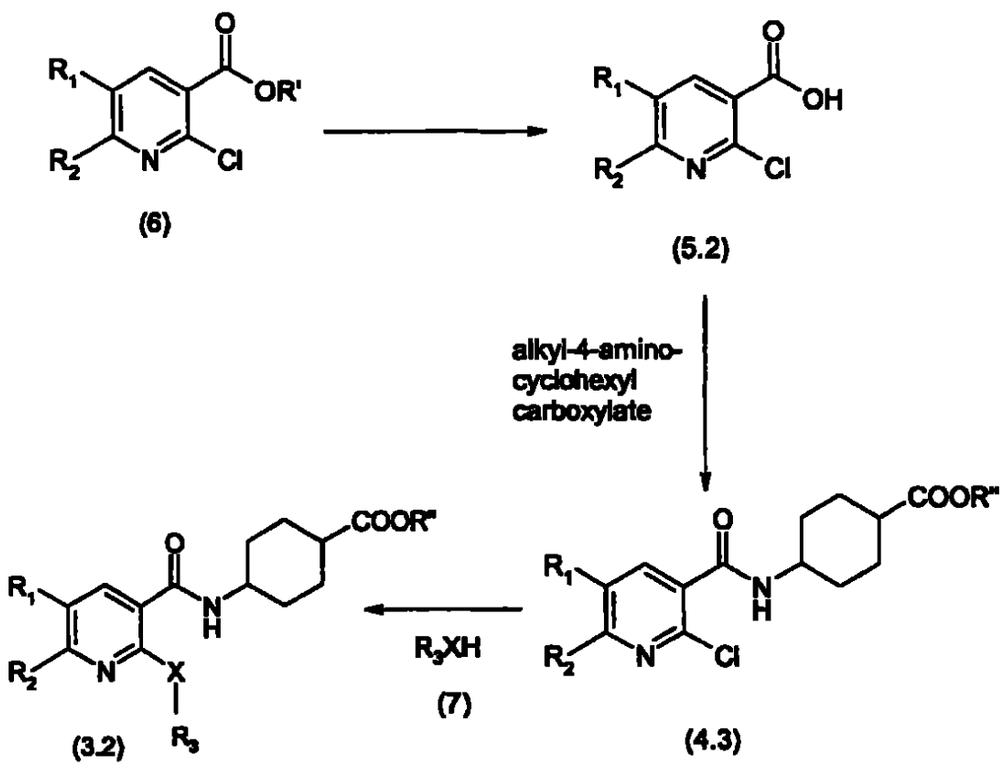



(3.2)

wherein $R_1$, $R_2$, X and $R_3$ are as previously described for the nicotinamide derivatives of formula (1) and R" represents a ($C_1$-$C_4$) alkyl radical or a benzyl radical. If R" represents a ($C_1$-$C_4$) alkyl radical, the compounds of formula (2.2)

are obtained via saponification according to the standard procedures, else the compounds of formula (2.2) are obtained via hydrogenation according to the standard procedures well known by the one skilled in the art.

The compounds of formula (3.2) may be prepared according to two synthetic routes. The first synthetic route is shown in scheme 3 :



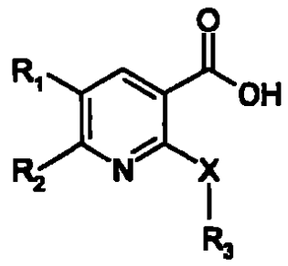

Scheme 3

where $R_1$, $R_2$, X, $R_3$, R'and R" are as previously described.

In a typical procedure, the nicotinic acid of formula (5.2), which is obtained from a compound of formula (6) as previously described, may be reacted with an alkyl-4-aminocyclohexylcarboxylate using one of the activation method outlined before. The chloropyridine of formula (4.3) is then reacted with the appropriate alcohol, thiol or amine of formula $R_3XH$ (7) in the appropriate solvent (for example dimethylformamide or dioxan) containing a base, such as

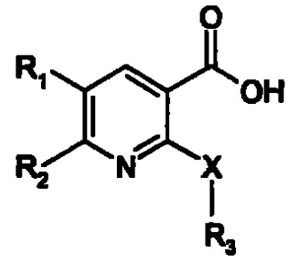
cesium carbonate, at temperatures ranging from room temperature (about 20°C) to 100°C.

According to another alternative, the compounds of formula (3.2) may also be prepared directly from compounds of formula (4.1) as previously described :


(4.1)

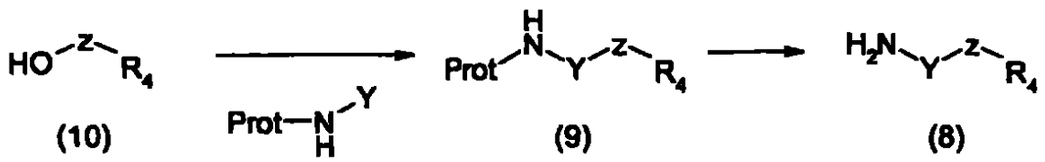
by reaction with an alkyl-4-aminocyclohexylcarboxylate using one of the activation method outlined before. Said compound of formula (4.1) may be prepared as already described here above.

According to a final alternative, the nicotinamide derivatives of formula (1) may also be prepared by reaction of the acid of formula (4.1) as previously described:


(4.1)

with an amine derivative of formula (8) : $NH_2$-Y-Z-$R_4$,
using one one of the activation method outlined before. Said compound of formula (4.1) may be prepared as already described here above.

The amine derivative of formula (8) may be prepared according to the following scheme 4 :




Scheme 4

wherein $R_4$, Z and Y are as previously described for the nicotinamide derivatives of formula (1) and Prot is a suitable protecting group, which includes but is not limited to benzyl or a carbamate (e.g. butoxycarbonyl).

In a typical procedure, the protected amine Prot-NH-Y may be reacted with the acid of formula (10), using one of the activation methods outlined previously. Deprotection of the resulting compound of formula (9) by methods well known to those skilled in the art, affords the amine of formula (8).

The compounds of formula (10) as well as the monoprotected amine of the formula Y-Prot-NH-Y, are either commercial or they can be prepared by conventional procedures well known to the one skilled in the art.

All of the above reactions and the preparations of novel starting materials using in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

For some of the steps of the here above described process of preparation of the nicotinamide derivatives of formula (1), it can be necessary to protect the potential reactive functions that are not wished to react. In such a case, any compatible protecting radical can be used. In particular methods such as those described by T.W. GREENE (*Protective Groups in Organic Synthesis*, A. Wiley-Interscience Publication, 1981) or by McOMIE (*Protective Groups in Organic Chemistry*, Plenum Press, 1973), can be used.

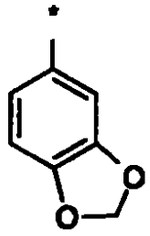
Also, the nicotinamide derivatives of formula (1) as well as intermediate for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

According to a first aspect, particularly preferred are nicotinamide derivatives of the formula (1) in which :

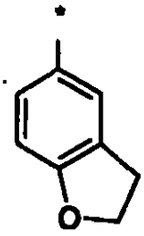
- $R_1$ and $R_2$ are each a member independently selected from the group consisting of hydrogen atom, halo, cyano, $(C_1-C_4)$alkyl and $(C_1-C_4)$alkoxy,
- X is -O-,
- $R_3$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 to 3 substituents each independently selected from the group consisting of halo, cyano, trifluoromethyl, trifluoromethoxy, $(C_1-C_4)$alkyl or $(C_1-C_4)$alkoxy, $(C_1-C_4)$thioalkyl, $-C(=O)NH_2$, $-C(=O)NH((C_1-C_4)alkyl)$, hydroxy, $-O-C(=O)(C_1-C_4)alkyl$, $-C(=O)-O-(C_1-C_4)alkyl$, hydroxy $(C_1-C_4)$alkyl, $(C_3-C_8)$cycloalkyl and $(C_3-C_8)$cycloalkyloxy, or

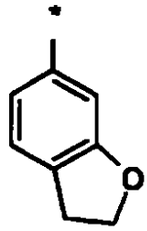
(b) the bicyclic groups conforming to one of the following structures (1.1) to (1.4) :



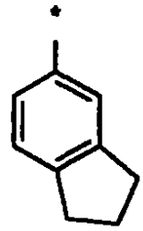
(1.1)



(1.2)



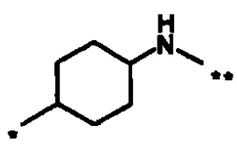
(1.3)



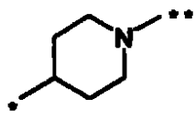
(1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1) through (1.4) to the remaining portion of formula (1),

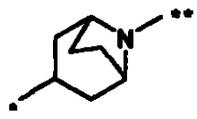
- Y is a member selected from the group consisting of partial formulas (1.5) through (1.8) :



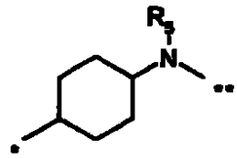
(1.5)



(1.6)



(1.7)

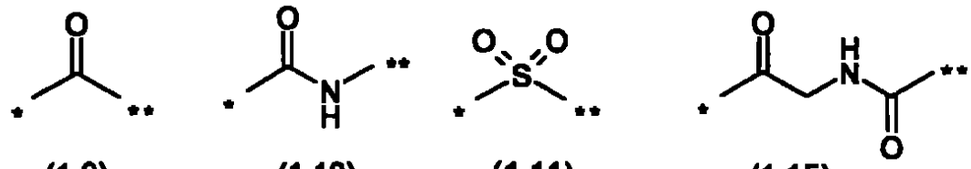


(1.8)

where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a member selected from the groups consisting of $(C_1$-$C_4)$alkyl and phenyl$(C_1$-$C_4)$alkyl, where said phenyl group is optionally substituted with 1 to 3 substituents each independently selected from the group consisting of halo, cyano, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, hydroxy, hydroxy$(C_1$-$C_4)$alkyl, carboxylic acid, -C(=O)-O-$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$haloalkyl and –C(=O)$NH_2$,

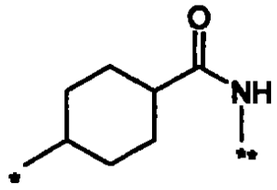
- Z is a member selected from the group consisting of partial formulas (1.9) through (1.11) and (1.15) :



(1.9) (1.10) (1.11) (1.15)

where the symbol "*" indicates the points of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions $R_4$ of formula (1),

- or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

- and $R_4$ is a member selected from the groups consisting of :

(a) phenyl, naphthyl, heteroaryl and $(C_3$-$C_8)$cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group

consisting of carboxylic acid (-COOH), -C(=O)-O-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl-COOH, ($C_1$-$C_4$)alkyl-C(=O)-O-($C_1$-$C_4$)alkyl, halo, cyano, –C(=O)$NH_2$, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)haloalkyl, hydroxy and hydroxy($C_1$-$C_4$)alkyl, or

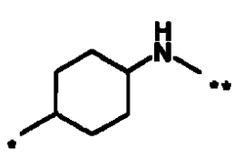
(b) ($C_1$-$C_6$)alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, -C(=O)-O-($C_1$-$C_4$)alkyl, phenyl, naphthyl, heteroaryl or ($C_3$-$C_8$)cycloalkyl group, where said phenyl, naphthyl, heteroaryl and ($C_3$-$C_8$)cycloalkyl groups are each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid, C(=O)O($C_1$-$C_4$)alkyl, halo, cyano, –C(=O)$NH_2$, ($C_1$-$C_4$)alkyl or ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)haloalkyl, hydroxy and hydroxy($C_1$-$C_4$)alkyl,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

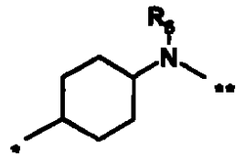
with the proviso that :

1) when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy,
- Y is a partial formula (1.5) or (1.8) :



(1.5)



(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1),

and wherein $R_5$ is a member selected from the groups consisting of $(C_1-C_4)$alkyl and phenyl$(C_1-C_4)$alkyl, where said phenyl group is optionally substituted by halo, $(C_1-C_3)$alkyl, $(C_1-C_3)$alkoxy or hydroxy, and

- Z is a radical –C(=O)-

then $R_4$ cannot be :

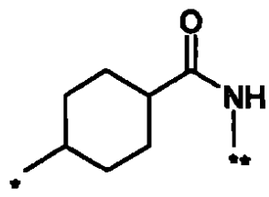
a) a $(C_3-C_8)$cycloalkyl optionally substituted by $(C_1-C_3)$alkyl,

b) a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, $(C_1-C_3)$alkyl or $(C_1-C_3)$alkoxy, or

c) a $(C_1-C_6)$alkyl optionally substituted with a hydroxy, or with a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, $(C_1-C_3)$alkyl or $(C_1-C_3)$alkoxy,

2) and when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a $(C_1-C_4)$thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, $(C_1-C_3)$alkyl and $(C_1-C_3)$alkoxy, and
- Y-Z represents a partial formula (1.16) :




(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

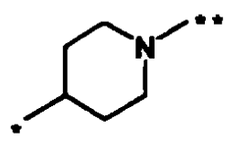
then $R_4$ cannot be :

a) a $(C_3-C_8)$cycloalkyl or

b) a $(C_1-C_6)$alkyl optionally substituted by a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, $(C_1-C_3)$alkyl or $(C_1-C_3)$alkoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a $(C_1-C_4)$thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 or 2 substituent(s) each independently selected from the group consisting of halo, $(C_1-C_3)$alkyl and $(C_1-C_3)$alkoxy, and
- Y is a partial formula (1.6) :



(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and

- Z is a radical –C(=O)-,

then $R_4$ cannot be a $(C_1-C_6)$alkyl optionally substituted by a hydroxy, or by a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S.

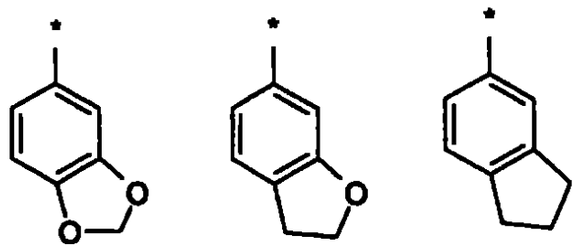
More particularly preferred are the nicotinamide derivatives of the formula (1) in which :

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- $R_1$ and $R_2$ are each a member independently selected from the group consisting of hydrogen atom and halo,
- X is -O-,
- $R_3$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 or 2 substituents each independently selected from the group consisting of halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, trifluoromethyl, trifluoromethoxy, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkyloxy and $(C_1\text{-}C_4)$thioalkyl, or

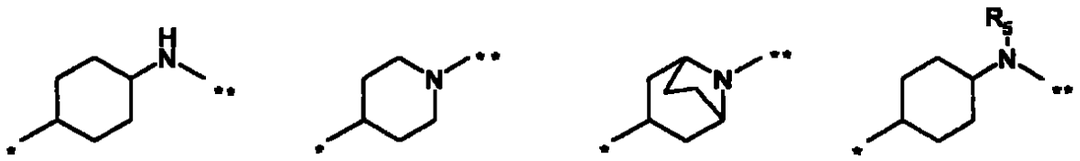
(b) the bicyclic groups conforming to one of the following structures (1.1), (1.3) or (1.4) :



(1.1) (1.3) (1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1), (1.3) or (1.4) to the remaining portion of formula (1),

- Y is a member selected from the group consisting of partial formulas (1.5) through (1.8) :



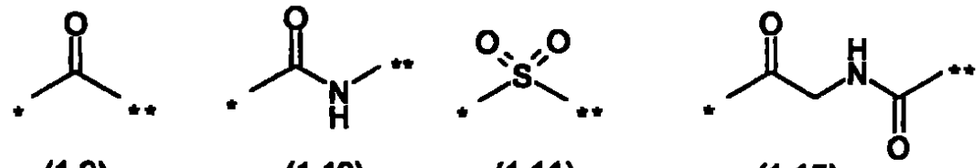
(1.5) (1.6) (1.7) (1.8)

where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a phenyl$(C_1\text{-}C_4)$alkyl where said phenyl is optionally substituted with 1 to 3 substituents each independently selected from the group

consisting of hydroxy, carboxylic acid, C(=O)O(C1-C4)alkyl and hydroxy(C1-C4)alkyl,

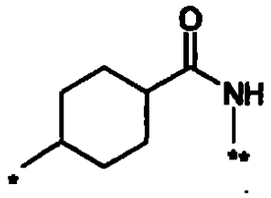
❖ Z is a member selected from the group consisting of partial formulas (1.9) through (1.11) and (1.15) :



(1.9) (1.10) (1.11) (1.15)

where the symbol "*" indicates the points of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions $R_4$ of formula (1),

❖ or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $–R_4$ of formula (1),

❖ and $R_4$ is a member selected from the groups consisting of :

(a) phenyl, naphthyl, heteroaryl and ($C_3$-$C_8$)cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (-COOH), -C(=O)-O-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkyl-COOH, ($C_1$-$C_4$)alkyl-C(=O)-O-($C_1$-$C_4$)alkyl, halo, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, hydroxy($C_1$-$C_4$)alkyl and hydroxy, or

(b) ($C_1$-$C_8$)alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, -C(=O)-O-($C_1$-$C_4$)alkyl, phenyl, naphthyl, heteroaryl or ($C_3$-$C_8$)cycloalkyl group, where said phenyl, naphthyl, heteroaryl and ($C_3$-$C_8$)cycloalkyl groups are each optionally

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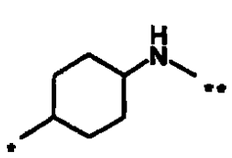
substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (–COOH), C(=O)O($C_1$-$C_4$)alkyl, halo, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, hydroxy($C_1$-$C_4$)alkyl and hydroxy,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

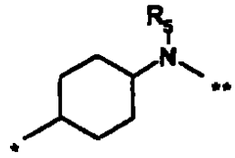
with the proviso that :

1) when :

- $R_1$ is selected from the group consisting of hydrogen atom and halo,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo and ($C_1$-$C_3$)alkyl,
- Y is a partial formula (1.5) or (1.8) :



(1.5)



(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and wherein $R_5$ is a phenyl($C_1$-$C_4$)alkyl, where said phenyl group is optionally substituted by hydroxy, and

- Z is a radical –C(=O)-

then $R_4$ cannot be :

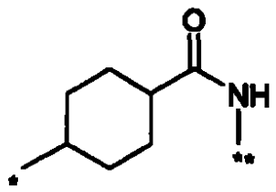
a) a ($C_3$-$C_8$)cycloalkyl optionally substituted by ($C_1$-$C_3$)alkyl,

b) a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy, or

c) a ($C_1$-$C_8$)alkyl optionally substituted with a hydroxy, or with a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

2) and when :

- $R_1$ is selected from the group consisting of hydrogen atom and halo,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo and ($C_1$-$C_3$)alkyl, and
- Y-Z represents a partial formula (1.16) :




(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions –$R_4$ of formula (1),

then $R_4$ cannot be :

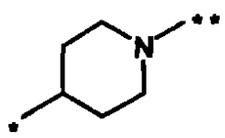
a) a ($C_3$-$C_8$)cycloalkyl or

b) a ($C_1$-$C_6$)alkyl optionally substituted by a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom and halo,
- $R_2$ is a hydrogen atom,

- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent(s) selected from the group consisting of halo and ($C_1$-$C_3$)alkyl,
- Y is a partial formula (1.6) :



(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and

- Z is a radical –C(=O)-,

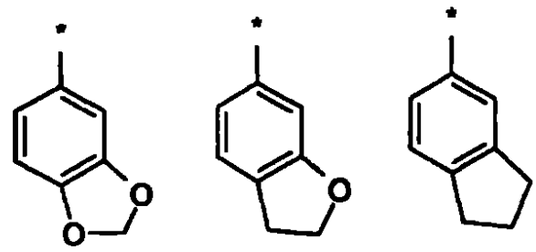
then $R_4$ cannot be a ($C_1$-$C_6$)alkyl optionally substituted by a hydroxy, or by a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S.

Still more particularly preferred are the nicotinamide derivatives of the formula (1) in which :

- $R_1$ is a hydrogen atom or fluoro and $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, chloro, bromo, methyl, ethyl, methoxy, trifluoromethyl, trifluoromethoxy, cyclopropyl, cyclobutyloxy, and methylthio, or

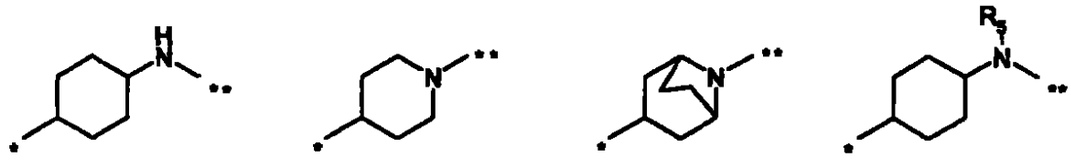
(b) the bicyclic groups conforming to one of the following structures (1.1), (1.3) or (1.4) :



(1.1) (1.3) (1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1), (1.3) or (1.4) to the remaining portion of formula (1),

- Y is a member selected from the group consisting of partial formulas (1.5) through (1.8) :

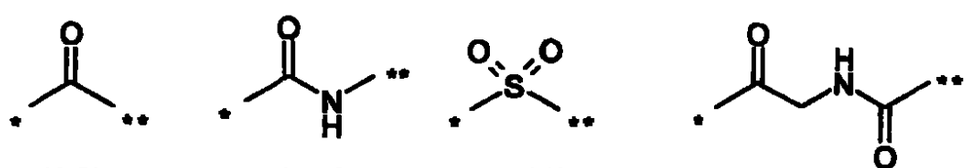


(1.5) (1.6) (1.7) (1.8)

where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a benzyl group substituted by a hydroxy substitutent on the ring,

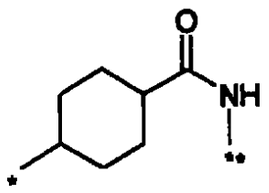
- Z is a member selected from the group consisting of partial formulas (1.9) through (1.11) and (1.15) :



(1.9) (1.10) (1.11) (1.15)

where the symbol "*" indicates the points of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions $R_4$ of formula (1),

- or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

- and $R_4$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid, -C(=O)-O-methyl, fluoro, chloro, methyl, *iso*-propyl, methoxy and hydroxy, or

(b) naphthyl optionally substituted by a hydroxy,

(c) pyridyl optionally substituted by a hydroxy or a –C(=O)Omethyl group,

(d) a $(C_3$-$C_8)$cycloalkyl optionally substituted with a substituent selected from the group consisting of hydroxy, -C(=O)-O-$(C_1$-$C_4)$alkyl and $(C_1$-$C_4)$alkyl-C(=O)-O-$(C_1$-$C_4)$alkyl,

(e) $(C_1$-$C_6)$alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, –C(=O)Omethyl, –C(=O)Oethyl, $(C_3$-$C_8)$cycloalkyl and phenyl, where said phenyl is optionally substituted with 1 or 2 substituents each independently selected from the group consisting of fluoro, chloro, methyl, methoxy and hydroxy,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

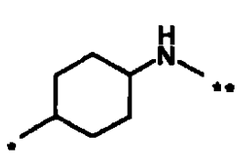
with the proviso that :

1) when :

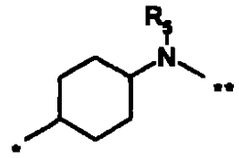
- $R_1$ is selected from the group consisting of hydrogen atom and fluoro,
- $R_2$ is a hydrogen atom,
- X is -O-,

❖ $R_3$ is a phenyl substituted by a –S-methyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of fluoro, chloro, methyl and ethyl,

❖ Y is a partial formula (1.5) or (1.8) :



(1.5)



(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1),

and wherein $R_5$ is a benzyl optionally substituted by hydroxy, and

❖ Z is a radical –C(=O)-

then $R_4$ cannot be :

a) an unsubstituted ($C_3$-$C_8$)cycloalkyl,

b) a phenyl optionally substituted by hydroxy, fluoro, chloro, methyl, *iso*-propyl or methoxy or ($C_1$-$C_3$)alkoxy,

c) a pyridyl optionally substituted by a hydroxy, or

d) a ($C_1$-$C_6$)alkyl optionally substituted with a hydroxy, or with a phenyl optionally substituted by hydroxy, fluoro, chloro, methyl or methoxy,

2) and when :

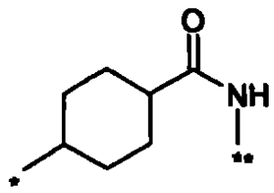
❖ $R_1$ is selected from the group consisting of hydrogen atom and fluoro,

❖ $R_2$ is a hydrogen atom,

❖ X is -O-,

❖ $R_3$ is a phenyl substituted by –S-methyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of fluoro, chloro, methyl and ethyl, and

❖ Y-Z represents a partial formula (1.16) :



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

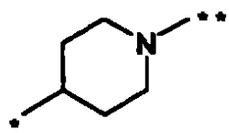
then $R_4$ cannot be :

a) a ($C_3$-$C_8$)cycloalkyl or

b) a ($C_1$-$C_8$)alkyl optionally substituted by a phenyl optionally substituted by hydroxy, fluoro, chloro, methyl and methoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom and fluoro,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by –S-methyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent(s) selected from the group consisting of fluoro, chloro, methyl and ethyl,
- Y is a partial formula (1.6) :



(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and

- Z is a radical –C(=O)-,

then $R_4$ cannot be a ($C_1$-$C_6$)alkyl optionally substituted by a hydroxy.

Particularly preferred examples of the nicotinamide derivatives compounds of the formula (1) are as described in the Examples section hereafter.

The nicotinamide derivatives of formula (1) may also be optionally transformed in pharmaceutically acceptable salts. In particular, these pharmaceutically acceptable salts of the nicotinamide derivatives of the formula (1) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from mineral or organic non-toxic acids which form non-toxic salts. Suitable examples of these acid addition salts are the hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, *p*-toluenesulphonate and pamoate salts.

Suitable base salts are formed from bases, which form non-toxic salts, such as alkali metal salts, earth metal salts or addition salts with ammonia and physiologically tolerable organic amines. Suitable examples of these base salts are the sodium, potassium, aluminium, calcium, magnesium, zinc or ammonium salts as well as addition salts with triethylamine, ethanolamine, diethanolamine, trimethylamine, methylamine, propylamine, diisopropylamine, N,N-dimethylethanolamine, benzylamine, dicylohexylamine, N-benzyl-β-phenethylamine, N,N'-dibenzylethylenediamine, diphénylènediamine, quinine, choline, arginine, lysine, leucine, dibenzylamine, tris(2-hydroxyethyl)amine, or α,α,α-tris(hydroxymethyl)methylamine.

Compounds, which contain both acidic groups and basic groups can also be present in the form of internal salts or betaines, which are also included by the present invention. For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19, 1977.

Salts can generally be obtained from the nicotinamide derivatives of the formula (1) according to customary procedures known to the person skilled in the art, for example by combining with an organic or inorganic acid or base solvent or dispersant, or alternatively from other salts by anion exchange or cation exchange. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

The nicotinamide derivatives of the formula (1) can also be present in stereoisomeric forms. If the nicotinamide derivatives of the formula (1) contain one or more centers of asymmetry, these can independently of one another have the (S) configuration or the (R) configuration. The invention includes all possible stereoisomers of the nicotinamide derivatives of the formula (1), for example enantiomers and diastereomers, and mixtures of two or more stereoisomeric forms, for example mixtures of enantiomers and/or diastereomers, in all ratios. The invention thus relates to enantiomers in enantiomerically pure form, both as levorotatory and dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. The invention likewise relates to diastereomers in diastereomerically pure form and in the form of mixtures in all ratios. In the presence of cis/trans isomerism, the invention relates to both the cis form and the trans form and mixtures of these forms in all ratios. Individual stereoisomers can be prepared, if desired, by use of stereochemically homogeneous starting substances in the synthesis, by stereoselective synthesis or by separation of a mixture according to customary methods, for example by chromatography, crystallization or by chromatography on chiral phases. If appropriate, derivatization can be carried out before separation of stereoisomers. A stereoisomer mixture can be separated at the stage of the nicotinamide derivatives of the formula (1) or at the stage of a starting substance or of an intermediate in the course of the synthesis.

The compounds of the formula (1) according to the invention can moreover contain mobile hydrogen atoms, i.e. be present in various tautomeric forms. The present invention also relates to all tautomers of the compounds of the formula (1).

The present invention furthermore includes other types of derivatives of nicotinamide derivatives of the formula (1), for example, solvates such as hydrates and polymorphs, i.e. the various different crystalline structures of the nicotinamide derivatives according to the present invention.

The present invention also includes all suitable isotopic variations of the nicotinamide derivatives of the formula (1) or a pharmaceutically acceptable salt thereof. An isotopic variation of the nicotinamide derivatives of the formula (1) or a pharmaceutically acceptable salt thereof is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into the nicotinamide derivatives of the formula (1) and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, sulphur, fluorine and chlorine such as $^{2}H$, $^{3}H$, $^{13}C$, $^{14}C$, $^{15}N$, $^{17}O$, $^{18}O$, $^{35}S$, $^{18}F$ and $^{36}Cl$, respectively. Certain isotopic variations of the nicotinamide derivatives of the formula (1) and pharmaceutically acceptable salts thereof, for example, those in which a radioactive isotope such as $^{3}H$ or $^{14}C$ is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., $^{3}H$, and carbon-14, i.e., $^{14}C$, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., $^{2}H$, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the nicotinamide derivatives of the formula (1) and pharmaceutically acceptable salts thereof of this invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples and Preparations sections hereafter using appropriate isotopic variations of suitable reagents.

If appropriate, the present invention also concerns the active metabolites of the nicotinamide derivatives of the formula (1), i.e. the derivatives which are formed during the cellular metabolism and that are active on organism. For

example, such metabolites can be glucuronide derivatives, N-oxide derivatives or sulfonate derivatives of the compounds of the formula (1).

According to a further aspect, the present invention concerns mixtures of nicotinamide derivatives of the formula (1), as well as mixtures with or of their pharmaceutically acceptable salts, solvates, polymorphs, isomeric forms, metabolites and/or isotope forms.

According to the present invention, all the here above mentioned forms of the nicotinamide derivatives of formula (1) except the pharmaceutically acceptable salts (i.e. said solvates, polymorphs, isomeric forms, metabolites and isotope forms), are defined as "derived forms" of the nicotinamide derivatives of formula (1) in what follows.

The nicotinamide derivatives of formula (1), their pharmaceutically acceptable salts and/or derived forms, are valuable pharmaceutical active compounds, which are suitable for the therapy and prophylaxis of numerous disorders in which the PDE4 enzymes are involved, in particular the inflammatory disorders, allergic disorders, respiratory diseases and wounds. The nicotinamide derivatives of formula (1) and their pharmaceutically acceptable salts and derived forms as mentioned above can be administered according to the invention to animals, preferably to mammals, and in particular to humans, as pharmaceuticals for therapy or prophylaxis. They can be administered per se, in mixtures with one another or in the form of pharmaceutical preparations which permit enteral (gastric) or parenteral (non-gastric) administration and which as active constituent contain an efficacious dose of at least one nicotinamide derivative of the formula (1), its pharmaceutically acceptable salts and/or derived forms, in addition to customary pharmaceutically innocuous excipients and/or additives.

Thus, the present invention also relates to pharmaceutical compositions containing an efficacious dose of at least one nicotinamide derivative of formula (1) and/or their pharmaceutically acceptable salts and/or derived forms, in addition to customary pharmaceutically innocuous excipients and/or additives.

Such compositions are prepared according to well-known methods compatible with the standard pharmaceutical practice. Said composition generally contain from 0.5 % to 60 % in weight of the active compound and from 40 % to 99.5 % in weight of excipients and/or additives. According to the present invention, said excipients and/or additives are agents well known to the artisan for providing favourable properties in the final pharmaceutical composition. Typical excipients and/or additives include, but are by no mean limited to, acidifying and alkalizing agents, aerosol propellants, anti-microbial agents (including anti-bacterial, anti-fungal and anti-protozoal agents), antioxidants, buffering agents, chelating agents, dermatologically active agents, dispersing agents, suspending agents, emollients, emulsifying agents, penetration enhancers, preservatives, sequestering agents, solvents, stabilizers, stiffening agents, sugars, surfactants and flavouring agents. Furthermore, said compositions are prepared in a form compatible for the intended route of administration, which is used for any given patient, as well as appropriate to the disease, disorder or condition for which any given patient is being treated. Suitable routes of administration that can be envisaged are enteral and parenteral routes of administration, such as for example the topical, oral, intranasal, pulmonary, rectal, intra-veinous, intra-arterial, intra-peritoneal, intra-thecal, intra-ventricular, intra-urethral, intra-sternal, intra-cranial, intra-muscular, subcutaneous or ocular routes.

When an administration by the oral route is intended, the nicotinamide derivatives of formula (1), their pharmaceutically acceptable salts and/or their derived forms, can be administered in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The nicotinamid derivatives of formula (1), their pharmaceutically acceptable salts and/or their derived forms, may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the nicotinamide derivatives of formula (1), their pharmaceutically acceptable salts and/or their derived forms, may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

As a general example, a formulation of the tablet could typically contain between about 0.01 mg and 500 mg of active compound whilst tablet fill weights may range from 50 mg to 1000 mg. The tablets may be manufactured by a standard process, for example direct compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can also be administered by injection, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such administration they are best used in

the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of such formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For both oral administration and injection to human patients, the daily dosage level of the nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, will usually be from 0.001 mg/kg to 100 mg/kg (in single or divided doses).

The nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can also be administered intra-nasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a nicotinamide derivative of the formula (1) and a suitable powder base such as lactose or starch.

Aerosol or dry powder formulations are preferably arranged so that each metered dose or "puff" contains from 1 µg to 4000 µg of a nicotinamide derivative of the formula (1) for delivery to the patient. The overall daily dose

with an aerosol will be in the range of from 1 µg to 20 mg, which may be administered in a single dose or, more usually, in divided doses throughout the day.

The nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can also be administered topically, or transdermally, in the form of creams, gels, suspensions, lotions, ointments, dusting powders, sprays, foams, mousses, drug-incorporated dressings, solutions, sponges, fibres, microemulsions, films, skin patches, ointments such as petrolatum or white soft paraffin based ointments or via a skin patch or other device. Penetration enhancers may be used, and the compound may be used in combination with cyclodextrins. In addition, the compound may be delivered using iontophoresis, electropration, phonophoresis or sonophoresis. They could be administered directly onto a wound site. They could be incorporated into a coated suture. For example they can be incorporated into a lotion or cream consisting of an aqueous or oily emulsion of mineral oils, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, water, polyethylene glycols and/or liquid paraffin, or they can be incorporated into a suitable ointment consisting of one or more of the following : mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water, or as hydrogel with cellulose or polyacrylate derivatives or other viscosity modifiers, or as a dry powder or liquid spray or aerosol with butane/propane, HFA, CFC, CO2 or other suitable propellant, optionally also including a lubricant such as sorbitan trioleate, or as a drug-incorporated dressing either as a tulle dressing, with white soft paraffin or polyethylene glycols impregnated gauze dressings or with hydrogel, hydrocolloid, alginate or film dressings.

For topical administration to human patients with acute/surgical wounds or scars, the daily dosage level of the compounds, in suspension or other formulation, could be from 0.01 to 50 mg/ml, preferably from 0.3 to 30 mg/ml.

The dosage will vary with the size of the wound, whether or not the wound is open or closed or partially closed, and whether or not the skin is intact.

Alternatively, the nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can be rectally administered, for example in the form of a suppository of a gel, although other forms can be considered.

They may also be administered via the ocular route, in particular for ocular scarring. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

The various pharmaceutical formulations as decribed here above are also detailed in "Pharmacie galénique" from A. Lehir (Ed. Mason, 1992, 2nd edition).

The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight, health state and sex of the patient as well as the severity of the disease, disorder or condition to treat, the optional combination with other treatment(s), the response of the particular patient and in general any factor peculiar to the concerned disease, disorder or condition and to the patient. Thus, the daily dose among men may usually contain from 50 mg to 5 g of active compound for administration singly or two or more at a time, as appropriate. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

According to the present invention, the nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation

of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. α-, β- and γ-cyclodextrins are most commonly used and suitable examples are described in WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

According to another embodiment of the present invention, the nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, can also be used as a combination with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result. The second and more additional therapeutic agents may also be a nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms, or one or more PDE4 inhibitors known in the art. More typically, the second and more therapeutic agents will be selected from a different class of therapeutic agents.

As used herein, the terms "co-administration", "co-administered" and "in combination with", referring to the nicotinamide derivatives of formula (1) and one or more other therapeutic agents, is intended to mean, and does refer to and include the following :

- simultaneous administration of such combination of nicotinamide derivative(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,

- substantially simultaneous administration of such combination of nicotinamide derivative(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 taken at substantially the

same time by said patient, whereupon said components are released at substantially the same time to said patient,

- sequential administration of such combination of nicotinamide derivative(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 taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and

- sequential administration of such combination of nicotinamide derivative(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 administered at the same and/or different times by said patient.

Suitable examples of other therapeutic agents which may be used in combination with the nicotinamide derivatives of the formula (1), their pharmaceutically acceptable salts and/or their derived forms include, but are by no mean limited to :

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

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

(c) Histaminic receptor antagonists including H1 and H3 antagonists,

(d) $\alpha_1$- and $\alpha_2$-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,

(e) Muscarinic M3 receptor antagonists or anticholinergic agents,

(f) $\beta_2$-adrenoceptor agonists,

(g) Theophylline,

(h) Sodium cromoglycate,

(i) COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors,

(j) Oral or inhaled Glucocorticosteroids,

(k) Monoclonal antibodies active against endogenous inflammatory entities,

(l) Anti-tumor necrosis factor (anti-TNF-α) agents,

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

(n) Kinin-$B_1$- and $B_2$-receptor antagonists,

(o) Immunosuppressive agents,

(p) Inhibitors of matrix metalloproteases (MMPs),

(q) Tachykinin $NK_1$, $NK_2$ and $NK_3$ receptor antagonists,

(r) Elastase inhibitors,

(s) Adenosine A2a receptor agonists,

(t) Inhibitors of urokinase,

(u) Compounds that act on dopamine receptors, e.g. D2 agonists and

(v) Modulators of the NFκβ pathway, e.g. IKK inhibitors.

According to the present invention, combination of the nicotinamide derivatives of formula (1) with :

- muscarinic M3 receptor agonists or anticholinergic agents including in particular ipratropium salts, namely bromide, tiotropium salts, namely bromide, oxitropium salts, namely bromide, perenzepine, and telenzepine,

- $\beta_2$-adrenoceptor agonists including albutarol, salbutamol, formoterol and salmeterol,

- glucocorticosteroids, in particular inhaled glucocorticosteroids with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate,

- or adenosine A2a receptor agonists,

are preferred.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment. The description which follows concerns the therapeutic applications to which the nicotinamide derivatives of formula (1) may be put.

The nicotinamide derivatives of formula (1) 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 increase, include inhibition of superoxide production, degranulation, chemotaxis and tumor necrosis factor (TNF) release in eosinophils, neutrophils and monocytes.

Therefore, a further aspect of the present invention relates to the use of the nicotinamide derivatives of formula (1), their pharmaceutically acceptable salts and/or derived forms, in the treatment of diseases, disorders, and conditions in which the PDE4 isozymes are involved. More specifically, the present invention also concerns the use of the nicotinamide derivatives of formula (1), their pharmaceutically acceptable salts and/or derived forms, in the treatment of diseases, disorders, and conditions selected from the group consisting of :

- asthma of whatever type, etiology, or pathogenesis, in particular 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, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma and 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, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of 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, in particular 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, in particular 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, in particular 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, in particular 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, in particular 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, in particular 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, allergic dermatitis, contact dermatitis, or allergic or atopic eczema,

- urticaria of whatever type, etiology, or pathogenesis, in particular 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, in particular 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, in particular 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, in particular 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, in particular 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, endocrin opthamopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, juvenile diabetes or diabetes mellitus type I, keratoconjunctivitis sicca, epidemic keratoconjunctivitis, diffuse interstitial pulmonary fibrosis or interstitial lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, glomerulonephritis with and without nephrotic syndrome, acute glomerulonephritis, idiopathic nephrotic syndrome, minimal change nephropathy, inflammatory/hyperproliferative skin diseases, 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, in particular inflammatory bowel disease that is a member selected from the group consisting of collagenous colitis, colitis polyposa, transmural colitis, ulcerative colitis and Crohn's disease (CD),
- septic shock of whatever type, etiology, or pathogenesis, in particular 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 of whatever type, etiology or pathogenesis including primary pulmonary hypertension / essential hypertension, pulmonary hypertension secondary to congestive heart failure, pulmonary hypertension secondary to chronic obstructive pulmonary disease, pulmonary venous hypertension, pulmonary arterial hypertension and hypoxia-induced pulmonary hypertension,

- bone loss diseases, primary osteoporosis and secondary osteoporosis,

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

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

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

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

- reduction of scar formation in the human or animal body, such as scar formation in the healing of acute wounds, and

- psoriasis, other dermatological and cosmetic uses, including antiphlogistic, skin-softening, skin elasticity and moisture-increasing activities.

A still further aspect of the present invention also relates to the use of the nicotinamide derivatives of formula (1), their pharmaceutically acceptable salts and/or derived forms, for the manufacture of a drug having a PDE4 inhibitory activity. In particular, the present inventions concerns the use of the nicotinamide derivatives of formula (1), their pharmaceutically acceptable salts and/or derived forms, for the manufacture of a drug for the treatment of inflammatory, respiratory, allergic and scar-forming diseases, disorders, and conditions, and more precisely for the treatment of diseases, disorders, and conditions that are listed above.

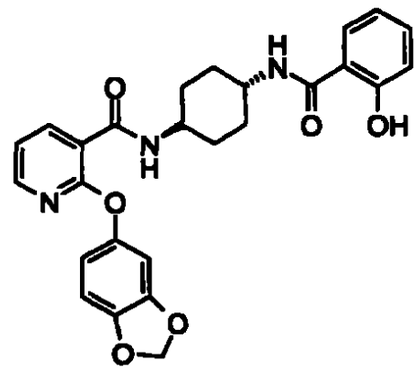
As a consequence, the present invention provides a particularly interesting method of treatment of a mammal, including a human being, with a PDE4 inhibitor including treating said mammal with an effective amount of a nicotinamide derivative of formula (1), its pharmaceutically acceptable salts and/or derived forms. More precisely, the present invention provides a particularly interesting method of treatment of a mammal, including a human being, to treat an inflammatory, respiratory, allergic and scar-forming disease, disorder or condition, including treating said mammal with an effective amount of a nicotinamide derivative of formula (1), its pharmaceutically acceptable salts and/or derived forms.

The following examples illustrate the preparation of the nicotinamide derivatives of the formula (1) :

43
44

## EXAMPLES

**Example 1 : *anti*-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(2-hydroxy-benzoyl amino)-cyclohexyl]-nicotinamide**



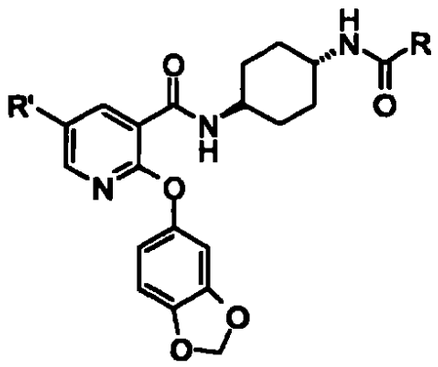
2-Hydroxybenzoic acid (101 mg, 0.767 mmol), 1-hydroxybenzotriazole hydrate (155 mg, 1.15 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (220 mg, 1.15 mmol) were stirred in N,N-dimethylformamide (5 ml) under an atmosphere of nitrogen at room temperature for 1.5 hours. *Anti*-N-(4-Amino-cyclohexyl)-2-(benzo[1,3]dioxol-5-yloxy)-nicotinamide hydrochloride (0.3 g, 0.767 mmol) (see Preparation 2) and N-methyl morpholine (0.167 ml, 0.767 mmol) were then added, and the reaction mixture stirred at room temperature for a further 18 hours. The mixture was then partitioned between dichloromethane (10 ml) and 10% citric acid (10 ml). The organic layer was separated and passed through a hydrophobic frit. The solvent was removed *in vacuo*, and the residue was triturated with methanol (5 ml) to give *anti*-2-(benzo[1,3]dioxol-5-yloxy)-N-[4-(2-hydroxy-benzoylamino)-cyclohexyl]-nicotinamide (160.7 mg) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): $\delta$ = 12.30 (1H, s), 8.57-8.61 (1H, d), 8.01-8.05 (1H, d), 7.74-7.79 (1H, d), 7.33-7.40 (1H, d), 7.12-7.17 (1H, m), 6.93-6.99 (1H, d), 6.78-6.84 (2H, m), 6.69-6.70 (1H, d), 6.59-6.63 (1H, d), 6.19-6.23 (1H, d), 6.02 (2H, s), 3.96-4.09 (2H, m), 2.14-2.26 (4H, m), 1.39-1.50 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 476.

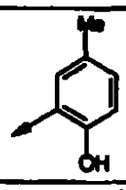
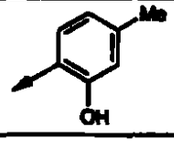
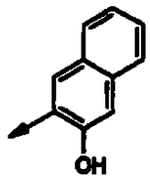
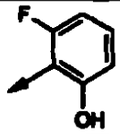
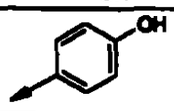
**Examples 2-10**

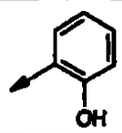
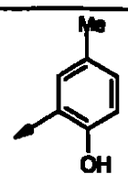
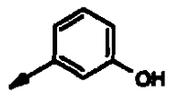
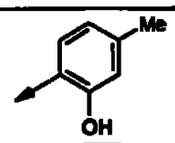
The compounds of the following tabulated examples (Table 1) of the general formula :



were prepared by a similar method to that of Example 1 using the appropriate carboxylic acid and amine as the starting materials.

**TABLE 1**

| ExampleNo. | Starting Amine Prep No. | R' | R |
|---|---|---|---|
| 2 | 2 | H |  |
| 3 | 2 | H |  |
| 4 | 2 | H |  |
| 5' | 39 | F |  |
| 6' | 39 | F |  |

| | | | |
|---|---|---|---|
| 7[1] | 39 | F |  |
| 8[1] | 39 | F |  |
| 9[1] | 39 | F |  |
| 10[1] | 39 | F |  |

[1] These examples were purified by flash column chromatography on silica gel eluting with a solvent mixture of dichloromethane : pentane (1 : 1, by volume) changing to dichloromethane : methanol (50 : 1, by volume) prior to trituration with diethylether.

**Example 2 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12.08 (1H, s), 8.57-8.61 (1H, d), 8.20-8.24 (1H, d), 7.74-7.79 (1H, d), 7.10-7.20 (3H, m), 6.81-6.89 (2H, m), 6.69 (1H, s), 6.59-6.63 (1H, d), 6.13-6.18 (1H, d), 6.02 (2H, s), 3.96-4.09 (2H, m), 2.31 (3H, s); 2.09-2.29 (4H, m), 1.39-1.53 (4H, m) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 490

**Example 3 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12.23 (1H, s), 8.73-8.78 (1H, d), 8.18-8.22 (1H, d), 7.67-7.76 (1H, d), 7.14-7.20 (1H, d), 7.05-7.12 (1H, m), 6.79-6.82 (1H, d), 6.77 (1H, s), 6.64 (1H, s), 6.56-6.62 (2H, m), 6.00-6.04 (1H, d), 5.99 (2H, s), 3.90-4.05 (2H, m), 2.30 (3H, s); 2.05-2.22 (4H, m), 1.36-1.49 (4H, m) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 490

**Example 4 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 11.68 (1H, s), 8.53-8.58 (1H, d), 8.17-8.19 (1H, d), 7.93 (1H, s), 7.70-7.78 (2H, m), 7.62-7.66 (1H, d), 7.38-7,44 (1H, t), 7.23-7.28 (2H, m), 7.03-7.08 (1H, m), 6.79-6.83 (1H, d), 6.64 (1H, s), 6.52-6.60 (2H, m), 6.00 (2H, s), 3.97-4.05 (2H, m), 2.17-2.23 (4H, brt), 1.39-1.58 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 526

**Example 5 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 13.24 (1H, s), 8.34-8.38 (1H, m), 8.05-8.07 (1H, d), 7.73-7.99 (1H, d), 7.25-7.32 (1H, m, partially masked by solvent), 6.88-6.96 (1H, m), 6.83-6.87 (1H, d), 6.76-6.81 (1H, d), 6.66 (1H, s), 6.53-6.63 (2H, m), 6.03 (2H, s), 3.95-4.15 (2H, m), 2.12-2.26 (4H, m), 1.39-1.54 (4H, m) ppm.

LCMS (electrospray) : m/z $[M-H]^+$ 510

**Example 6 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.28-8.35 (1H, m), 8.03-8.08 (1H, d), 7.73-7.84 (1H, d), 7.57-7.71 (2H, d), 6.76-6.91 (3H, m), 6.67 (1H, s), 6.57-6.62 (1H, d), 6.16 (1H, s), 6.02 (2H, s), 5.83-5.92 (1H, d), 3.90-4.08 (2H, m), 2.08-2.23 (4H, m), 1.35-1.50 (4H, m) ppm.

LCMS (electrospray) : m/z $[M-H]^+$ 492

**Example 7 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.30-8.36 (1H, m), 8.04-8.08 (1H, d), 7.73-7.82 (1H, d), 7.29-7.41 (2H, m), 6.93-6.98 (1H, d), 6.79-6.87 (2H, m), 6.66 (1H, s), 6.57-6.63 (1H, d), 6.11-6.20 (1H, d), 6.03 (2H, s), 3.93-4.10 (2H, m), 2.10-2.29 (4H, m), 1.39-1.57 (4H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 492

**Example 8 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.27-8.36 (1H, m), 8.01-8.07 (1H, m), 7.73-7.82 (1H, m), 7.15-7.22 (1H, m), 6.78-6.90 (2H, m), 6.63-6.67 (1H, m), 6.54-6.62

(1H, m), 6.05-6.15 (1H, m), 6.02 (2H, s), 3.88-4.09 (2H, m), 2.29 (3H, s), 2.09-2.26 (4H, m), 1.37-1.49 (4H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 506

**Example 9 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.03-8.09 (1H, d), 7.93-7.99 (1H, m), 7.17-7.27 (3H, m), 6.87-6.93 (1H, m), 6.77-6.84 (1H, d), 6.70-6.73 (1H, d), 6.57-6.62 (1H, d), 5.97 (2H, s), 3.80-3.98 (2H, m), 1.96-2.18 (4H, m), 1.41-1.63 (4H, m) ppm.

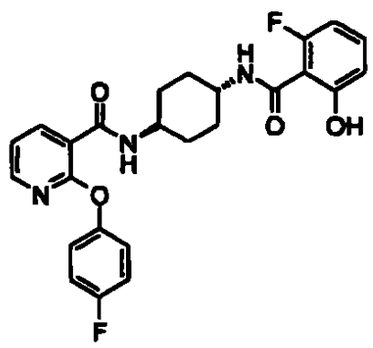
LRMS (electrospray) : m/z $[M-H]^+$ 492

**Example 10 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12.26 (1H, s), 8.30-8.36 (1H, m), 8.04-8.07 (1H, d), 7.74-7.82 (1H, d), 7.17-7.22 (1H, d), 6.83-6.86 (1H, d), 6.77 (1H, s), 6.55-6.67 (3H, m), 6.03-6.12 (1H, d), 6.02 (2H, s), 3.92-4.08 (2H, m), 2.33 (3H, s), 2.12-2.25 (4H, m), 1.36-1.51 (4H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 506

**Example 11 : *anti*-N-[4-(2-fluoro-6-hydroxy-benzoylamino)-cyclohexyl]-2-(4-fluoro-phenoxy)-nicotinamide**




2-Fluoro-6-hydroxylbenzoic acid (128 mg, 0.82 mmol), 1-hydroxybenzotriazole (166 mg, 1.23 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (204 mg, 1.07 mmol), *anti*-N-(4-amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (300 mg, 0.82 mmol) (see Preparation 4) and N-methyl morpholine (0.18 ml, 1.64 mmol) were stirred in N,N-

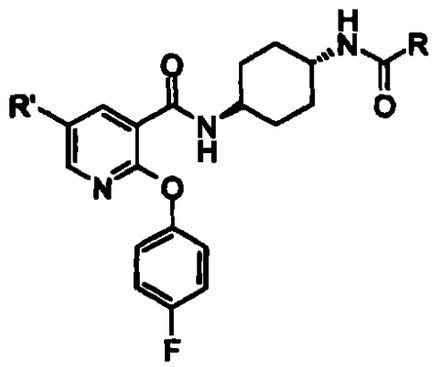
dimethylformamide (5 ml) under at atmosphere of nitrogen at room temperature for 18 hours. The mixture was then partitioned between dichloromethane (6 ml) and 10 % acetic acid (6 ml) and the organic layer separated. The organic layer was dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The residue was triturated with diethylether (5 ml) to give *anti*-N-[4-(2-fluoro-6-hydroxy-benzoylamino)-cyclohexyl]-2-(4-fluoro-phenoxy)-nicotinamide (110 mg) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 10.95 (1H, brs), 8.23-8.28 (1H, d), 8.19-8.22 (1H, d), 8.04-8.18 (1H, m), 7.98-8.03 (1H, d), 7.15-7.28 (5H, m), 6.60-6.75 (2H, m), 3.70-3.80 (2H, m), 1.80-2.00 (4H, m), 1.31-1.49 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 468

**Examples 12-40**

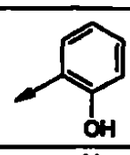
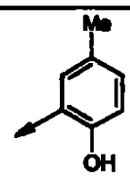
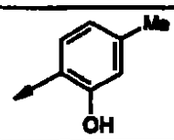
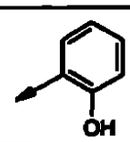
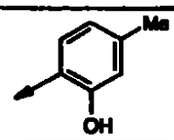
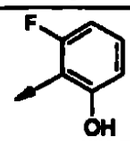
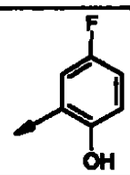
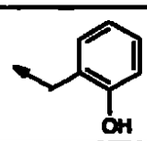
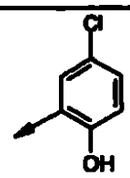
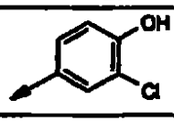
The compounds of the following tabulated examples (Table 2) of the general formula :

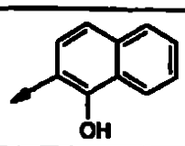
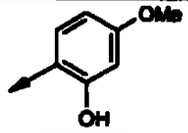
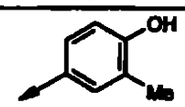
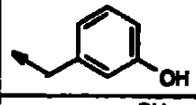
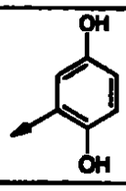
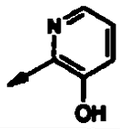
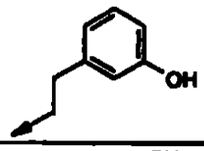
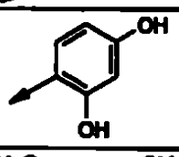
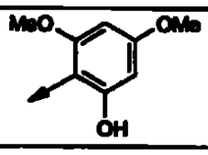
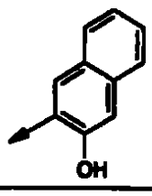
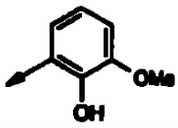


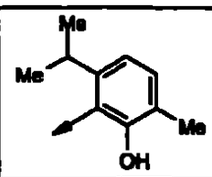
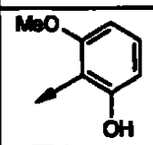
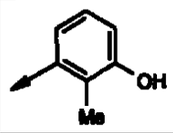
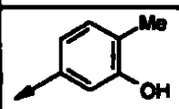
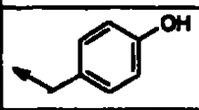
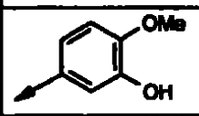
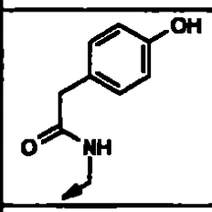
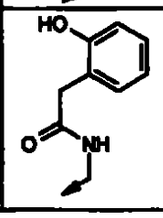

were prepared by a similar method to that of Example 11 using the appropriate carboxylic acid and amine as the starting materials.

46
47

**TABLE 2**

| Example No. | Starting Amine Prep No. | R' | R |
|---|---|---|---|
| 12 | 4 | H |  |
| 13 | 4 | H |  |
| 14 | 4 | H |  |
| 15[1] | 7 | F |  |
| 16[1] | 7 | F |  |
| 17[1] | 7 | F |  |
| 18[1] | 7 | F |  |
| 19[1,2] | 7 | F |  |
| 20[1] | 7 | F |  |
| 21[1] | 7 | F |  |

| | | | |
|---|---|---|---|
| 22' | 7 | F |  |
| 23' | 7 | F |  |
| 24' | 7 | F |  |
| 25' | 7 | F |  |
| 26' | 7 | F |  |
| 27' | 7 | F |  |
| 28' | 7 | F |  |
| 29' | 7 | F |  |
| 30' | 7 | F |  |
| 31' | 7 | F |  |
| 32' | 7 | F |  |

| | | | |
|---|---|---|---|
| 33[1] | 7 | F |  |
| 34[1] | 7 | F |  |
| 35[1] | 7 | F |  |
| 36[1] | 7 | F |  |
| 37[1] | 7 | F |  |
| 38[1] | 7 | F |  |
| 39[1] | 9 | F |  |
| 40[1] | 9 | F |  |

[1] These examples were partitioned between ethyl acetate and water, and the organic phase was washed with a saturated aqueous solution of sodium chloride.

[2] These examples were purified by flash column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol (100 : 0 changing to 95 : 5, by volume) to give the final compound.

**Example 12 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12.29 (1H, s), 8.56-8.60 (1H, d), 8.18-8.21 (1H, d), 7.66-7.72 (1H, d), 7.36-7.40 (2H, m), 7.12-7.18 (4H, d), 6.96-6.99 (1H, d), 6.78-6.83 (1H, d), 6.17-6.22 (1H, d), 3.96-4.12 (2H, m), 2.12-2.29 (4H, m), 1.40-1.53 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 450

**Example 13 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12.05 (1H, s), 8.58-8.62 (1H, d), 8.18-8.22 (1H, d), 7.68-7.75 (1H, d), 7.09-7.20 (6H, m), 6.83-6.88 (1H, d), 6.15-6.19 (1H, d), 3.94-4.11 (2H, m), 2.29 (3H, s), 2.13-2.24 (4H, m), 1.40-1.55 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 464

**Example 14 :**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 12.26 (1H, s), 8.58-8.62 (1H, d), 8.18-8.22 (1H, m), 7.68-7.73 (1H, d), 7.20-7.24 (1H, d), 7.10-7.19 (4H, m), 6.78 (1H, s), 6.61-6.67 (2H, d), 6.04-6.10 (2H, d), 3.92-4.10 (2H, m), 2.32 (3H, s), 2.15-2.23 (4H, m), 1.40-1.55 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 464

Found C, 67.14; H, 5.62; N, 8.82. $C_{26}H_{28}FN_3O_4$ requires C, 67.37; H, 5.65; N, 9.07%.

**Example 15 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12.55 (1H, s), 8.43-8.49 (1H, d), 8.24-8.30 (1H, d), 8.08-8.14 (1H, d), 7.84-7.90 (1H, d), 7.22-7.35 (1H, t), 7.08-7.20 (4H, m), 6.74-6.83 (2H, d), 3.60-3.80 (2H, m), 1.76-1.90 (4H, m), 1.20-1.50 (4H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

48
49

**Example 16 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 12.28 (1H, s), 8.50-8.57 (1H, m), 8.02-8.06 (1H, d), 7.70-7.78 (1H, d), 7.10-7.20 (4H, m), 6.68 (1H, s), 6.62-6.67 (1H, d), 6.12-6.21 (1H, d), 3.85-3.95 (2H, m), 2.33 (3H, s), 2.00-2.28 (4H, m), 1.40-1.50 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 482

**Example 17 :**

$^1$H NMR (300MHz, $CDCl_3$): δ = 13.25 (1H, s), 8.33-8.40 (1H, m), 8.03-8.07 (1H, d), 7.70-7.79 (1H, d) 7.25-7.35 (1H, m, partially masked by solvent), 7.12-7.20 (4H, m), 6.85-7.00 (1H, dd), 6.75-6.83 (1H, d), 6.50-6.63 (1H, dd), 3.87-4.12 (2H, m), 2.13-2.26 (4H, m), 1.41-1.52 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+NH_4]^+$ 503

**Example 18 :**

$^1$H NMR (300MHz, DMSO-d$^5$): δ = 8.55-8.63 (1H, d), 8.32-8.38 (1H, d), 8.19-8.23 (1H, d), 7.92-7.99 (1H, m), 7.70-7.80 (1H, d), 7.17-7.28 (5H, m), 6.88-6.96 (1H, m), 3.69-3.85 (2H, m), 1.83-2.00 (4H, m), 1.33-1.53 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+NH_4]^+$ 503

**Example 19 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.69 (1H, s), 8.23-8.34 (1H, d), 8.18 (1H, s), 7.90-7.98 (2H, m), 7.15-7.28 (5H, m), 6.98-7.07 (1H, t), 6.66-6.80 (2H, m), 3.61-3.78 (1H, m), 3.40-3.60 (1H, m), 3.35 (2H, s, masked by solvent), 1.75-1.95 (4H, m), 1.22-1.46 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 482

**Example 20 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.63-8.69 (1H, d), 8.32-8.37 (1H, d), 8.17-8.21 (1H, d), 7.92-7.99 (2H, m), 7.37-7.42 (1H, m), 7.16-7.27 (4H, m), 6.86-6.93 (1H, d), 3.70-3.86 (2H, m), 1.85-2.01 (4H, m), 1.30-1.52 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 502, 504

**Example 21 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 10.72 (1H, s) 8.29-8.36 (1H, m), 8.17-8.22 (1H, m), 8.05-8.15 (1H, m), 7.92-7.98 (1H, m), 7.85 (1H, s), 7.63-7.68 (1H, d), 7.15-7.26 (4H, m), 6.92-6.99 (1H, d), 3.63-3.82 (2H, m), 1.76-1.98 (4H, m), 1.28-1.48 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 502, 504

**Example 22 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 14.67 (1H, s), 8.63-8.76 (1H, m), 8.34-8.43 (1H, d), 8.16-8.32 (2H, m), 7.83-8.03 (3H, m), 7.59-7.69 (1H, t), 7.32-7.40 (1H, d), 7.17-7.31 (4H, m), 6.88-6.96 (1H, m), 3.69-3.85 (2H, m), 1.83-2.00 (4H, m), 1.33-1.53 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 518

**Example 23 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 13.08 (1H, s) 8.28-8.36 (2H, t), 8.18-8.22 (1H, d), 7.91-7.97 (1H, m), 7.77-7.82 (1H, d), 7.15-7.31 (4H, m), 6.40-6.44 (1H, d), 6.38 (1H, s), 3.65-3.88 (2H, m), 1.78-2.04 (4H, m), 1.30-1.60 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 498

**Example 24 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9.76 (1H, s) 8.29-8.35 (1H, d), 8.18-8.21 (1H, d), 7.90-7.96 (1H, m), 7.83-7.89 (1H, d), 7.58 (1H, s), 7.45-7.52 (1H, d), 7.16-7.23 (4H, m), 6.72-6.78 (1H, d), 3.63-3.83 (2H, m), 2.11 (3H, s), 1.80-1.98 (4H, m), 1.30-1.52 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 482

**Example 25 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9.24 (1H, s), 8.25-8.32 (1H, d), 8.20 (1H, s), 7.84-7.99 (2H, t), 7.17-7.27 (4H, m), 6.99-7.10 (1H, t), 6.54-6.68 (3H, m), 3.60-

3.77 (2H, m), 3.35 (2H, s, masked by solvent), 1.74-1.95 (4H, m), 1.12-1.42 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 482

**Example 26 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 11.68 (1H, s), 8.96 (1H, s), 8.45-8.50 (1H, d), 8.32-8.37 (1H, d), 8.18-8.22 (1H, d), 7.92-7.99 (1H, m), 7.16-7.32 (5H, m), 6.81-6.87 (1H, m), 6.68-6.74 (1H, d), 3.67-4.06 (2H, m), 1.78-1.98 (4H, m), 1.35-1.56 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 484

**Example 27 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12.59 (1H, s), 8.89-8.97 (1H, d), 8.32-8.38 (1H, d), 8.19-8.22 (1H, d), 8.13-8.17 (1H, m), 7.93-8.01 (1H, m), 7.93-8.01 (1H, m), 7.48-7.53 (1H, m), 7.38-7.42 (1H, d), 7.16-7.36 (4H, m), 3.67-3.90 (2H, m), 1.79-2.02 (4H, m), 1.48-1.77 (2H, m), 1.32-1.47 (2H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 469

Found C, 60.94; H, 4.79; N, 11.83. $C_{24}H_{22}F_2N_4O_4$. 0.1mol $CH_2Cl_2$ requires C, 60.69; H, 4.69; N, 11.75%.

**Example 28 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9.19 (1H, s), 8.23-8.31 (1H, d), 8.18-8.21 (1H, m), 7.91-7.96 (1H, d), 7.65-70 (1H, d), 7.16-7.25 (4H, m), 6.98-7.09 (1H, m), 6.51-6.62 (3H, m), 3.56-3.77 (2H, m), 2.61-2.47 (2H, m), 2.23-2.33 (2H, m), 1.72-1.93 (4H, m), 1.18-1.40 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 496

**Example 29 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12.96 (1H, s), 10.04 (1H, s), 8.18-8.42 (3H, m), 7.90-8.10 (1H, m), 7.63-7.76 (1H, d), 7.07-7.45 (4H, m), 6.13-6.40 (2H, m), 3.60-3.90 (2H, m), 1.72-2.15 (4H, m), 1.28-1.60 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 484

Found C, 60.11; H, 4.99; N, 7.95. $C_{25}H_{23}F_2N_3O_5$. 0.25mol $CH_2Cl_2$ requires C, 60.09; H, 4.64; N, 8.33%.

**Example 30 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 14.27 (1H, s), 8.33-8.38 (1H, d), 8.19-8.23 (1H, d), 7.92-8.01 (1H, m), 7.17-7.37 (5H, m), 6.12 (1H, s), 6.08 (1H, s), 3.60-4.00 (8H, partially masked by solvent), 1.82-2.03 (4H, d), 1.24-1.60 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 528

**Example 31 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 12.08 (1H, brs), 8.80-8.86 (1H, d), 8.51 (1H, s), 8.35-8.42 (1H, d), 8.20-8.24 (1H, d), 7.92-7.99 (1H, m), 7.84-7.89 (1H, d), 7.72-7.78 (1H, d), 7.44-7,52 (1H, t), 7.28-7.36 (1H, t), 7.19-7.24 (5H, m), 3.72-3.93 (2H, m), 1.93-2.06 (4H, d), 1.36-1.62 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 518

**Example 32 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 12.77 (1H, s), 8.50-8.58 (1H, d), 8.33-8.38 (1H, d), 8.18-8.23 (1H, d), 7.92-8.02 (1H, m), 7.42-7.48 (1H, d), 7.16-7.38 (4H, m), 7.07-7.14 (1H, d), 6.73-6.83 (1H, t), 3.70-3.92 (5H, m), 1.80-2.08 (4H, m), 1.23-1.58 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 498

**Example 33 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.26-8.38 (1H, d), 8.19-8.22 (1H, m), 7.92-8.08 (2H, m), 7.16-7.36 (4H, m), 6.96-7.05 (1H, d), 6.68-6.75 (1H, d), 3.62-3.83 (2H, m), 2.80-2.95 (1H, m), 2.16 (3H, s), 1.78-2.02 (4H, m), 1.23-1.48 (4H, m), 1.08-1.16 (6H, d) ppm.

LRMS (electrospray): m/z $[M-H]^+$ 522

**Example 34 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 13.43 (1H, s), 8.32-8.39 (2H, m), 8.22-8.25 (1H, d), 7.92-8.02 (1H, m), 7.18-7.37 (5H, m), 6.54-6.60 (1H, d), 6.47-6.53 (1H, d), 3.89 (3H, s), 3.73-3.88 (2H, m), 1.89-2.04 (4H, d), 1.37-1.43 (4H, m) ppm.

LCMS (electrospray) : m/z $[M-H]^+$ 496

**Example 35 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.41 (1H, s), 8.32-8.38 (1H, d), 8.08-8.10 (1H, d), 7.96-8.04 (2H, m), 7.20-7.30 (4H, m), 6.96-7.02 (1H, t), 6.78-6.83 (1H, d), 6.64-6.70 (1H, d), 3.61-3.78 (2H, brs), 2.08 (3H, s), 1.80-1.98 (4H, m), 1.30-1.44 (4H, m) ppm.

LCMS (thermospray) : m/z $[M+H]^+$ 482, $[M+NH_4]^+$ 499.

**Example 36 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.42 (1H, s), 8.32-8.38 (1H, d), 8.18-8.20 (1H, d), 8.00-8.05 (1H, d), 7.93-8.00 (1H, m), 7.15-7.26 (6H, m), 7.08-7.13 (1H, d), 3.66-3.80 (2H, brs), 2.14 (3H, s), 1.80-1.97 (4H, m), 1.27-1.50 (4H, m) ppm.

LCMS (thermospray) : m/z $[M+H]^+$ 482, $[M+NH_4]^+$ 499.

**Example 37 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.18 (1H, s), 8.28-8.33 (1H, d), 8.18-8.20 (1H, d), 7.93-7.99 (1H, m), 7.83-7.89 (1H, d), 7.17-7.28 (4H, m), 6.98-7.05 (2H, d), 6.63-6.67 (2H, d), 3.60-3.80 (2H, brs), 3.30 (2H, s, masked by solvent), 1.73-1.92 (4H, m), 1.19-1.40 (4H, m) ppm.

LCMS (thermospray) : m/z $[M+H]^+$ 482, $[M+NH_4]^+$ 499.

**Example 38 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.08-9.13 (1H, brs), 8.32-8.37 (1H, d), 8.09-8.11 (1H, m), 7.94-8.00 (2H, m), 7.19-7.32 (6H, m), 6.91-6.96 (1H, d), 3.64-3.84 (5H, s + brs), 1.80-1.98 (4H, m), 1.30-1.50 (4H, m) ppm.

LCMS (thermospray) : m/z $[M+H]^+$ 498.

**Example 39 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.18-9.28 (1H, brs), 8.28-8.34 (1H, d), 8.19-8.21 (1H, d), 8.02-8.08 (1H, t), 7.95-7.99 (1H, m), 7.67-7.71 (1H, d), 7.18-7.29 (4H, m), 7.00-7.08 (2H, d), 6.65-6.70 (2H, d), 3.60-3.79 (3H, brs + d), 3.35-3.59 (3H, m, masked by solvent), 1.74-1.96 (4H, m), 1.19-1.42 (4H, m) ppm.

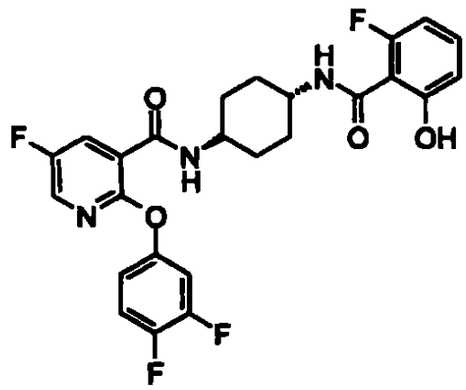
LCMS (thermospray) : m/z $[M+H]^+$ 539.

**Example 40 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.63 (1H, s), 8.25-8.35 (1H, d), 8.19-8.21 (1H, d), 8.00-8.07 (1H, t), 7.93-7.98 (1H, m), 7.58-7.63 (1H, d), 7.15-7.30 (4H, m), 7.00-7.14 (2H, m), 6.77-6.82 (1H, d), 6.70-6.76 (1H, t), 3.60-3.80 (3H, m + d), 3.41-3.58 (3H, m + s), 1.69-1.99 (4H, m), 1.20-1.44 (4H, m) ppm.

LCMS (thermospray) : m/z $[M+H]^+$ 539.

**Example 41 : *anti*-5-Fluoro-2-(3,4-difluoro-phenoxy)-N-[4-(2-fluoro-6-hydroxy-benzoyl mino)-cyclohexyl]-nicotinamide**



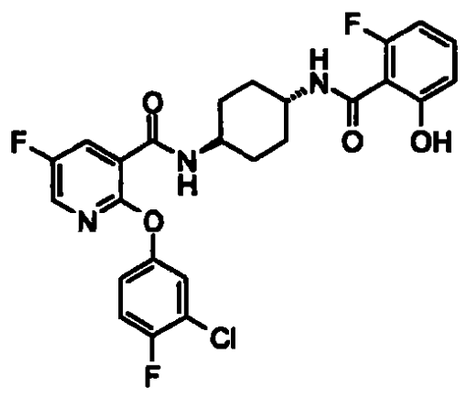
2-Fluoro-6-hydroxybenzoic acid (115 mg, 0.736 mmol), 1-hydroxybenzotriazole hydrate (149 mg, 1.11 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (184 mg, 0.957 mmol), *anti*-N-(4-amino-cyclohexyl)-5-fluoro-2-(3,4-difluoro-phenoxy)-nicotinamide hydrochloride (296 g, 0.736 mmol) (see Preparation 11) and N-methyl morpholine (0.16 ml, 1.46 mmol) were stirred in N,N-dimethylformamide (6 ml) under an atmosphere of nitrogen at room temperature for 18 hours. The mixture was then partitioned between ethyl

acetate (6 ml) and water (6 ml). The organic layer was separated, washed with a saturated aqueous solution of sodium chloride (6 ml) and dried over anhydrous magnesium sulphate. It was then concentrated *in vacuo*, and the residue triturated with diethylether (3-fold 5 ml) to give *anti*-5-fluoro-2-(3,4-difluoro-phenoxy)-N-[4-(2-fluoro-6-hydroxy-benzoylamino)-cyclohexyl]-nicotinamide (240 mg) as an off- white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 10.92 (1H, brs) 8.29-8.33 (1H, d), 8.23-8.27 (1H, d), 8.08-8.17 (1H, m), 7.90-8.03 (1H, m), 7.31-7.52 (2H, m), 7.18-7.30 (1H, m), 7.02-7.12 (1H, m), 6.60-6.71 (2H, m), 3.65-3.82 (2H, m), 1.82-2.00 (4H, m), 1.28-1.50 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 504

**Example 42 : *anti*-5-Fluoro-2-(3-chloro-4-fluoro-phenoxy)-N-[4-(2-fluoro-6-hydroxy-benzoylamino)-cyclohexyl]-nicotinamide**



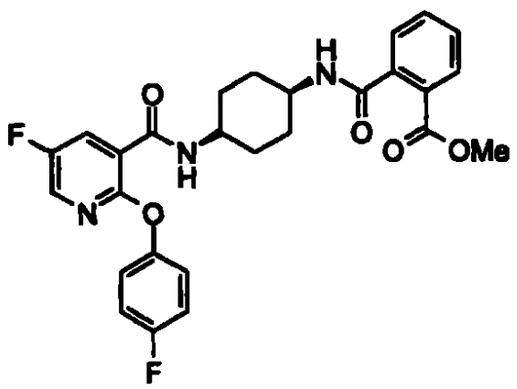
2-Fluoro-6-hydroxybenzoic acid (117 mg, 0.753 mmol), 1-hydroxybenzotriazole hydrate (153 mg, 1.13 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (188 mg, 0.979 mmol), *anti*-N-(4-amino-cyclohexyl)-5-fluoro-2-(3-chloro-4-fluoro-phenoxy)-nicotinamide hydrochloride (315 mg, 0.736 mmol) (see Preparation 13) and N-methyl morpholine (0.17 ml, 1.51 mmol) were stirred in N,N-dimethylformamide (6 ml) under an atmosphere of nitrogen at room temperature for 18 hours. The mixture was then partitioned between ethyl acetate (6 ml) and water (6 ml). The organic layer was separated, washed with

a saturated aqueous solution of sodium chloride (6 ml) and dried over anhydrous magnesium sulphate. It was then concentrated *in vacuo*, and the residue was triturated with diethylether (3-fold 5 ml) to give *anti*-5-fluoro-2-(3-chloro-4-fluoro-phenoxy)-N-[4-(2-fluoro-6-hydroxy-benzoylamino)-cyclohexyl]-nicotinamide (250 mg) as an off- white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 10.94 (1H, brs) 8.28-8.35 (1H, d), 8.23-8.26 (1H, d), 8.07-8.17 (1H, m), 7.92-8.03 (1H, m), 7.42-7.54 (2H, m), 7.17-7.28 (2H, m), 6.58-6.73 (2H, m), 3.64-3.83 (2H, m), 1.83-2.00 (4H, m), 1.31-1.50 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 520, 522

**Example 43 : *syn*-N-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-phthalamic acid methyl ester**



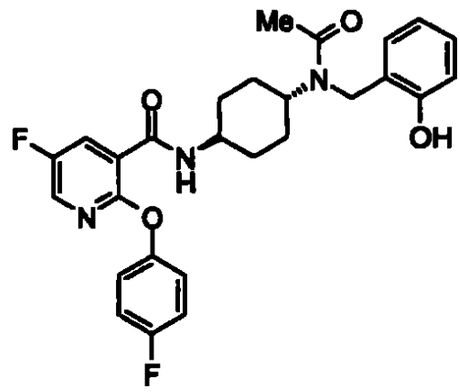
Phthalic acid monomethyl ester (141 mg, 0.781 mmol), 1-hydroxybenzotriazole hydrate (158 mg, 1.17 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (195 mg, 1.02 mmol) were stirred in N,N-dimethylformamide (6 ml) at room temperature and *syn*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (300 mg, 0.781 mmol) (see Preparation 22) added followed by addition of N-methyl morpholine (0.17 ml, 1.56 mmol). The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours, the reaction mixture then partitioned between ethyl acetate (20 ml) and water (20 ml), and the

organic layer separated. The organic layer was then washed with a saturated aqueous solution of sodium chloride (20 ml) dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (5 ml) giving *syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-phthalamic acid methyl ester (385 mg) as an off-white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.28-8.35 (1H, d), 8.20-8.24 (1H, d), 8.01-8.08 (2H, m), 7.75-7.80 (1H, d), 7.48-7.64 (2H, m), 7.38-7.43 (1H, d), 7.20-7.38 (4H, m), 4.04-4.16 (1H, m), 3.84-3.99 (1H, m), 3.74 (3H, s), 1.56-1.88 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 510

**Example 44 : *anti*-N-{4-[Acetyl-(2-hydroxybenzyl)-amino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**



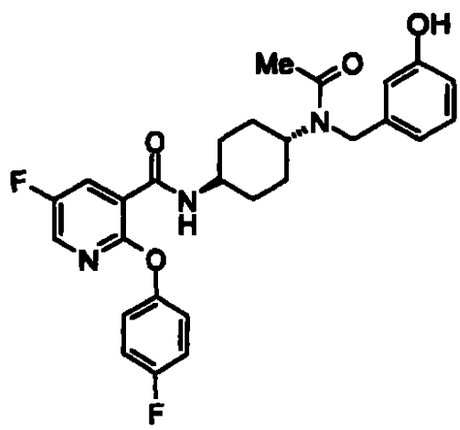

*Anti*-Acetic acid 1-{[acetyl-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-amino]-methyl}-phenyl ester (275 mg, 0.512 mmol) (see Preparation 19) and lithium hydroxide (monohydrate, 32 mg, 0.767 mmol) were dissolved in tetrahydrofuran (10 ml) and water (10 ml) and the reaction mixture stirred at room temperature for 2 hours. 2M Hydrochloric acid (0.4 ml) was added and the resultant precipitate filtered off and washed with water (30 ml). The solid was then dissolved in dichloromethane/diethylether and dried over anhydrous sodium sulphate. The

solvent was removed *in vacuo* giving *anti*-N-{4-[acetyl-(2-hydroxybenzyl)-amino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (100 mg) as a white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.77 (1H, s), 8.32-8.39 (1H, m), 8.01-8.05 (1H, d), 7.68-7.78 (1H, d), 7.07-7.23 (6H, m), 6.85-6.90 (1H, d), 6.77-6.84 (1H, t), 4.52 (2H, s), 3.92-4.10 (1H, m), 3.59-3.70 (1H, m), 2.22-2.31 (2H, d), 2.18 (3H, s), 1.75-1.98 (4H, m), 1.26-1.43 (2H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 494

**Example 45 : *anti*-N-{4-[Acetyl-(3-hydroxybenzyl)-amino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**



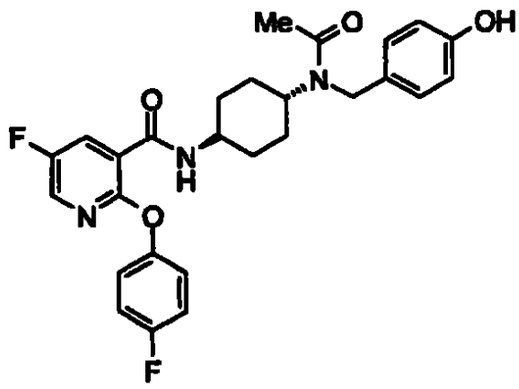

*Anti*-N-{4-[3-(tert-Butyl-dimethyl-silanyloxy)-benzylamino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (337 mg, 0.512 mmol) (see Preparation 18) was dissolved in dichloromethane (10 ml) and diisopropylethylamine (0.15 ml, 0.831 mmol) added followed by addition of acetyl chloride (0.051 ml, 0.712 mmol). The reaction mixture was held at room temperature under an atmosphere of nitrogen for 2 hours, and the solvent then removed *in vacuo*. The residue was dissolved in methanol (15 ml) and amberlyst 15 resin (1 g) was added. The reaction was held at room temperature for a further 18 hours. The mixture was then filtered through a short column of celite (5 g) and the celite washed with methanol (2-fold 10 ml). The filtrates were then combined, concentrated *in vacuo* and the residue azeotroped with diethylether. The

resulting white solid was slurried with pentane and filtered off giving *anti*-N-{4-[acetyl-(3-hydroxybenzyl)-amino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (290 mg) as a white solid.

$^1$H NMR (400 MHz, DMSO-d$^6$): δ = 9.32 (0.5H, s), 9.18 (0.5H, s), 8.20-8.25 (1H, m), 8.15-8.19 (1H, d), 7.90-7.98 (1H, m), 7.17-7.22 (4H, m), 6.98-7.16 (1H, 2xt), 6.52-6.65 (3H, m), 4.36-4.48 (2H, 2xs), 4.20-4.33 (0.5H, m), 3.57-3.76 (1.5H, m), 2.13 (1.3H, s), 1.78-1.90 (2.7H, m), 1.25-1.64 (7H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 494

**Example 46 : *anti*-N-{4-[Acetyl-(4-hydroxybenzyl)-amino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**



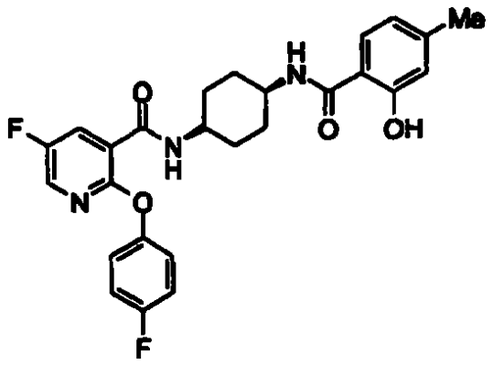

*Anti*-N-{4-[4-(tert-Butyl-dimethyl-silanyloxy)-benzylamino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (97 mg, 0.171 mmol) (see Preparation 17) was dissolved in dichloromethane (5 ml) and diisopropylethylamine (0.042 ml, 0.239 mmol) added followed by addition of acetyl chloride (0.015 ml, 0.205 mmol). The reaction mixture was held at room temperature under and atmosphere of nitrogen for 2 hours, before removing the solvent *in vacuo*. The residue was dissolved in methanol (10 ml) and amberlyst 15 resin (1 g) and trifluoroacetic acid (0.1 ml) added. The reaction mixture was held at room temperature for a further 18 hours. The mixture was then filtered through a short column of celite (5 g) and the celite washed with methanol (2-fold 10ml). The filtrates were combined, concentrated *in vacuo* and the residue azeotroped

with diethylether. The resulting white solid was slurried with pentane and filtered off giving *anti*-N-[4-[acetyl-(4-hydroxybenzyl)-amino]-cyclohexyl]-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (46 mg) as a white solid.

$^1$H NMR (400 MHz, DMSO-d$^6$): δ = 8.17-8.21 (1H, m), 8.13-8.16 (1H, d), 7.88-7.95 (1H, m), 7.11-7.21 (4H, m), 6.92-6.99 (2H, d), 6.67-6.73 (1H, d), 6.57-6.63 (1H, d), 4.30-4.41 (2H, 2xs), 4.12-4.22 (1H, m), 3.57-3.72 (1H, m), 2.10 (1H, s), 1.86 (2H, s), 1.76-1.83 (2H, d), 1.43-1.60 (4H, m), 1.20-1.40 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 496

**Example 47 : *syn*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide**




2-Hydroxy-4-methylbenzoic acid (91 mg, 0.595 mmol), 1-hydroxybenzotriazole hydrate (80 mg, 0.595 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (134 mg, 0.703 mmol), *syn*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (200 mg, 0.541 mmol) (see Preparation 22) and N-methyl morpholine (0.18 ml, 1.62 mmol) were stirred in N,N-dimethylformamide (5 ml) under an atmospherer of nitrogen at room temperature for 18 hours. The N,N-dimethylformamide was removed *in vacuo*, and the residue partitioned between dichloromethane (15 ml) and water (15 ml). The organic phase was separated and washed sequentially with a 10 % solution of citric acid in water (15 ml) followed by a saturated aqueous solution of sodium hydrogen carbonate (15 ml). The organic phase was then dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*.

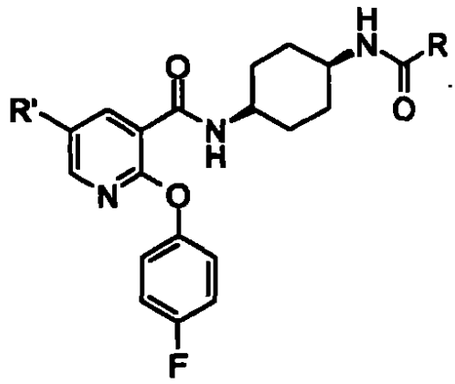
The residue was triturated with ethyl acetate/pentane (1:1, by volume, 5 ml) giving *syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-4-methyl-benzoyl amino)-cyclohexyl]-nicotinamide (130 mg) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 12.17 (1H, s), 8.32-8.38 (1H, m), 8.00-8.08 (2H, m), 7.15-7.22 (4H, d), 6.97-7.01 (1H, d), 6.78 (1H, s), 6.60-6.65 (1H, d), 5.84-5.92 (1H, d), 4.23-4.31 (1H, m), 4.02-4.15 (1H, m), 2.34 (3H, s), 1.80-2.00 (6H, m), 1.49-1.67 (2H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 480

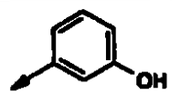
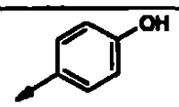
**Examples 48-71**

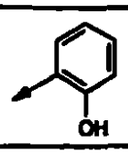
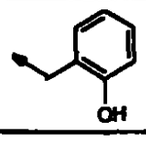
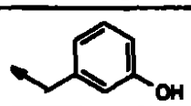
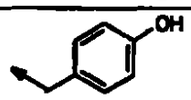
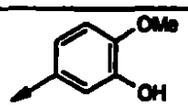
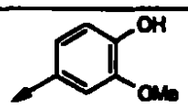
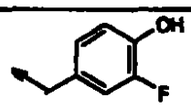
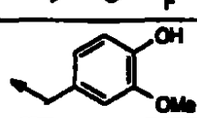
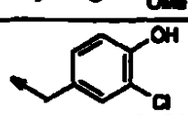
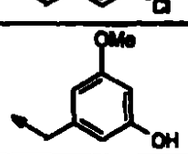
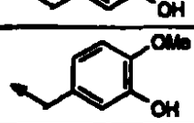
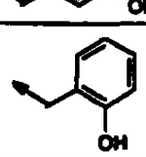
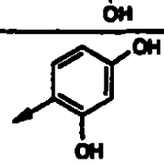
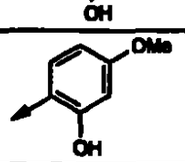
The compounds of the following tabulated examples (Table 3) of the general formula :

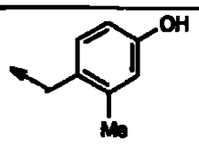
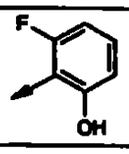
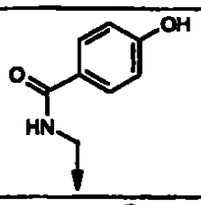
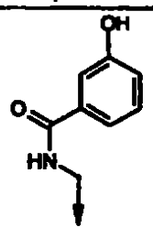
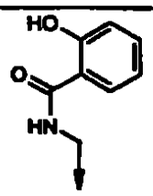
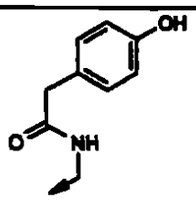
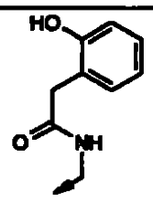
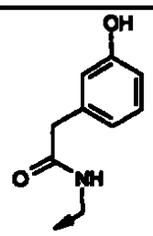



were prepared by a similar method to that of Example 47 using the appropriate carboxylic acid and amine as the starting materials.

**TABLE 3**

| Example No. | Starting Amine Prep No. | R' | R |
|---|---|---|---|
| 48 | 22 | F |  |
| 49 | 22 | F |  |

| | | | |
|---|---|---|---|
| 50 | 22 | F |  |
| 51 | 22 | F |  |
| 52 | 22 | F |  |
| 53 | 22 | F |  |
| 54[1] | 22 | F |  |
| 55[1] | 22 | F |  |
| 56[1] | 22 | F |  |
| 57[1] | 22 | F |  |
| 58[1] | 22 | F |  |
| 59[1] | 22 | F |  |
| 60[1] | 22 | F |  |
| 61[2] | 22 | H |  |
| 62[1] | 22 | F |  |
| 63[1] | 22 | F |  |

| | | | |
|---|---|---|---|
| 64[1] | 22 | F |  |
| 65[1] | 22 | F |  |
| 66[1,3] | 24 | F |  |
| 67[1,3] | 24 | F |  |
| 68[1,3] | 24 | F |  |
| 69[1,3] | 24 | F |  |
| 70[1,3] | 24 | F |  |
| 71[1,3] | 24 | F |  |

[1] These examples were worked up by partitioning the reaction mixture between ethyl acetate and water, and the organic phase was washed with a saturated aqeous solution of sodium chloride.

[2] These examples were purified by flash column chromatography on silica gel eluting with a solvent gradient of dichloromethane : methanol (100 : 0 changing to 95 : 5 then 70 : 30, by volume). The product was then dissolved in ethyl acetate, washed sequentially with water and a saturated aqeous solution of sodium chloride, dried over anhydrous magnesium sulphate and concentrated under reduced pressure to give the desired compound.

[3] These compounds were diluted with methanol and ethyl acetate until completely soluble before drying over anhydrous magnesium sulphate.

**Example 48 :**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 9.50 (1H, s), 8.22-8.26 (1H, d), 8.17-8.21 (1H, d), 7.95-7.99 (1H, m), 7.84-7.92 (1H, d), 7.12-7.23 (7H, m), 6.80-6.85 (1H, d), 3.86-3.95 (1H, m), 3.72-3.82 (1H, m), 1.56-1.82 (8H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

**Example 49 :**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 9.83 (1H, s), 8.21-8.24 (1H, m), 8.17-8.20 (1H, d), 7.93-7.97 (1H, m), 7.63-7.67 (1H, d), 7.57-7.62 (1H, d), 7.17-7.24 (4H, m), 6.70-6.77 (1H, d), 3.87-3.92 (1H, m), 3.72-3.80 (1H, m), 1.76-1.83 (2H, m), 1.55-1.72 (6H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

**Example 50 :**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 12.18 (1H, brs), 8.34-8.41 (1H, m), 8.16-8.19 (1H, d), 7.93-7.97 (1H, m), 7.80-7.86 (1H, d), 7.28-7.35 (1H, t), 7.15-7.23 (4H, m), 6.78-6.86 (2H, m), 3.89-3.94 (1H, m), 3.80-3.88 (1H, m), 1.58-1.80 (8H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

56
57

**Example 51 :**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.03-8.07 (2H, m), 7.10-7.21 (4H, m), 6.96-7.08 (2H, m), 6.68-6.78 (2H, m), 3.97-4.07 (1H, m), 3.75-3.80 (1H, m), 3.43 (2H, s), 1.63-1.80 (6H, m), 1.52-1.62 (6H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 480

**Example 52 :**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.00-8.08 (2H, m), 7.09-7.19 (4H, m), 7.00-7.08 (1H, t), 6.57-6.72 (3H, m), 4.00-4.09 (1H, m), 3.72-3.81 (1H, m), 3.37 (2H, s), 1.66-1.80 (6H, m), 1.51-1.62 (6H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 480

**Example 53 :**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 9.08 (1H, s), 8.22-8.26 (1H, d), 8.14-8.17 (1H, d), 7.92-7.96 (1H, d), 7.63-7.67 (1H, d), 7.16-7.23 (4H, d), 6.94-6.99 (2H, d), 6.57-6.62 (2H, d), 3.78-3.86 (1H, m), 3.52-3.61 (1H, m), 3.23 (2H, s), 1.46-1.86 (8H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 480

**Example 54 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9.08 (1H, s), 8.26-8.32 (1H, d), 8.21-8.25 (1H, d), 8.01-8.07 (1H, m), 7.75-7.82 (1H, m), 7.19-7.38 (6H, m), 6.92-6.97 (1H, d), 3.76-4.01 (5H, m), 1.54-1.80 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 498

**Example 55 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9.48 (1H, brs), 8.26-8.33 (1H, d), 8.20-8.25 (1H, d), 7.98-8.06 (1H, m), 7.74-7.80 (1H, d), 7.18-7.41 (6H, m), 6.77-6.82 (1H, d), 3.76-4.03 (5H, m), 1.50-1.92 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 498

**Example 56 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.58 (1H, s), 8.25-8.30 (1H, d), 8.20-8.24 (1H, d), 8.00-8.07 (1H, m), 7.77-7.83 (1H, d), 7.20-7.30 (4H, d), 6.96-7.03 (1H, d), 6.77-6.83 (2H, m), 3.82-3.93 (1H, m), 3.55-3.64 (1H, m), 3.26 (2H, s, partially masked by solvent), 1.52-1.80 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 500

**Example 57 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.73 (1H, s), 8.27-8.32 (1H, d), 8.21-8.25 (1H, d), 7.96-8.05 (1H, m), 7.70-7.78 (1H, d), 7.20-7.30 (4H, d), 6.57-6.80 (3H, m), 3.82-3.94 (1H, m), 3.58-3.78 (4H, m), 3.24 (2H, s, partially masked by solvent), 1.52-1.78 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 512

**Example 58 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 9.92 (1H, s), 8.26-8.32 (1H, d), 8.19-8.24 (1H, d), 7.91-8.05 (1H, m), 7.78-7.84 (1H, d), 7.16-7.30 (5H, m), 6.95-7.02 (1H, m), 6.83-6.88 (1H, d), 3.82-3.96 (1H, m), 3.57-3.69 (1H, m), 3.26 (2H, s, partially masked by solvent), 1.53-1.78 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 516

**Example 59 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.70 (1H, s), 8.28-8.33 (1H, d), 8.20-8.24 (1H, d), 7.96-8.02 (1H, m), 7.70-7.77 (1H, d), 7.20-7.28 (4H, d), 6.57-6.82 (3H, m), 3.81-3.94 (1H, m), 3.60-3.80 (4H, m), 3.24 (2H, s, partially masked by solvent), 1.52-1.78 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 512

**Example 60 :**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.80 (1H, brs), 8.25-8.33 (1H, d), 8.18-8.23 (1H, d), 7.95-8.05 (1H, m), 7.73-7.78 (1H, d), 7.17-7.34 (4H, d), 6.56-6.82 (3H,

m), 3.81-3.91 (1H, m), 3.67 (2H, s), 3.50-3.65 (1H, m), 3.22 (3H, s), 1.51-1.78 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 512

**Example 61 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.63 (1H, s), 8.68-8.75 (1H, d), 7.79-7.83 (2H, m), 7.16-7.20 (1H, t), 7.11-7.14 (4H, 2xd), 7.00-7.10 (2H, m), 6.92-6.98 (1H, d), 6.78-6.84 (1H, t), 6.23-6.31 (1H, d), 4.00-4.08 (1H, m), 3.58 (2H, s), 2.43-2.54 (1H, m), 1.78-1.90 (6H, m), 1.60-1.75 (2H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 462

**Example 62 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12.58 (1H, s), 10.00 (1H, s), 8.30-8.36 (1H, d), 8.01-8.03 (1H, d), 8.06-8.13 (1H, m), 7.99-8.06 (1H, m), 7.70-7.76 (1H, d), 7.20-7.29 (4H, d), 6.20-6.30 (2H, d + s), 3.88-3.99 (1H, brs), 3.60-3.88 (1H, brs), 1.53-1.88 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 484

**Example 63 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12.74-12.80 (1H, brs), 8.30-8.36 (1H, d), 8.18-8.23 (2H, m), 7.98-8.04 (1H, m), 7.80-7.85 (1H, d), 7.20-7.25 (4H, d), 6.39-6.48 (2H, d + s), 3.93-4.01 (1H, brs), 3.80-3.91 (1H, brs), 3.77 (3H, s), 1.62-1.90 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 498.

**Example 64 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 8.26-8.32 (1H, d), 8.01-8.03 (1H, d), 7.98-8.04 (1H, dd), 7.58-7.64 (1H, d), 7.19-7.28 (4H, d), 7.12-7.18 (1H, t), 6.68-6.79 (3H, m), 4.42 (2H, s), 3.85-3.97 (1H, brs), 3.70-3.80 (1H, brs), 2.24 (3H, s), 1.53-1.79 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 496.

**Example 65 :**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 11.00 (1H, s), 8.26-8.31 (1H, d), 8.20-8.21 (1H, d), 7.93-8.03 (2H, m), 7.18-7.34 (5H, m), 6.60-6.73 (2H, m), 3.83-3.99 (2H, brs), 1.52-1.80 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 486.

**Example 66 :**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.02-8.10 (2H, m), 7.71-7.76 (2H, m), 7.11-7.22 (4H, m), 6.78-6.84 (2H, d), 4.04-4.11 (1H, brs), 3.95 (2H, s), 3.80-3.90 (1H, brs), 1.73-1.87 (6H, m), 1.60-1.72 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 547, $[M-H]^+$ 523.

**Example 67 :**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.05-8.09 (2H, m), 7.22-7.30 (3H, m), 7.13-7.21 (4H, m), 6.91-6.96 (1H, m), 4.05-4.10 (1H, m), 3.96 (2H, s), 3.82-3.90 (1H, m), 1.73-1.85 (6H, m), 1.60-1.72 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 547, $[M-H]^+$ 523.

**Example 68 :**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 8.93-9.00 (1H, brs), 8.26-8.32 (1H, d), 8.20 (1H, s), 7.95-8.00 (1H, m), 7.81-7.87 (2H, m), 7.34-7.40 (1H, t), 7.18-7.27 (4H, d), 6.83-6.91 (2H, m), 3.83-3.93 (3H, m), 3.64-3.72 (1H, m), 1.56-1.75 (8H, 2xm) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 547, $[M-H]^+$ 523.

Found C, 59.29; H, 4.85; N, 10.38. $C_{27}H_{26}F_2N_4O_5$. 0.1mol N,N-dimethyl formamide, 1mol $H_2O$ requires C, 59.63; H, 5.26; N, 10.44%.

**Example 69 :**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.25-8.35 (1H, brs), 8.07-8.12 (2H, m), 7.53-7.63 (1H, m), 7.06-7.22 (6H, 2xm), 6.68-6.73 (2H, d), 3.99-4.08 (1H, brs), 3.75-3.85 (3H, m), 3.43 (2H, s), 1.65-1.80 (6H, m), 1.53-1.63 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 561, $[M-H]^+$ 537.

**Example 70 :**

$^1H$ NMR (400MHz, $CD_3OD$): δ = 8.05-8.12 (2H, m), 7.52-7.57 (1H, m), 7.09-7.21 (5H, m), 7.00-7.08 (1H, t), 6.73-6.79 (2H, m), 4.00-4.08 (1H, brs), 3.74-3.85 (3H, m), 3.52 (2H, s), 1.67-1.82 (6H, m), 1.57-1.66 (2H, m) ppm.

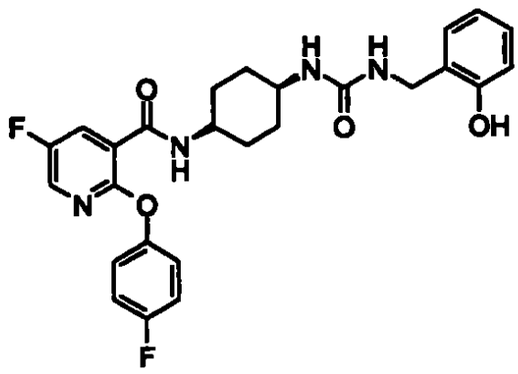
LRMS (electrospray) : m/z $[M+Na]^+$ 561, $[M-H]^+$ 537.

**Example 71 :**

$^1H$ NMR (400MHz, $CD_3OD$): δ = 8.25-8.33 (1H, d), 8.04-8.10 (2H, m), 7.53-7.60 (1H, m), 7.11-7.22 (4H, m), 7.06-7.11 (1H, t), 6.72-6.76 (2H, m), 6.59-6.64 (1H, d), 4.00-4.08 (1H, brs), 3.74-3.85 (3H, m), 3.47 (2H, s), 1.66-1.83 (6H, m), 1.56-1.65 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 561, $[M-H]^+$ 537.

**Example 72 : *syn*-5-Fluoro-2-(4-fluoro-phenoxy)-N-{4-[3-(2-hydroxy-benzyl)-ureido]-cyclohexyl}-nicotinamide**



2-Aminomethyl phenol (62 mg, 0.386 mmol), *syn*-5-fluoro-2(4-fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclohexyl}-nicotinamide (142 mg, 0.322 mmol) (see Preparation 25) and triethylamine (0.06 ml, 0.386 mmol) were stirred in dichloromethane (10 ml) under an atmosphere of nitrogen at room temperature for 18 hours. The reaction mixture was then washed sequentially with water (6 ml) and a 10 % solution of citric acid in water (6 ml).

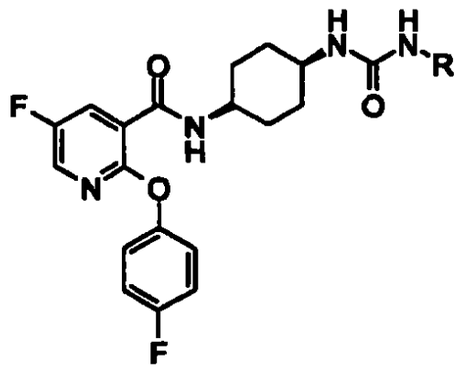
The organic phase was separated and dried over anhydrous magnesium sulphate. The solvent was then removed *in vacuo* and the residue triturated with diethylether (3-fold 5 ml) to give *syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-[4-[3-(2-hydroxy-benzyl)-ureido]-cyclohexyl]-nicotinamide (102 mg) as a pale yellow solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.75 (1H, s), 8.29-8.35 (1H, m), 8.00-8.04 (1H, d), 7.88-7.95 (1H, d), 7.05-7.21 (5H, m), 6.97-7.03 (1H, d), 6.85-6.92 (1H, d), 6.74-6.79 (1H, t), 4.76-4.85 (1H, t), 4.27-4.35 (1H, m), 4.21-4.26 (2H, d), 4.07-4.17 (1H, m), 3.56-3.68 (1H, m), 1.62-1.86 (6H, m), 1.35-1.51 (2H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 495

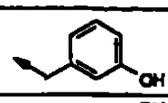
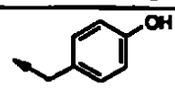
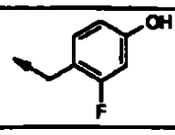
**Examples 73-75**

The compounds of the following tabulated examples (Table 4) of the general formula :



were prepared by a similar method to that of Example 72 using the appropriate amine starting material.

**TABLE 4**

| Example No. | Starting Intermediate Prep No. | R |
|---|---|---|
| 73 | 25 |  |
| 74[1] | 25 |  |
| 75 | 25 |  |

[1] This compound was isolated by filtering the aqueous phase after work-up. The solid was dissolved in methanol, dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The residue was triturated with diethylether to give the desired compound.

**Example 73**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.00-8.06 (2H, m), 7.01-7.20 (5H, m), 6.64-6.70 (2H, m), 6.58-6.63 (1H, d), 4.19 (2H, s), 3.98-4.06 (1H, brs), 3.62-3.71 (1H, brs), 1.64-1.82 (6H, m), 1.50-1.61 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 519, $[M-H]^+$ 495.

**Example 74**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 9.17 (1H, s), 8.21-8.25 (1H, d), 8.16-8.18 (1H, d), 7.93-7.97 (1H, dd), 7.15-7.21 (4H, d), 6.95-7.00 (2H, d), 6.40-6.44 (2H, d), 5.99-6.04 (1H, t), 5.68-5.75 (1H, d), 3.97-4.01 (2H, d), 3.78-3.87 (1H, brs), 3.44-3.55 (1H, brs), 1.40-1.64 (8H, m) ppm.

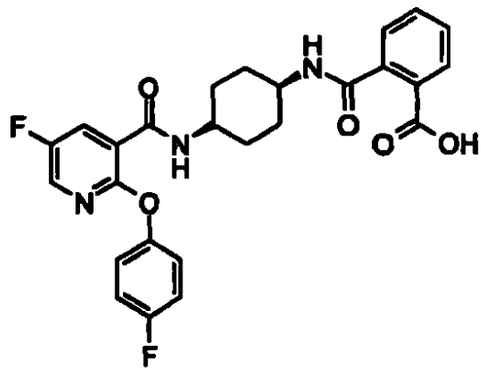
LRMS (electrospray) : m/z $[M+H]^+$ 497, $[M+Na]^+$ 519, $[M-H]^+$ 495.

**Example 75**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.00-8.06 (2H, m), 7.02-7.18 (4H, m), 6.93-6.99 (1H, t), 6.48-6.52 (1H, d), 6.39-6.46 (1H, m), 4.34 (1H, s), 4.18 (1H, s), 3.97-4.06 (1H, brs), 3.60-3.72 (1H, m), 1.61-1.82 (6H, m), 1.48-1.60 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 537, $[M-H]^+$ 513.

**Example 76 : *syn*-N-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-phthalamic acid**



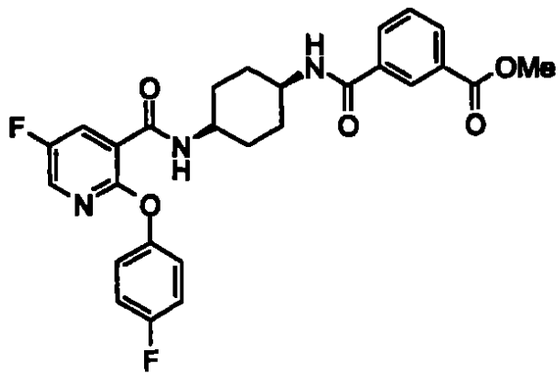
*syn*-N-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-phthalamic acid methyl ester (378 mg, 0.742 mmol) (see Example 43) and a 1 M solution of lithium hydroxide in water (1.5 ml, 1.484 mmol) were dissolved in tetrahydrofuran (5 ml) and the reaction was stirred at room temperature for 18 hours. 2 M Hydrochloric acid (0.8 ml) was added, and the reaction mixture extracted with dichloromethane (3-fold 10 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (5 ml) giving *syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-phthalamic acid (235 mg) as an off-white solid.

$^1$H NMR (300MHz, DMSO-$d^6$): $\delta$ = 12.63 (1H, brs), 8.20-8.30 (2H, m), 8.12-8.17 (1H, d), 7.98-8.06 (1H, m), 7.73-7.81 (1H, d), 7.48-7.58 (2H, m), 7.30-7.35 (1H, d), 7.18-7.28 (4H, d), 3.78-3.96 (2H, m), 1.60-1.83 (8H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 494

60
61

**Example 76a : *syn*-N-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-isophthalamic acid methyl ester**

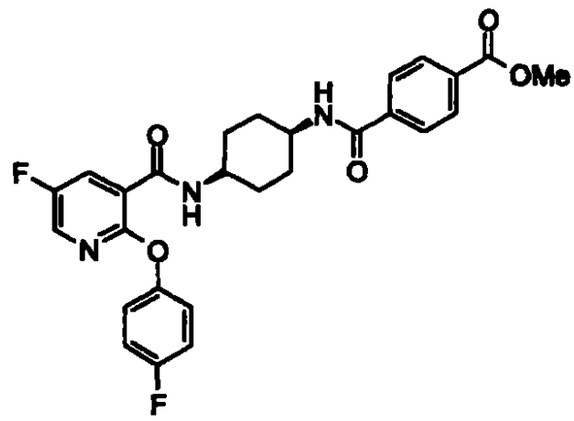


Isophthalic acid monomethyl ester (141 mg, 0.781 mmol), 1-hydroxybenzotriazole hydrate (158mg, 1.17 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (195 mg, 1.02 mmol) were dissolved in N,N-dimethylformamide (6 ml) at room temperature and *syn*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (300 mg, 0.781 mmol) (see Preparation 22) added followed by addition of N-methyl morpholine (0.17 ml, 1.56 mmol). The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours and then partitioned between ethyl acetate (20 ml) and water (20 ml) and the organic layer separated. The organic phase was then washed with a saturated aqueous solution of sodium chloride (20 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (5ml) giving *syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-isophthalamic acid methyl ester (398 mg) as an off-white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.32-8.45 (2H, m), 8.28 (1H, s), 7.92-8.18 (4H, m), 7.60-7.68 (1H, t), 7.20-7.40 (4H, m), 3.80-4.20 (5H, m), 1.56-1.97 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 510

**Example 76b : *syn*-N-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-terephthalamic acid methyl ester**



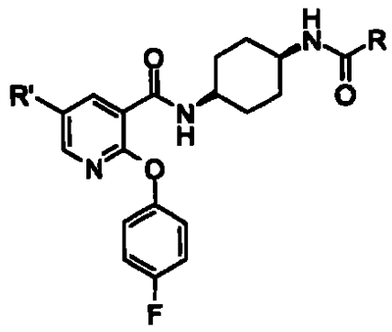
Terephthalic acid monomethyl ester (141 mg, 0.781 mmol), 1-hydroxybenzotriazole hydrate (158 mg, 1.17 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (195 mg, 1.02 mmol) were dissolved in N,N-dimethylformamide (6 ml) at room temperature and *syn*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (300 mg, 0.781 mmol) (see Preparation 22) added followed by addition of N-methyl morpholine (0.17 ml, 1.56 mmol). The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours, and then partitioned between ethyl acetate (20 ml) and water (20 ml) and the organic layer separated. The organic layer was then washed with a saturated aqueous solution of sodium chloride (20 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (5 ml) giving *syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-terephthalamic acid methyl ester (395 mg) as an off-white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.21-8.37 (3H, m), 8.00-8.16 (3H, d), 7.89-7.94 (2H, d), 7.40-7.34 (4H, d), 3.80-4.08 (5H, m), 1.56-1.95 (8H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 510

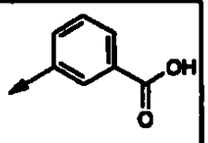
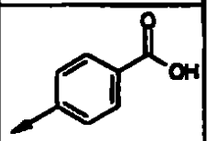
**Examples 77-78**

The compounds of the following tabulated examples (Table 5) of the general formula :



were prepared by a similar method to that of Example 76 using the appropriate ester as the starting materials.

**TABLE 5**

| Example No. | Starting Material Prep No. | R' | R |
|---|---|---|---|
| 77 | Example 76a | F |  |
| 78 | Example 76b | F |  |

**Example 77**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 13.14 (1H, brs), 8.39 (1H, s), 8.29-8.35 (2H, d), 8.20-8.28 (1H, d), 7.96-8.16 (3H, m), 7.52-7.62 (1H, t), 7.18-7.40 (4H, m), 3.91-4.00 (1H, m), 3.78-3.90 (1H, m), 1.56-1.89 (8H, m) ppm.

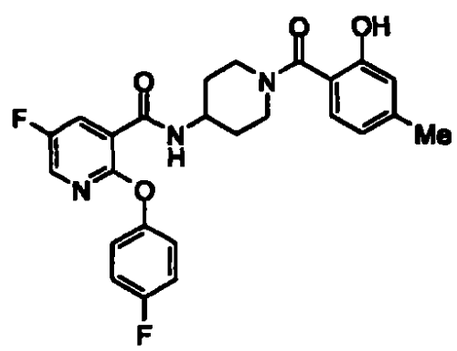
LRMS (electrospray) : m/z [M-H]$^+$ 494

**Example 78**

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 13.16 (1H, brs), 8.30-8.35 (1H, d), 8.20-8.28 (2H, m), 7.97-8.09 (3H, m), 7.85-7.91 (2H, d), 7.20-7.35 (4H, d), 3.91-4.02 (1H, m), 3.80-3.90 (1H, m), 1.60-1.92 (8H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 494

**Example 79 : 5-Fluoro-2-(4-fluoro-phenoxy)-N-[1-(2-hydroxy-4-methyl-benzoyl)-piperidin-4-yl]-nicotinamide**



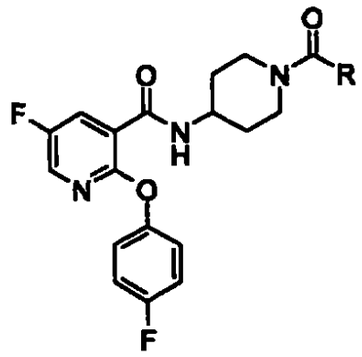

4-Methylsalicylic acid (91 mg, 0.595 mmol), 1-hydroxybenzotriazole hydrate (110 mg, 0.811 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (135 mg, 0.703 mmol), 5-fluoro-2-(4-fluoro-phenoxy)-N-piperidin-4-yl-nicotinamide hydrochloride (200 mg, 0.541 mmol) (see Preparation 29) and N-methyl morpholine (0.12 ml, 1.08 mmol) were stirred in N,N-dimethylformamide (4 ml) under an atmosphere of nitrogen at room temperature for 18 hours. The reaction mixture was then partitioned between ethyl acetate (10 ml) and water (10 ml), the organic layer separated, washed with a saturated aqueous solution of sodium chloride (10 ml) and dried over anhydrous magnesium sulphate. The solvent was then removed *in vacuo* and the residue purified via flash column chromatography on silica gel eluting with a solvent gradient of 100 % dichloromethane changing to 99:1, by volume, dichloromethane : methanol. The resulting white foam was triturated with pentane (5 ml) giving 5-fluoro-2-(4-fluoro-phenoxy)-N-[1-(2-hydroxy-4-methyl-benzoyl)-piperidin-4-yl]-nicotinamide (169mg) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.34-8.38 (1H, m), 8.01-8.03 (1H, d), 7.80-7.84 (1H, d) 7.08-7.18 (5H, m), 7.81 (1H, s). 6.60-6.65 (1H, d), 4.24-4.36 (3H, m), 3.17-3.25 (2H, t), 2.30 (3h, s), 2.10-2.18 (2H, d), 1.50-1.62 (2H, m) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 468, $[M+Na]^+$ 490

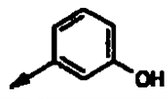
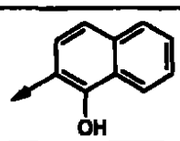
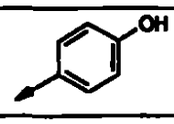
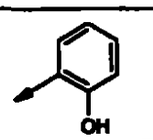
**Examples 80-91**

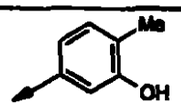
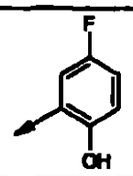
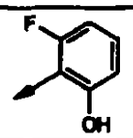
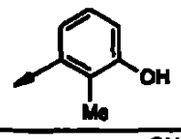
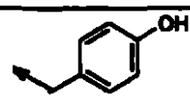
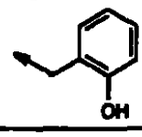
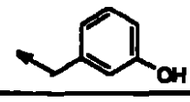
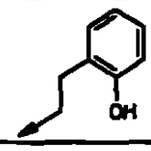
The compounds of the following tabulated examples (Table 6) of the general formula :



were prepared by a similar method to that of Example 79 using the appropriate carboxylic acid as the starting material.

**TABLE 6**

| Example No. | Starting Material Prep No. | R |
|---|---|---|
| 80 | 29 |  |
| 81 | 29 |  |
| 82 | 29 |  |
| 83 | 29 |  |

| | | |
|---|---|---|
| 84 | 29 |  |
| 85 | 29 |  |
| 86 | 29 |  |
| 87 | 29 |  |
| 88 | 29 |  |
| 89 | 29 |  |
| 90 | 29 |  |
| 91 | 29 |  |

**Example 80 :**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 9.55 (1H, brs), 8.36-8.41 (1H, d), 8.17 (1H, s), 7.90-7.96 (1H, m) 7.12-7.23 (5H, m), 6.74-6.79 (1H, d), 6.65-6.72 (1H, d), 6.64 (1H, s), 4.08-4.30 (1H, m), 3.98-4.06 (1H, m), 3.41-3.60 (1H, m), 2.91-3.20 (2H, m), 1.72-1.91 (2H, d), 1.30-1.54 (2H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 454, $[M+Na]^+$ 476

**Example 81 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 11.16 (1H, s), 8.31-8.37 (2H, m), 7.98-8.02 (1H, d), 7.80-7.85 (1H, d), 7.72-7.77 (1H, d), 7.44-7.56 (2H, m), 7.19-7.23 (2H, d),

7.04-7.16 (4H, m), 4.23-4.39 (3H, m), 3.22-3.30 (2H, t), 2.12-2.19 (2H, d), 1.50-1.63 (2H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 502

**Example 82 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.32-8.37 (1H, m), 8.02-8.05 (1H, d), 7.80-7.86 (1H, d), 7.20-7.26 (1H, m, partially masked by solvent), 7.08-7.20 (4H, m), 6.71-6.81 (3H, m), 4.00-4.35 (3H, m), 3.08-3.23 (2H, m), 2.05-2.18 (2H, d), 1.40-1.60 (2H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 452

**Example 83 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.55 (1H, s), 8.34-8.39 (1H, m), 8.04-8.07 (1H, d), 7.79-7.88 (1H, d), 7.28-7.36 (1H, m), 7.21-7.24 (1H, d), 7.08-7.16 (4H, m), 6.96-7.02 (1H, d), 6.78-6.85 (1H, t), 4.24-4.37 (3H, m), 3.18-3.28 (2H, t), 2.12-2.21 (2H, d), 1.69-1.83 (2H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 452

Found C, 61.85; H, 4.68; N, 9.19. $C_{24}H_{21}F_2N_3O_4$. 0.7mol $H_2O$ requires C, 61.85; H, 4.84; N, 9.02%.

**Example 84 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.33-8.37 (1H, m), 8.04 (1H, s), 7.79-7.85 (1H, d), 7.08-7.18 (4H, m), 7.02-7.07 (1H, d), 6.85-6.92 (1H, brs), 6.74-6.78 (1H, d), 4.38-4.65 (1H, m), 4.21-4.36 (1H, m), 3.78-3.94 (1H, m), 3.01-3.24 (2H, m), 2.21 (3H, s), 1.98-2.19 (2H, d), 1.38-1.60 (2H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

**Example 85 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.18 (1H, s), 8.32-8.37 (1H, m), 8.02-8.04 (1H, d), 7.80-7.86 (1H, d), 7.02-7.18 (2H, m), 7.08-7.20 (5H, m), 6.86-6.97 (2H, m),

4.22-4.37 (3H, m), 3.18-3.22 (2H, t), 2.13-2.22 (2H, d), 1.50-1.63 (2H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 470

**Example 86 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.28-8.36 (1H, m), 8.01-8.04 (1H, d), 7.75-7.84 (1H, d), 7.18-7.27 (1H, m, partially masked by solvent), 7.04-7.17 (4H, m), 6.75-6.80 (1H, d), 6.52-6.60 (1H, t), 4.35-4.63 (1H, m), 4.18-4.33 (1H, m), 3.60-3.90 (1H, m), 3.03-3.30 (2H, m), 2.02-2.19 (2H, d), 1.40-1.70 (2H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 470

**Example 87 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.26-8.32 (1H, m), 7.99-8.02 (1H, d), 7.77-7.84 (1H, d), 7.04-7.16 (4H, m), 6.93-7.02 (1H, m), 6.62-6.73 (2H, m), 5.88-6.00 (1H, d), 4.52-4.68 (1H, dd), 4.16-4.27 (1H, m), 3.41-3.48 (1H, d), 2.96-3.16 (1H, m), 2.10-2.19 (1H, m), 2.09 (3H, s), 1.88-2.02 (1H, m), 1.68-1.80 (1H, m, partially masked by solvent), 1.24-1.39 (1H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

**Example 88 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.25-8.31 (1H, m), 7.98-8.02 (1H, d), 7.71-7.78 (1H, d), 6.96-7.18 (6H, m), 6.67-6.75 (2H, m), 5.84 (1H, s), 4.37-4.47 (1H, m), 4.10-4.22 (1H, m), 3.72-3.83 (1H, d), 3.62 (2H, s), 3.08-3.21 (1H, t), 2.82-2.95 (1H, t), 1.90-2.05 (2H, t), 1.35-1.46 (1H, m), 1.13-1.23 (1H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

**Example 89 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.57 (1H, s), 8.30-8.36 (1H, m), 8.01-8.04 (1H, d), 7.72-7.80 (1H, d), 7.05-7.20 (5H, m), 6.90-7.02 (2H, m), 6.76-6.84 (1H, t), 4.43-4.55 (1H, d), 4.20-4.32 (1H, m), 4.08-4.18 (1H, d), 3.71 (2H, s), 3.32-3.44

(1H, t), 2.86-2.95 (1H, t), 2.15-2.24 (1H, d), 2.02-2.14 (1H, d), 1.37-1.50 (2H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 466

**Example 90 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.28-8.31 (1H, m), 8.01-8.04 (1H, d), 7.72-7.79 (1H, d), 7.22 (1H, s), 7.05-7.17 (5H, m), 6.84 (1H, s), 6.65-6.70 (2H, d), 4.37-4.47 (1H, d), 4.12-4.22 (1H, m), 3.77-3.84 (1H, d), 3.64 (2H, s), 3.12-3.21 (1H, t), 2.81-2.88 (1H, t), 1.90-2.03 (2H, 2xd), 1.38-1.51 (1H, m), 1.10-1.20 (1H, m) ppm.

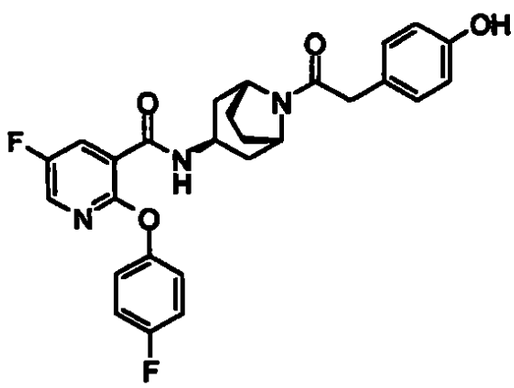
LRMS (electrospray) : m/z $[M-H]^+$ 466

**Example 91 :**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.36 (1H, s), 8.30-8.35 (1H, m), 8.02-8.04 (1H, d), 7.75-7.81 (1H, d), 7.00-7.16 (6H, m), 6.65-6.89 (1H, d), 6.76-6.82 (1H, t), 4.44-4.53 (1H, d), 4.17-4.27 (1H, m), 3.72-3.81 (1H, d), 3.13-3.24 (1H, t), 2.82-2.96 (3H, m), 2.68-2.75 (2H, m), 1.97-2.16 (2H, 2xd), 1.28-1.46 (2H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 480

**Example 92 : *endo*-5-Fluoro-2-(4-fluoro-phenoxy)-N-{8-[2-(4-hydroxy-phenyl)-acetyl]-8-aza-bicyclo[3.2.1]oct-3-yl}-nicotinamide**




4-Hydroxy-phenyl-acetic acid (88 mg, 0.57 mmol), 1-hydroxybenzotriazole (84 mg, 0.62 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

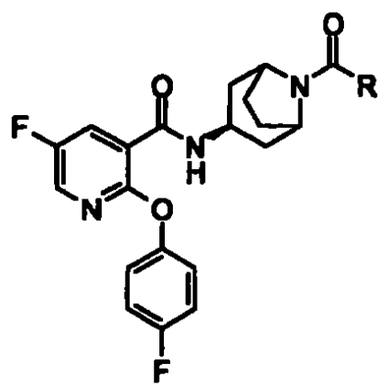
hydrochloride (122 mg, 0.62 mmol), *endo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (204 mg, 0.57 mmol) (see Preparation 32) and N-methyl morpholine (0.07 ml, 0.62 mmol) were stirred in dichloromethane (5 ml) under an atmosphere of nitrogen at room temperature for 18 hours. The reaction mixture was then washed with a saturated aqueous solution of sodium chloride (6 ml), the organic layer separated and dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel eluting with a solvent gradient of dichloromethane : pentane (50 : 50, by volume) changing to dichloromethane : methanol (100 : 0 then 97 : 3, by volume) to give *endo*-5-fluoro-2-(4-fluoro-phenoxy)-N-{8-[2-(4-hydroxy-phenyl)-acetyl]-8-aza-bicyclo[3.2.1]oct-3-yl}-nicotinamide (50 mg) as a white foam.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.48-8.57 (1H, d), 8.29-8.33 (1H, dd), 7.98-8.00 (1H, d), 7.00-7.14 (6H, m), 6.70-6.75 (2H, d), 5.88 (1H, s), 4.68-4.74 (1H, m), 4.28-4.35 (1H, m), 4.18-4.23 (1H, brs), 3.48-3.62 (2H, quartet), 2.24-2.29 (1H, m), 1.72-1.92 (7H, m) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 494, $[M+Na]^+$ 516, $[M-H]^+$ 492.

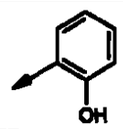
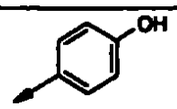
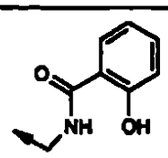
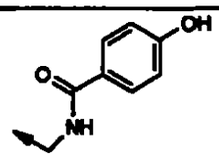
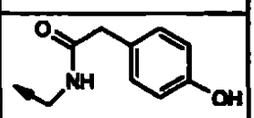
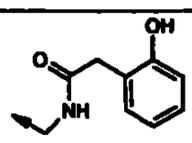
**Examples 93-98**

The compounds of the following tabulated examples (Table 7) of the general formula :



were prepared by a similar method to that of Example 92 using the appropriate amine and carboxylic acid as the starting material.

**TABLE 7**

| Example No. | Starting Amine Prep No. | Stereochem. of Ring | R |
|---|---|---|---|
| 93[1,2] | 35 | *exo* |  |
| 94[1,3] | 35 | *exo* |  |
| 95[1] | 37 | *exo* |  |
| 96[1] | 37 | *exo* |  |
| 97 | 37 | *exo* |  |
| 98 | 37 | *exo* |  |

[1] The eluent for flash column chromatography was dichloromethane : methanol (100 : 0 changing to 98 : 2, by volume).

[2]The compound was slurried in 20% ethyl acetate in pentane after chromatography, and was filtered, washed with pentane and dried *in vacuo* to give the desired product.

[3]The compound was triturated with diethylether after chromatography to give the desired product.

**Example 93**

$^1$H NMR (400MHz, $CDCl_3$): δ = 10.42 (1H, s), 8.30-8.35 (1H, dd), 8.00-8.02 (1H, d), 7.64-7.73 (1H, d), 7.29-7.38 (2H, m), 7.05-7.19 (4H, m), 6.97-7.01 (1H, d), 6.80-6.85 (1H, t), 4.73-4.83 (2H, brs), 4.60-4.72 (1H, m), 2.15-2.24 (2H, d), 2.00-2.14 (2H, m), 1.92-2.00 (2H, d), 1.69-1.80 (2H, t) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 502, $[M-H]^+$ 478.

**Example 94**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 9.91 (1H, s), 8.30-8.37 (1H, dd), 8.08-8.10 (1H, d), 7.90-7.97 (1H, dd), 7.27-7.33 (2H, d), 7.16-7.25 (4H, m), 6.74-6.80 (2H, d), 4.02-4.64 (3H, 2xbrs + m), 1.48-2.01 (8H, m) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 502, $[M-H]^+$ 478.

**Example 95**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12.08 (1H, s), 8.28-8.36 (1H, d), 8.02 (1H, s), 7.60-7.70 (1H, d), 7.16-7.30 (3H, m), 7.03-7.16 (4H, m), 6.94-6.99 (1H, d), 6.81-6.88 (1H, t), 4.77-4.84 (1H, brs), 4.60-4.75 (1H, m), 4.10-4.30 (3H, m), 2.22-2.30 (1H, d), 1.99-2.20 (3H, m), 1.87-1.98 (1H, d), 1.60-1.72 (1H, t), 1.46-1.60 (2H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 559, $[M-H]^+$ 535.

**Example 96**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.30-8.36 (1H, dd), 8.00-8.02 (1H, d), 7.62-7.73 (3H, d), 7.06-7.16 (4H, m), 7.01 (1H, s), 6.86-7.00 (1H, brs), 6.80-6.86 (2H, d), 4.77-4.81 (1H, brs), 4.60-4.76 (1H, m), 4.16-4.33 (3H, m), 3.67-3.77 (1H, m), 2.20-2.37 (1H, d), 1.98-2.20 (4H, m), 1.88-1.98 (1H, d), 1.51-1.70 (1H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 559, $[M-H]^+$ 535.

**Example 97**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.27-8.32 (1H, d), 8.01 (1H, s), 7.58-7.65 (1H, d), 7.07-7.18 (6H, m), 6.71-6.79 (2H, d), 6.43-6.49 (1H, brs), 6.04-6.13 (1H, brs), 4.66-4.74 (1H, brs), 4.56-4.66 (1H, m), 4.16-4.23 (1H, m), 3.92-4.07 (2H, m), 3.53 (2H, s), 2.14-2.23 (1H, d), 1.81-2.13 (5H, m), 1.50-1.64 (1H, m, partially masked by solvent), 1.40-1.50 (1H, t) ppm.

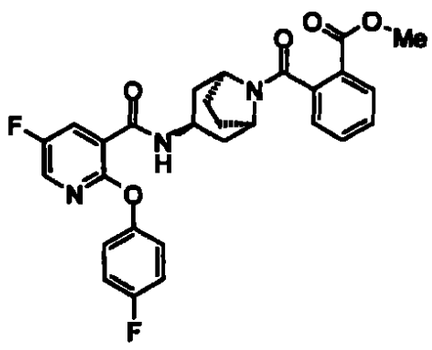
LRMS (electrospray) : m/z $[M+Na]^+$ 573, $[M-H]^+$ 549.

**Example 98**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.40 (1H, s), 8.27-8.35 (1H, d), 8.02 (1H, s), 7.57-7.64 (1H, d), 6.92-7.20 (8H, m), 6.79-6.87 (1H, t), 4.72-4.79 (1H, brs), 4.58-4.70 (1H, m), 4.14-4.21 (1H, m), 3.95-4.05 (2H, m), 3.61 (2H, s), 2.17-2.24 (1H, d), 1.83-2.17 (5H, m), 1.57-1.64 (1H, t, partially masked by solvent), 1.40-1.51 (1H, t) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 573, $[M-H]^+$ 549.

**Example 99 : exo-2-{3-[[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-azo-bicyclo[3.2.1]-octane-8-carbonyl)-benzoic acid methyl ester**



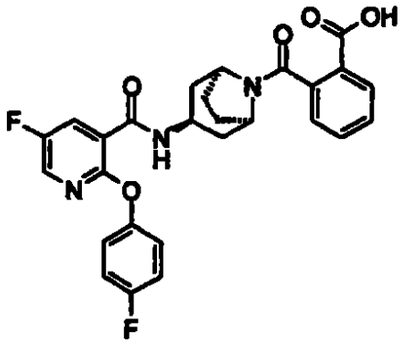

Phthalic acid monomethyl ester (155 mg, 0.83 mmol), 1-hydroxybenzotriazole (135 mg, 1 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (196 mg, 1 mmol) were stirred in dichloromethane (5 ml) at room temperature and *exo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-

phenoxy)-nicotinamide (299 mg, 0.83 mmol) (see Preparation 35) added followed by addition of N-methyl morpholine (0.11 ml, 1 mmol). The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours, then washed with a saturated aqueous solution of sodium chloride (5 ml and the organic phase separated. The organic phase was concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with 100:0 changing to 97:3, by volume, dichloromethane : methanol giving *exo*-2-(3-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-azo-bicyclo[3.2.1]-octane-8-carbonyl)-benzoic acid methyl ester (298 mg) as a white foam.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.30-8.36 (1H, dd), 8.00-8.01 (1H, d), 7.93-7.98 (1H, d), 7.75-7.82 (1H, d), 7.49-7.56 (1H, t), 7.40-7.47 (1H, t), 7.28-7.33 (1H, d), 7.12-7.19 (4H, d), 4.93-4.98 (1H, m), 4.59-4.71 (1H, m), 3.76-3.81 (1H, m), 3.63 (3H, s), 1.83-2.21 (6H, m), 1.39-1.49 (2H, t) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 544, $[M-H]^+$ 520.

**Example 100 : exo-2-(3-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoic acid**



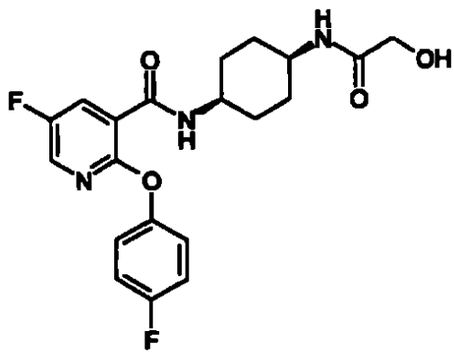
*Exo*-2-(3-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoic acid methyl ester (see Example 99) (225 mg, 0.43 mmol) and 1N aqueous lithium hydroxide (0.5 ml, 0.5 mmol) were stirred in methanol (5 ml) at room temperature for 18 hours. Starting material remained, so the reaction was heated at reflux and stirred for a further

5 hours. The reaction mixture was then cooled and glacial acetic acid added until the pH reached 5. The methanol was removed under reduced pressure, and the residue extracted with ethyl acetate (10 ml). The organic phase was separated, washed with a saturated aqueous solution of sodium chloride (10 ml), concentrated *in vacuo* and the residue triturated with diethylether (5 ml) to give *exo*-2-(3-[[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino)8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoic acid (103 mg) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8.26-8.38 (1H, brs), 8.18-8.20 (1H, d), 7.91-7.97 (1H, dd), 7.70-7.88 (1H, brs), 7.55-7.63 (1H, m), 7.43-7.53 (1H, m), 7.16-7.31 (5H, m), 4.63-4.72 (1H, brs), 4.27-4.40 (1H, m), 3.52-3.62 (1H, brs), 1.84-2.00 (4H, m), 1.63-1.82 (4H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 506.

**Example 101: *Syn*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-acetylamino)cyclohexyl]-nicotinamide**



Glycolic acid (40 mg, 0.52 mmol), 1-hydroxybenzotriazole hydrate (80 mg, 0.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol), triethylamine (181 µl, 1.3 mmol) and *syn*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (150 mg, 0.39 mmol)(see Preparation 22) were dissolved in N,N-dimethylformamide and were stirred for 18 hours at room temperature. The mixture was partitioned between ethyl acetate and water, the organic phase was dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by

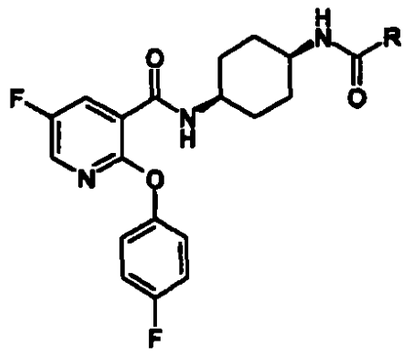
chromatography on silica gel using methanol in dichloromethane (5:95) and then further purified by chromatography on silica gel using methanol in ethyl acetate (gradient from 0:100 to 5:95) to give *syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-acetylamino)cyclohexyl]-nicotinamide as a white powder (100mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.33 (1H, d), 8.03 (1H, s), 7.99 (1H, d), 7.12 (4H, m), 6.22 (1H, d), 4.22 (1H, m), 4.09 (2H, s), 4.00 (1H, m), 2.20 (1H, s), 1.86 (5H, m), 1.79 (3H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 404

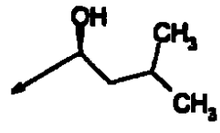
**Examples 102-125**

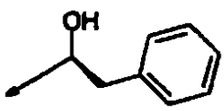
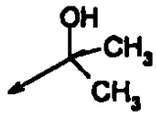
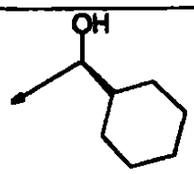
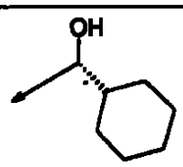
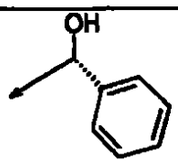
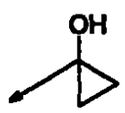
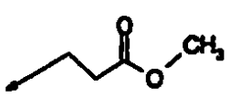
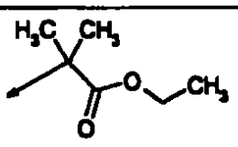
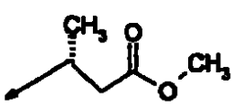
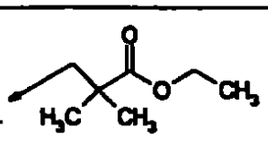
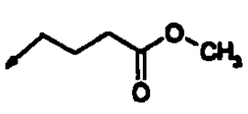
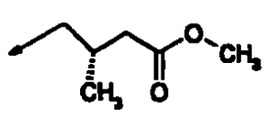
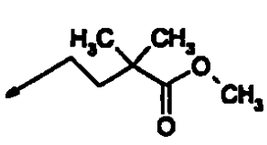
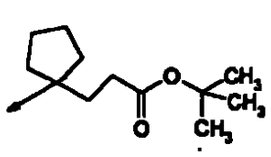
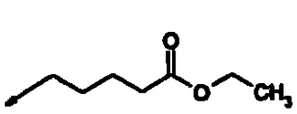
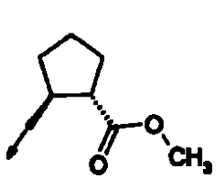
The compounds of the following tabulated examples (Table 8) of the general formula:

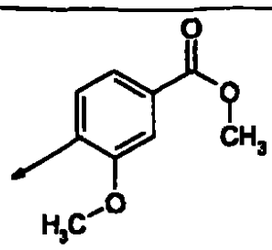
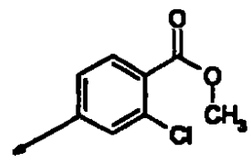
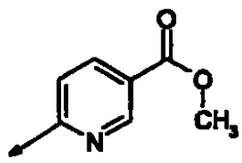
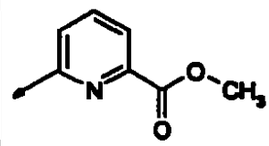
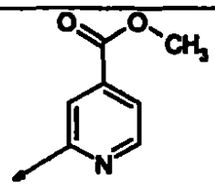
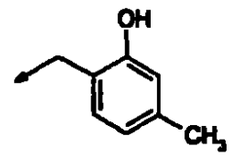


were prepared by a similar method to that of example 101 using the amine of Preparation 22 and the appropriate carboxylic acid.

**TABLE 8**

| Example N° | R group | Example N° | R group |
|---|---|---|---|
| 102[1] |  | 103[2] |  |

| | | | |
|---|---|---|---|
| 104[2] |  | 105[2] |  |
| 106[2] |  | 107[2] |  |
| 108[2,4] |  | 109[2] |  |
| 110 |  | 111 |  |
| 112 |  | 113 |  |
| 114 |  | 115 |  |
| 116 |  | 117 |  |
| 118 |  | 119 |  |

| | | | |
|---|---|---|---|
| 120 |  | 121[3] |  |
| 122 |  | 123 |  |
| 124 |  | 125 |  |

[1] Purification by chromatography using a gradient from 95:5:0.5 to 90:10:0.5 ethyl acetate: methanol: ammonium hydroxide solution, then 95:5:0.5 dichloromethane: methanol: ammonium hydroxide solution.

[2] Triethylamine was replaced with N-methylmorpholine.

Aqueous solutions were further extracted four times with dichloromethane (5 ml)

Purification by chromatography on silica gel used 99:1:01 dichloromethane: methanol: ammonium hydroxide solution, then 97:3:0.1 dichloromethane: methanol: ammonium hydroxide solution

[3] The compound was pre-adsorbed onto silica gel prior to purification by chromatography on silica gel using 1% methanol in dichloromethane.

[4] After stirring 18 hours L-mandelic acid (10 mg, 0.065 mmol) was added and the mixture left to stir 24 hours

**Example 102**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8.20 (1H, m), 7.99 (1H, m), 7.70 (1H, d), 7.21 (4H, m), 4.18 (1H, m), 3.84 (1H, m), 3.63 (1H, m), 3.52 (2H, m), 2.40 (1H, m), 2.28 (2H, m), 1.63-1.56 (8H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 418

**Example 103**

$^1$H NMR (400MHz, $CDCl_3$) δ 8.35 (1H, d), 8.04 (1H, d), 7.93 (1H, d), 7.13 (4H, m), 6.40 (1H, s), 4.20 (1H, s), 4.08 (1H, m), 3.91 (1H, m), 2.05 (1H, m), 1.82 (8H, m), 1.60 (1H, m), 1.45 (2H, m) 0.90 (6H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 484

**Example 104**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.38 (1H, m), 8.04 (1H, s), 7.97 (1H, d), 7.20 (9H, m), 6.25 (1H, d), 4.29 (1H, m), 4.18 (1H, m), 3.91 (1H, m), 3.91 (1H, m), 3.18 (1H, m), 2.92 (1H, m), 1.79 (4H, m), 1.61 (2H, m), 1.42 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 494

**Example 105**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.33 (1H, m), 8.04 (1H, d), 7.93 (1H, d), 7.18 (4H, m), 6.59 (1H, s), 4.21 (1H, s), 3.96 (2H, m), 1.84 (4H, m), 1.77 (2H, m), 1.60 (6H, s), 1.48 (2H, m).

LCMS (electrospray): *m/z* $[M+H]^+$ 434

**Example 106**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.33 (1H, m), 8.02 (2H, m), 7.16 (4H, m), 6.40 (1H, d), 4.20 (1H, s), 3.90 (2H, m), 1.74 (12H, m), 1.43 (3H, m), 1.14 (5H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 486

**Example 107**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.37 (1H, m), 8.02 (2H, m), 7.16 (4H, m), 6.40 (1H, d), 4.20 (1H, s), 3.90 (2H, m), 1.75 (12H, m), 1.43 (3H, m), 1.18 (5H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 486

**Example 108**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.31 (1H, m), 8.04 (1H, s), 7.94 (1H, s), 7.25 (6H, m), 7.14 (4H, m), 6.21 (1H, d), 4.98 (1H, s), 4.14 (1H, m), 3.96 (1H, m), 1.79 (4H, m), 1.63 (2H, s), 1.24 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 504

**Example 109**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.32 (1H, m), 8.01 (2H, m), 7.14 (4H, m), 6.81 (1H, d), 4.18 (1H, s), 3.90 (1H, m), 1.81 (6H, m), 1.51 (2H, m), 1.25 (2H, m), 1.19 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 454

**Example 110**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.38 (1H, m), 8.04 (1H, s), 7.97 (1H, d), 7.14 (4H, m), 5.56 (1H, d), 4.20 (1H, s), 3.92 (1H, m), 3.89 (3H, s), 2.66 (2H, m), 2.41 (2H, m), 1.82 (4H, m), 1.73 (2H, m),1.48 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 486

**Example 111**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.38 (1H, d), 8.06 (1H, s), 7.98 (1H, d), 7.16 (4H, m), 6.50 (1H, d), 4.20 (1H, s), 4.11 (2H, q), 3.89 (1H, m), 1.93 (4H, m), 1.71 (2H, m), 1.48 (2H, m), 1.40 (6H, s), 1.22 (3H, t).

LCMS (electrospray): *m/z* $[M-H]^-$ 488

**Example 112**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.37 (1H, d), 8.04 (1H, s), 7.98 (1H, d), 7.17 (4H, m), 5.79 (1H, d), 4.20 (1H, m), 3.90, (1H, m), 3.60, (3H, s), 2.71 (1H, m), 2.60 (1H, m), 2.36 (1H, m), 1.83 (4H, m), 1.74 (2H, m), 1.49 (2H, m), 1.14 (3H, d).

LCMS (electrospray): *m/z* $[M+Na]^+$ 498

**Example 113**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.37 (1H, d), 8.04 (1H, s), 7.96 (1H, d), 7.17 (4H, m), 5.85 (1H, d), 4.19 (1H, s), 4.04 (2H, q), 3.90 (1H, s), 2.40 (2H, s), 1.82 (4H, m), 1.70 (2H, m), 1.43 (2H, m), 1.24 (6H, s) 1.21 (3H, t).

LCMS (electrospray): *m/z* $[M+Na]^+$ 526

**Example 114**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.37 (1H, d), 8.04 (1H, s), 7.96 (1H, d), 7.14 (4H, m), 5.38 (1H, s), 4.20 (1H, s), 3.91 (1H, s), 3.66 (3H, s), 2.18 (2H, t), 2.19 (2H, t), 1.91 (2H, m), 1.81 (4H, m), 1.76 (2H, m), 1.23 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 474

**Example 115**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.18 (2H, s), 7.20 (4H, m), 4.10 (1H, s), 3.80 (1H, s), 3.66 (3H, s), 2.39 (2H, m), 2.20 (2H, m), 2.19 (1H, m), 1.80 (6H, m), 1.60 (2H, m) (0.95 (3H, d).

LCMS (thermospray): *m/z* $[M-H]^-$ 488

**Example 116**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.37 (1H, d), 8.04 (1H, s), 7.97 (1H, d), 7.16 (4H, m), 5.25 (1H, d), 4.20 (1H, s), 3.91 (1H, s), 3.68 (3H, s), 2.07 (2H, m), 1.84 (6H, m), 1.77 (2H, m), 1.44 (2H, m), 1.20 (6H, s).

LCMS (electrospray): *m/z* $[M-H]^-$ 502

**Example 117**

$^1H$ NMR (400MHz, $CDCl_3$): δ 8.37 (1H, d), 8.05 (1H, s), 7.99 (1H, d), 7.17 (4H, m), 5.38 (1H, d), 4.22 (1H, s), 3.88 (1H, s), 2.15 (2H, t), 1.92 (2H, m), 1.81 (6H, m), 1.60 (4H, m), 1.18 (15H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 570

**Example 118**

$^1H$ NMR (400MHz, $CDCl_3$): δ 8.37 (1H, d), 8.04 (1H, s), 7.96 (1H, d), 7.18 (4H, m), 5.30 (1H, d), 4.20 (1H, s), 4.10 (2H, q), 3.93 (1H, s), 2.31 (2H, m), 2.13 (2H, m), 1.91 (6H, m), 1.76 (2H, m), 1.64 (2H, m), 1.43 (2H, m) 1.24 (3H, t).

LCMS (electrospray): *m/z* $[M-H]^-$ 502

**Example 119**

$^1H$ NMR (400MHz, $CD_3OD$): δ 8.17 (2H, s), 7.20 (4H, m), 4.09 (1H, s), 3.80 (1H, s), 3.60 (3H, s), 3.03 (1H, m), 2.86 (1H, m), 2.04 (1H, m), 1.98 (1H, m), 1.70 (14H, m).

LCMS (electrospray): m/z $[M-H]^-$ 500

**Example 120**

$^1H$ NMR (400MHZ, $CD_3OD$): δ 8.08 (2H, M), 7.88 (1H, D), 7.70 (2H, M), 7.21 (2H, M), 7.16 (2H, M), 4.10 (2H, S), 3.93 (3H, S), 3.90 (3H, S), 1.83 (8H, M),

LCMS (electrospray): *m/z* $[M-H]^-$ 538

**Example 121**

$^1H$ NMR (400MHz, $CDCl_3$): δ 8.38 (1H, d), 8.04 (1H, s), 8.00 (1H, d), 7.85 (1H, d), 7.74 (1H, s), 7.57 (1H, d), 7.18 (4H, m), 5.80 (1H, d), 4.28 (1H, s), 4.10 (1H, m), 3.98 (3H, s), 1.93 (6H, m), 1.58 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 542, 544

Found; C, 59.57; H, 4.50; N, 7.51; $C_{27}H_{24}ClF_2N_3O_5$ requires; C, 59.62; H, 4.45; N, 7.72%.

**Example 122**

$^1H$ NMR (400MHz, $CD_3OD$): δ 9.13 (1H, s) 8.50 (1H, d), 8.19 (1H, d), 8.10 (1H, m), 8.06 (1H, m), 7.22 (2H, m), 7.16 (2H, m), 4.18 (1H, m), 4.06 (1H, s) 3.93 (3H, s), 3.90 (6H, s), 1.79 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 509

**Example 123**

$^1H$ NMR (400MHz, $CDCl_3$): δ 8.37 (2H, m), 8.20 (1H, d), 8.02 (4H, m), 7.08 (4H, m), 4.29 (1H, s), 4.10 (1H, m), 3.99 (3H, s), 1.90 (6H, m), 2.69 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 509

**Example 124**

$^1H$ NMR (400MHz, $CD_3OD$): δ 8.79 (1H, d) 8.57 (1H, s), 8.07 (3H, m), 7.20 (4H, m), 4.19 (1H, m), 4.05 (1H, m) 3.99 (3H, s), 1.90 (6H, s), 1.78 (2H, m).

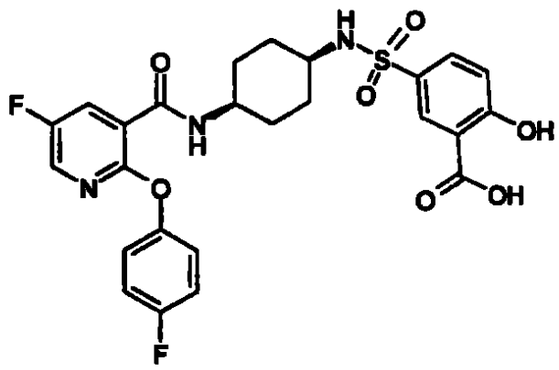
LCMS (electrospray): *m/z* $[M-H]^-$ 509

**Example 125**

$^1H$ NMR (300MHz, $CD_3OD$): δ 8.10 (2H, m), 7.19 (7H, m), 4.07 (2H, m), 3.50 (2H, m), 2.22 (3H, s), 1.75 (8H, m).

LCMS (electrospray): *m/z* $[M+H]^+$ 496

**Example 126: *Syn*-5-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexylsulphamoyl)-2-hydroxy-benzoic acid**

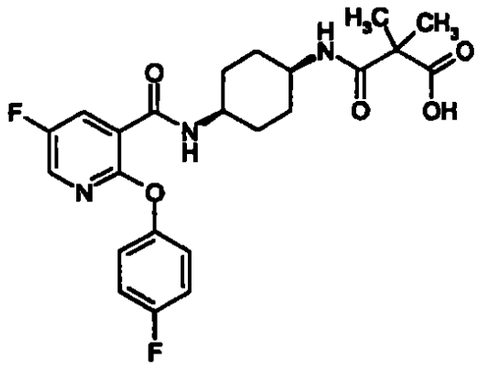


5-Chlorosulfonyl-2-hydroxy-benzoic acid (123 mg, 0.52 mmol) was added to a stirred suspension of *syn*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (200 mg, 0.521 mmol, see Preparation 22) in dichloromethane (5 ml) containing triethylamine (220 µl, 1.58 mmol) and was stirred under a nitrogen atmosphere for 18 hours at room temperature. The mixture was partitioned between dichloromethane and water. The dichloromethane layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulphate and evaporated *in-vacuo*. The residue was triturated with diethylether to give *syn*-5-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexylsulphamoyl)-2-hydroxy-benzoic acid (170 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.12 (3H, m), 7.92 (3H, m), 7.59 (1H, m), 7.07 (4H, m), 6.79 (1H, m), 5.53 (1H, s), 4.08 (1H, s), 3.97 (1H, m), 1.78 (8H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 546

**Example 127: *Syn*-N-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-2,2-dimethyl-malonamic acid**



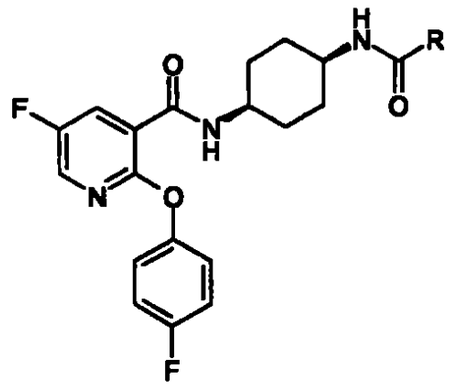
*Syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-2,2-dimethyl-malonamic acid ethyl ester (125 mg, 0.26 mmol, see Example 111) was dissolved in tetrahydrofuran (4 ml) and 1M lithium hydroxide solution (600 µl, 0.6 mmol) was added. The mixture was stirred at room temperature for 18 hours and then was diluted with dichloromethane (5 ml). The dichloromethane layer was separated by pipette and the aqueous layer was partitioned between 1N hydrochloric acid and dichloromethane (5 ml). The aqueous phase was extracted with dichloromethane (5 x 5 ml) and the combined dichloromethane layers were evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane containing ammonium hydroxide solution (stepwise from 10:90:1 to 20:80:3) to give *syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-2,2-dimethyl-malonamic acid (90 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.07 (1H, s), 8.01 (1H, d), 7.19 (4H, m), 4.06 (1H, s), 3.83 (1H, s), 1.78 (8H, m), 1.34 (6H, s),

LCMS (electrospray): *m/z* $[M-H]^-$ 460

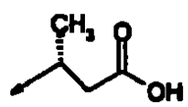
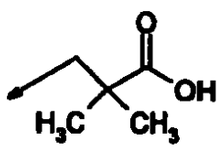
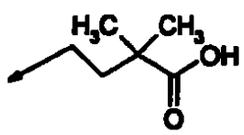
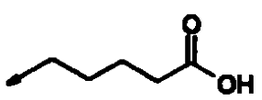
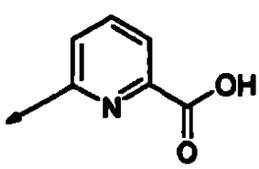
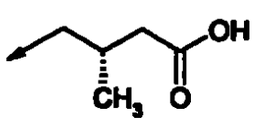
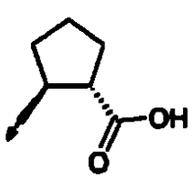
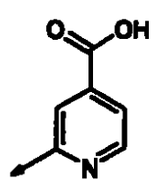
**Examples 128-133**

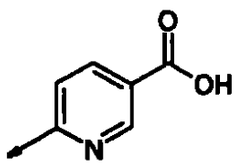
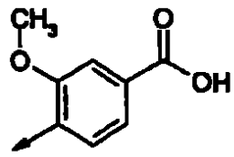
The compounds of the following tabulated examples (Table 9) of the general formula:



were prepared by a similar method to that of example 127 using the appropriate ester from the compounds of table 8.

**TABLE 9**

| Example N° | R group | Example N° | R group |
|---|---|---|---|
| 128 |  | 129 |  |
| 130 |  | 131 |  |
| 132 |  | 133 |  |
| 134 |  | 135 |  |

| | | | |
|---|---|---|---|
| 136 |  | 137 |  |

**Example 128**

$^1$H NMR (400MHZ, $CD_3OD$): δ 8.04 (1H, S), 8.03 (1H, D), 7.19 (4H, M), 4.14 (1H, T), 3.79 (1H, S), 2.72 (1H, M), 2.50 (1H, M), 2.21(1H, M), 1.70 (8H, M), 1.11 (3H, M)

LCMS (electrospray): *m/z* $[M+Na]^+$ 484

**Example 129**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.07 (1H, m), 8.02 (1H, m), 7.20 (4H, m), 4.08 (1H, s), 3.79 (1H, s), 2.26 (2H, d), 1.79 (8H, m), 1.17 (6H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 498

**Example 130**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.07 (2H, m), 7.20 (4H, m), 4.07 (1H, s), 3.78 (1H, m), 2.18 (2H, m), 1.77 (8H, m), 1.59 (2H, m), 1.18 (6H, s).

LCMS (electrospray): *m/z* $[M+Na]^+$ 512

**Example 131**

1H NMR (400MHz, CD3OD): δ 8.07 (2H, m), 7.18 (4H, m), 4.08 (1H, m), 3.80 (1H, m), 2.25 (2H, m), 2.18 (2H, m), 1.78 (6H, m), 1.60 (6H, m).

LCMS (electrospray) *m/z* $[M+Na]^+$ 498

**Example 132**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.19 (2H, m), 8.10 (3H, m), 7.19 (4H, m), 4.16 (1H, m), 4.02 (1H, m), 1.85 (8H, m).

LCMS (electrospray): *m/z* [M-H]$^-$ 495

**Example 133**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.07 (2H, m), 7.19 (4H, m), 4.08 (1H, s), 3.82 (1H, s), 2.29 (2H, m), 2.15 (2H, m), 2.00 (1H, m), 1.79 (6H, m), 1.63 (2H, m), 0.97 (3H, d).

LCMS (electrospray): *m/z* [M-H]$^-$ 474

**Example 134**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.08 (1H, d), 8.02 (1H, m), 7.19 (4H, m), 4.04 (1H, s), 3.86 (1H, s), 2.86 (2H, m), 2.03 (1H, m), 1.98 (1H, m), 1.74 (12H, m).

LCMS (electrospray): *m/z* [M-H]$^-$ 486

**Example 135**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.64 (1H, d) 8.53 (1H, s), 8.09 (1H, m), 8.06 (1H, m), 7.95 (1H, m) 7.22 (2H, m), 7.16 (2H, m), 4.14 (1H, s) 4.06 (1H, s), 1.89 (6H, s), 1.78 (2H, m).

LCMS (electrospray): *m/z* [M-H]$^-$ 495

**Example 136**

$^1$H NMR (400MHz, $CD_3OD$): δ 9.07 (1H, s) 8.39 (1H, d), 8.05 (3H, m), 7.21 (2H, m), 7.15 (2H, s), 4.06 (1H, s), 1.88 (6H, s), 1.79 (2H, m).

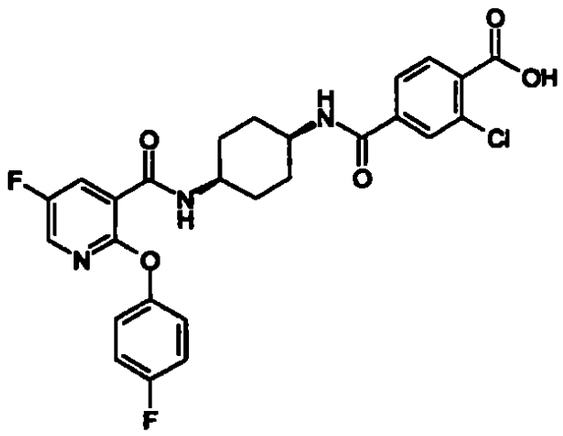
LCMS (electrospray): *m/z* [M-H]$^-$ 495

**Example 137**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.30 (1H, d), 8.06 (2H, m), 7.86 (1H, d), 7.68 (1H, s), 7.61 (1H, d), 7.19 (4H, m), 4.08 (2H, s), 3.89 (3H, s), 1.84 (8H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 524

**Example 138: *Syn*-2-Chloro-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-terephthalamic acid**

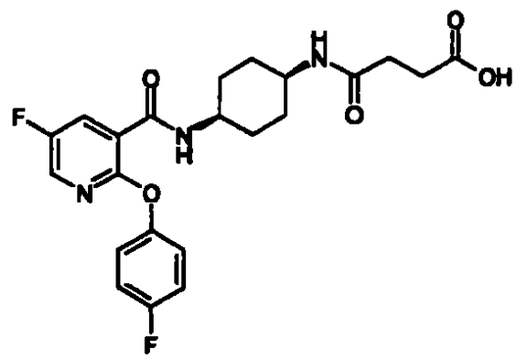


*Syn*-2-chloro-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-terephthalamic acid methyl ester (95 mg, 0.18 mmol, see Example 121) was suspended in 1,4-dioxane (3 ml) and 1M lithium hydroxide solution (350 µl, 0.35 mmol) was added. The mixture was stirred at room temperature for 18 hours, after which 1,4-dioxane (3 ml) and 1M lithium hydroxide solution (500 µl, 0.5 mmol) were added and the mixture stirred a further 24 hours. The reaction mixture was diluted with 1M hydrochloric acid (20 ml) and was extracted with dichloromethane (4 x 200 ml) and the combined dichloromethane layers were dried over magnesium sulphate and evaporated *in-vacuo* to give *syn*-2-chloro-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-terephthalamic acid as a white solid (66 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8.32 (2H, m), 8.20 (1H, s), 7.99 (1H, d), 7.90 (1H, s), 7.79 (1H, s), 7.22 (4H, m), 3.95 (1H, s), 3.91 (1H, s), 1.78 (8H, m).

LCMS (electrospray): *m/z* [M-H]$^-$ 528, 530

**Example 139: *Syn*-N-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-succinamic acid**

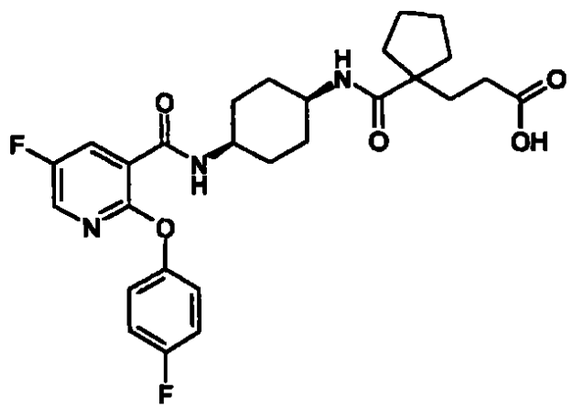


*Syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-succinamic acid methyl ester (65 mg, 0.14 mmol, see Example 110) was dissolved in tetrahydrofuran (3 ml) and 1M lithium hydroxide solution (750 µl, 0.75 mmol) was added. The mixture was stirred at room temperature for 18 hours after which the solvent was evaporated *in-vacuo*. The residue was diluted with 1M hydrochloric acid (20 ml) and was extracted with dichloromethane (3 x 150 ml), the combined dichloromethane layers were dried over magnesium sulphate and evaporated *in-vacuo* to give *syn*-N-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-succinamic acid as a white solid (60 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8.26 (1H, d), 8.20 (1H, s), 7.98 (1H, d), 7.63 (1H, d), 7.22 (4H, m), 3.86 (1H, s), 3.63 (1H, d), 2.39 (2H, t), 2.30 (3H, t), 1.60 (8H, m).

LCMS (electrospray): *m/z* [M-H]$^-$ 446

**Example 140: *Syn*-3-[1-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexylcarbamoyl)-cyclopentyl]-propionic acid**

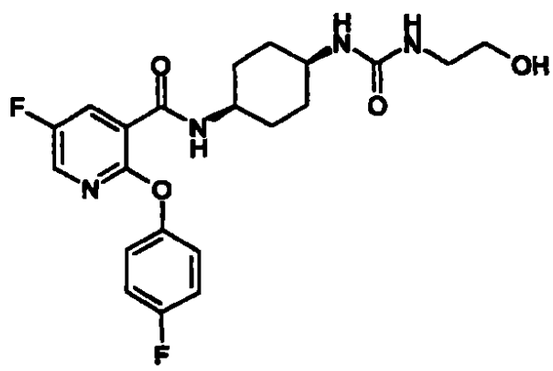


*Syn*-3-[1-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexylcarbamoyl)-cyclopentyl]-propionic acid tert-butyl ester (170 mg, 0.3 mmol, see Example 117) was dissolved in 1,4-dioxane and hydrogen chloride (4M solution in 1,4-dioxane) was added. The mixture was stirred at room temperature for 18 hours after which the solvent was evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane containing ammonium hydroxide solution (from 10:90:1 to 15:85:2 to 20:80:3) to give *syn*-3-[1-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexylcarbamoyl)-cyclopentyl]-propionic acid (60 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.06 (2H, m), 7.19 (4H, m), 7.04 (1H, d), 4.13 (1H, s), 3.78 (1H, s), 2.10 (2H, m), 2.01 (2H, m), 1.88 (4H, m), 1.77 (4H, m), 1.61(6H, m) 1.31 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 514

**Example 141: *Syn*-5-Fluoro-2-(4-fluoro-phenoxy)-N-{4-[3-(2-hydroxy-ethyl)-ureido]-cyclohexyl}-nicotinamide**

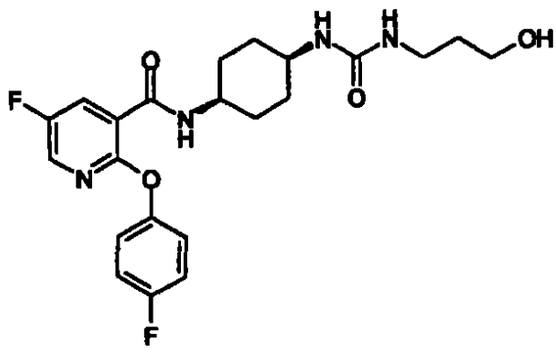


*Syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclohexyl}-nicotinamide (110 mg, 0.25 mmol, see Preparation 25) was dissolved in dichloromethane (7 ml) containing triethylamine (42 µl, 0.3 mmol) and 2-aminoethanol (46 µl, 0.75 mmol) and was stirred at room temperature for 18 hours. The reaction mixture was diluted with water (200 ml) and the aqueous solution was extracted with dichloromethane (5 x 200 ml). The combined dichloromethane layers were dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane (gradient from 4:96 to 10:90) to give *syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-{4-[3-(2-hydroxy-ethyl)-ureido]-cyclohexyl}-nicotinamide as a white solid (40 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.07 (2H, m), 7.17 (4H, m), 4.04 (1H, s), 3.68 (1H, s), 3.57 (2H, t), 3.21 (2H, t), 1.79 (6H, m), 1.59 (2H, m).

LCMS (electrospray): *m/z* [M-H]$^-$ 434

**Example 142: *Syn*-5-Fluoro-2-(4-fluoro-phenoxy)-N-{4-[3-(3-hydroxy-propyl)-ureido]-cyclohexyl}-nicotinamide**

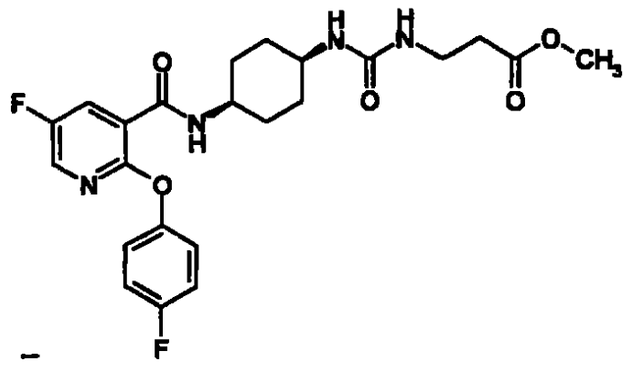


*Syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclo hexyl}-nicotinamide (150 mg, 0.34 mmol, see Preparation 25) was dissolved in dichloromethane (10 ml) containing triethylamine (57 µl, 0.41 mmol) and 3-amino-1-propanol (78 µl, 1.02 mmol) and was stirred at room temperature under a nitrogen atmosphere for 66 hours. The reaction mixture was washed with water (2 x 50 ml) and the dichloromethane layer was dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane and ammonium hydroxide solution (gradient from 4:96:0 to 10:90:1) to give *syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-{4-[3-(3-hydroxy-propyl)-ureido]-cyclohexyl}-nicotinamide as a white solid (90 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.07 (2H, m), 7.20 (4H, m), 4.04 (1H, s), 3.66 (1H, s), 3.59 (2H, t), 3.19 (2H, t), 1.79 (6H, m), 1.60 (4H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 447

**Example 143: *Syn*-3-[3-(4-[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-propionic acid methyl ester**

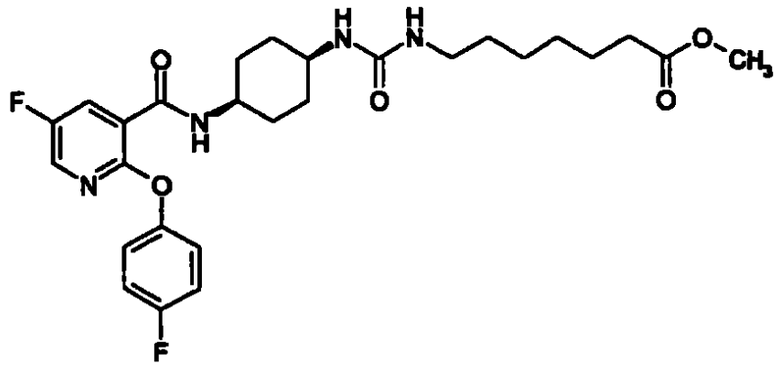


*Syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-(4-[(imidazole-1-carbonyl)-amino]-cyclohexyl)-nicotinamide (150 mg, 0.34 mmol, see Preparation 25) was dissolved in dichloromethane (10 ml) containing triethylamine (57 µl, 0.41 mmol) and 3-aminopropionic acid methyl ester (48 mg, 0.41 mmol) and was stirred at room temperature under a nitrogen atmosphere for 66 hours. The reaction mixture was washed with 1M hydrochloric acid (50 ml), the dichloromethane layer was dried over magnesium sulphate and evaporated *in-vacuo* to give *syn*-3-[3-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-propionic acid methyl ester as a white solid (130 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.37 (1H, d), 8.04 (1H, s), 7.96 (1H, d), 7.18 (4H, m), 4.19 (1H, s), 3.70 (4H, m), 3.47 (2H, t), 2.55 (2H, t), 1.79 (8H, m), 1.50 (2H, m).

LCMS (electrospray): *m/z* [M-H]$^-$ 475

**Example 144: *Syn*-7-[3-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-heptanoic acid methyl ester**

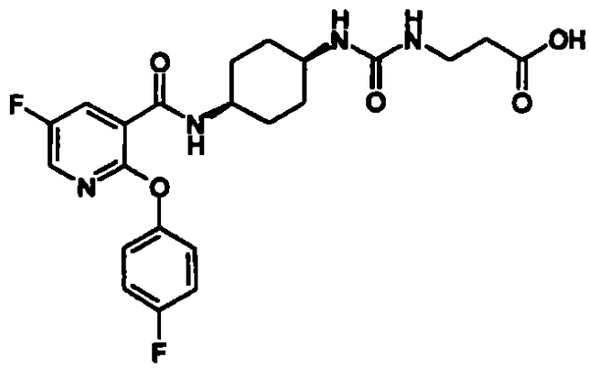


*Syn*-5-fluoro-2-(4-fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclohexyl}-nicotinamide (150 mg, 0.34 mmol, see Preparation 25) was dissolved in dichloromethane (10 ml) containing triethylamine (57 µl, 0.41 mmol) and 7-aminoheptanoic acid methyl ester (68 mg, 0.43 mmol) and was stirred at room temperature for 18 hours. The reaction mixture was washed with water (2 x 50 ml) and then with 1M hydrochloric acid (2 x 50 ml). The dichloromethane layer was dried over magnesium sulphate and evaporated *in-vacuo* to give *syn*-7-[3-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-heptanoic acid methyl ester as a white solid (168 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.36 (1H, d), 8.02 (1H, s), 7.96 (1H, d), 7.16 (4H, m), 4.19 (1H, s), 3.67(4H, m), 3.13 (2H, t), 2.30 (2H, t), 1.82 (4H, m), 1.76 (3H, m), 1.61 (4H, m), 1.44 (4H, m), 1.36 (3H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 555

**Example 145: *Syn*-3-[3-(4-[[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-propionic acid**

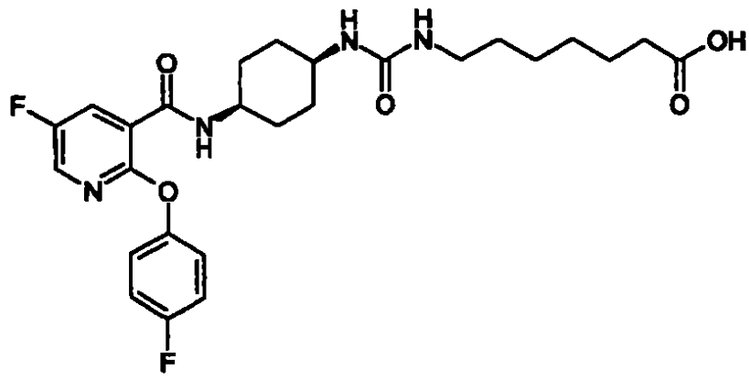


*Syn*-3-[3-(4-[[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-propionic acid methyl ester (110 mg, 0.23 mmol, see Example 143) was dissolved in tetrahydrofuran (1.5 ml). 1M Lithium hydroxide solution (460 µl, 0.46 mmol) was added and the mixture stirred at room temperature for 18 hours. The reaction mixture was dissolved in water and was washed with dichloromethane (2 x 50 ml). The aqueous layer was diluted with 1M hydrochloric acid (20 ml) and extracted with dichloromethane (4 x 150 ml). The combined dichloromethane layers were evaporated *in-vacuo*. The residue was re-dissolved in dichloromethane and was washed with 10% potassium carbonate solution (300 ml). The aqueous solution was acidified with 1M hydrochloric acid and extracted with dichloromethane (2 x 200 ml). These combined dichloromethane layers were dried over magnesium sulphate and evaporated *in-vacuo* to give *syn*-3-[3-(4-[[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-propionic acid as a white solid (30 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.09 (2H, m), 7.04 (4H, m), 4.19 (1H, s), 3.66 (1H, s), 2.42 (2H, t), 1.79 (8H, m), 1.59 (2H, m).

LCMS: (electrospray) *m/z* $[M-H]^-$ 461

**Example 146: *Syn*-7-[3-(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-heptanoic acid**

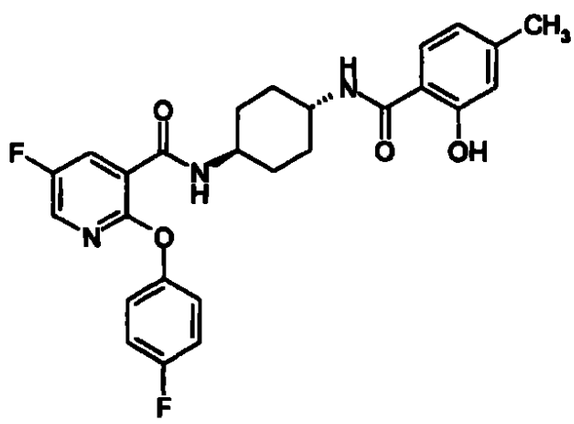


*Syn*-7-[3-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-heptanoic acid methyl ester (130 mg, 0.24 mmol, see Example 144) was dissolved in tetrahydrofuran (1.5 ml) containing 1M lithium hydroxide solution (500 µl, 0.5 mmol) and the mixture was stirred at room temperature for 66 hours. The reaction mixture was dissolved in water (200 ml) and was washed with dichloromethane (2 x 200 ml). The aqueous layer was acidified with 1M hydrochloric acid (50 ml) and extracted with dichloromethane (3 x 150 ml). The combined dichloromethane layers were evaporated *in-vacuo*, to give *syn*-7-[3-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-ureido]-heptanoic acid (60 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.36 (1H, d), 8.01 (2H, m), 7.04 (4H, m), 4.99 (1H, s), 4.50 (1H, s), 4.13 (1H, m), 3.74 (1H, m), 3.06 (2H, t) 2.33 (2H, t), 1.79 (6H, s), 1.63 (2H, m) 1.44 (4H, m), 1.37 (5H, s).

LCMS (electrospray): *m/z* [M-H]$^-$ 517

**Example 147: *Anti*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide**

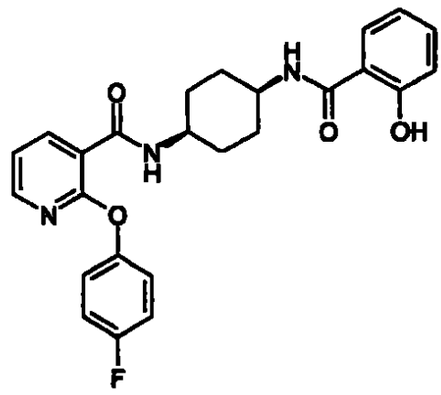


2-Hydroxy-4-methyl-benzoic acid (119 mg, 0.78 mmol), 1-hydroxybenzotriazole hydrate (158 mg, 1.17 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol), were dissolved in N,N-dimethylformamide (6 ml) under a nitrogen atmosphere and were stirred 30min. *Anti*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (300 mg, 0.782 mmol, see Preparation 7) and 4-methyl morpholine (170 µl, 1.56 mmol) were added and the mixture was stirred for 18 hours at room temperature. The mixture was partitioned between ethyl acetate and water and the organic phase was washed with a saturated solution of sodium chloride, dried over magnesium sulphate and evaporated *in-vacuo*. The residue was triturated with diethylether to give *anti*-5-fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide (210 mg).

$^1$H NMR (300MHz, $CDCl_3$): δ 8.34 (1H, m), 8.03 (1H, m), 7.77 (1H, m), 7.22 (1H, m) 7.12 (5H, m), 6.79 (1H, s) 6.63 (1H, d), 6.19 (1H, d), 4.00 (2H, s), 2.34 (3H, s), 2.19 (4H, m), 1.42 (4H, m).

*LCMS* (thermospray): $[M+H]^+$ *m/z* 482

**Example 148: *Syn*-2-(4-Fluoro-phenoxy)-N-[4-(2-hydroxy-benzoylamin )-cyclohexyl]-nicotinamide**

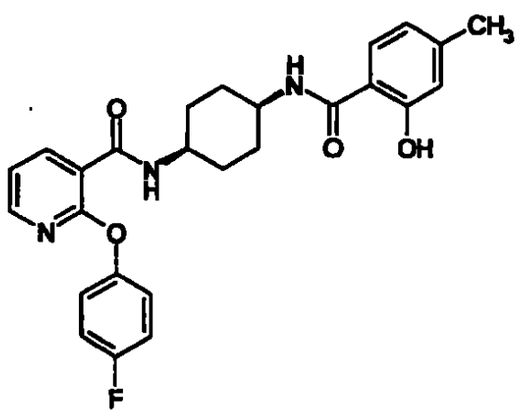


1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (225 mg, 1.17 mmol) was added to a suspension of 2-hydroxybenzoic acid (108 mg, 0.78 mmol), *syn*-N-(4-amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (300 mg, 0.78 mmol, see Preparation 47), and 1-hydroxybenzotriazole hydrate (115 mg, 0.85 mmol) in N,N-dimethylformamide (5 ml) containing triethylamine (545 µl, 3.9 mmol) and the mixture was stirred for 18 hours. The solvent was removed *in-vacuo* and the residue was partitioned between ethyl acetate and 2N hydrochloric acid. The ethyl acetate layer was washed with water then concentrated sodium chloride solution then dried over magnesium sulphate and the solvent was removed *in-vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate in cyclohexane as eluant (gradient from 10:90 to 60:40) to give *syn*-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-benzoylamino)-cyclohexyl]-nicotinamide (150 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.26 (1H, m), 8.18 (1H, m) 7.76 (1H, d), 7.36 (1H, t), 7.23 (3H, m), 7.15 (2H, m), 6.88 (2H, m), 4.17, (1H, m), 4.03 (1H, m), 1.88 (6H, m), 1.77 (2H, m).

LCMS (electrospray): *m/z* $[M-H]^-$ 449

**Example 149: *Syn*-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-4-methyl-benz yl-amino)-cyclohexyl]-nicotinamide**

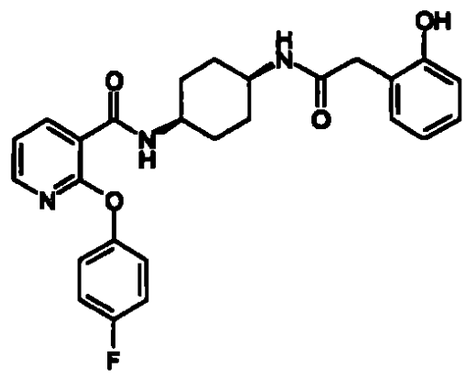


The title compound was obtained from *syn*-N-(4-amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride and 2-hydroxy-4-methylbenzoic acid in 35% yield following the procedure described in example 148.

$^1$H NMR (400MHz, $CD_3OD$): δ 8.27 (1H, m), 8.19 (1H, m) 7.63 (1H, d), 7.23 (3H, m), 7.16 (2H, m), 6.73 (2H, m), 4.16, (1H, m), 4.01 (1H, m), 2.31 (3H, s), 1.88 (6H, m), 1.75 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 486

**Example 150: *Syn*-2-(4-Fluoro-phenoxy)-N-{4-[2-(2-hydroxy-phenyl)-acetylamino]-cyclohexyl}-nicotinamide**

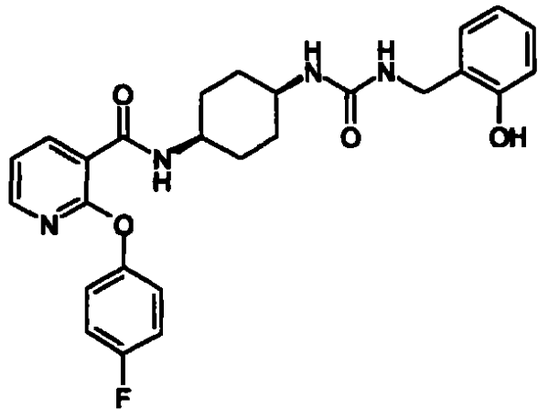


O-(7-Azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (234 mg, 0.49 mmol) was added to a suspension of (2-hydroxyphenyl)acetic acid (74.9 mg, 0.49 mmol) and *syn*-N-(4-amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (150 mg, 0.41 mmol, see Preparation 47), in N,N-dimethylformamide (2.7 ml) containing Hünigs base (820 µl, 0.82 mmol) and the mixture was stirred for 18 hours. The reaction mixture was diluted with water (10 ml) and was extracted with diethylether (2 x 12.5 ml). The combined organic layers were washed with concentrated sodium chloride solution then dried over magnesium sulphate and the solvent was removed *in-vacuo*. The residue was purified by chromatography on silica gel using methanol and ammonium hydroxide solution in dichloromethane as eluant (5:0.5:95) followed by a further purification by chromatography on silica gel using cyclohexane in ethyl acetate (33:67) as eluant to give *syn*-2-(4-fluoro-phenoxy)-N-{4-[2-(2-hydroxy-phenyl)-acetylamino]-cyclohexyl}-nicotinamide as an off white foam (25.1 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 9.68 (1H, s), 8.62 (1H, d), 8.21 (1H, d) 7.97 (1H, m), 7.19 (6H, m), 6.98 (2H, m), 6.82 (1H, m), 5.78 (1H, m), 4.16, (1H, m), 3.89 (1H, m), 3.48 (2H, s), 1.80 (6H, m), 1.51 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$486

**Example 151: *Syn*-2-(4-fluoro-phenoxy)-N-{4-[3-(2-hydroxy-benzyl)-ureido]-cyclohexyl}-nicotinamide**

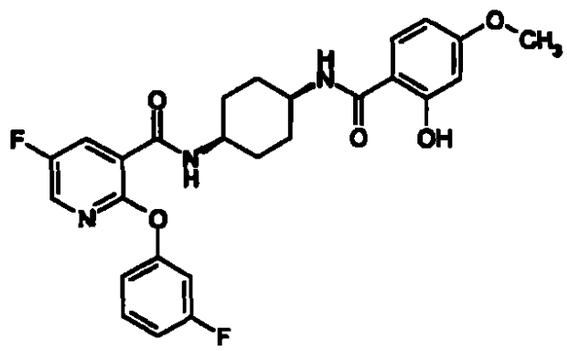


2-Aminomethylphenol (65 mg, 0.53 mmol) was added to a solution of 2-(4-fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclohexyl}-nicotinamide (150 mg, 0.35 mmol, see Preparation 47) and 4-dimethylaminopyridine (43.3 mg, 0.35 mmol) in dichloromethane (3 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred for 18 hours and then was washed with water (20 ml) and then diluted with 10% citric acid solution (20 ml). The mixture was extracted with dichloromethane (2 x 10 ml) and the combined organic layers were washed with a saturated solution of sodium chloride (20 ml) and dried over magnesium sulphate. The solvent was removed *in-vacuo* and the residue purified by chromatography on silica gel using cyclohexane in ethyl acetate (33.3:66.6) to give *syn*-2-(4-fluoro-phenoxy)-N-{4-[3-(2-hydroxy-benzyl)-ureido]-cyclohexyl}-nicotinamide as an off white foam (96 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 9.75 (1H, s), 8.60 (1H, d), 8.20 (1H, d) 7.91 (1H, d), 7.18 (6H, m), 7.02 (1H, d), 6.98 (2H, m), 6.79 (1H, m), 4.84 (1H, m), 4.29, (2H, d), 3.71 (1H, m), 1.82 (6H, m), 1.49 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 501

**Example 152: *Syn*-2-(3-fluoro-phenoxy)-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-nicotinamide**



Caesium carbonate (170 mg, 0.52 mmol) was added to a solution of *syn*-2-chloro-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-nicotinamide (110 mg, 0.26 mmol, see Preparation 45) and 3-fluorophenol (35 mg, 0.31 mmol) in N,N-dimethylformamide (2 ml) and was stirred at 65°C for

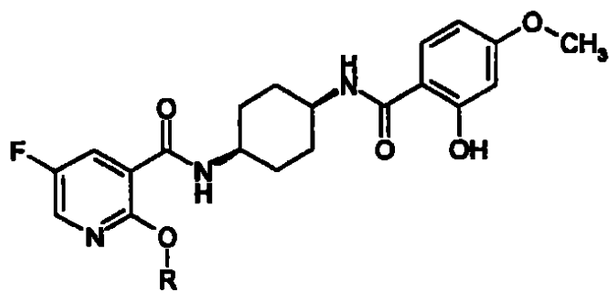
18 hours. The mixture was partitioned between ethyl acetate and water and the organic solution was dried using a Chem Elut® cartridge and evaporated *in-vacuo*. The residue was purified by chromatography on a Biotage™ cartridge to give *syn*-2-(3-fluoro-phenoxy)-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-nicotinamide (19 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 12.56 (1H, s), 8.38 (1H, d), 8.09 (1H, s), 7.94 (1H, d), 7.44 (1H, m), 7.00 (4H, m), 6.46 (1H, s), 6.39 (1H, d), 5.78 (1H, d), 4.26 (1H, m), 4.07 (1H, m), 3.82 (3H, s), 1.90 (8H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 520

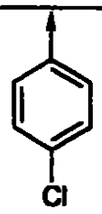
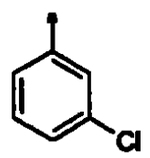
**Examples 153-159**

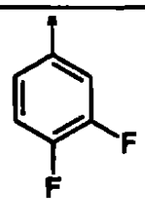
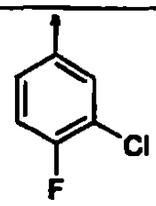
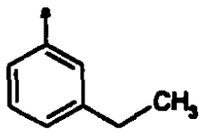
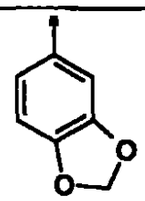
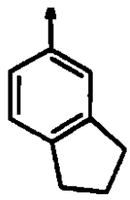
The compounds of the following tabulated examples (Table 10) of the general formula :




were prepared by a similar method to that of example 152 using 2-chloro-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-nicotinamide (see Preparation 45) and the appropriate phenol.

**Table 10**

| Example N° | R group | Example N° | R group |
|---|---|---|---|
| 153 |  | 154 |  |

| | | | |
|---|---|---|---|
| 155 |  | 156 |  |
| 157 |  | 158 |  |
| 159 |  | | |

**Example 153**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.54 (1H, s), 8.37 (1H, d), 8.06 (1H, s), 7.97 (1H, d), 7.44 (2H, d), 7.14 (2H, d), 7.00 (1H, d), 6.43 (2H, m), 5.74 (1H, d), 4.28 (1H, m), 4.07 (1H, m), 3.82 (3H, s), 1.91 (8H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 536, 538

**Example 154**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.54 (1H, s), 8.38 (1H, d), 8.09 (1H, s), 7.93 (1H, d), 7.40 (1H, m), 7.30 (1H, m), 7.21 (1H, m), 7.07 (2H, m), 6.44 (1H, s), 6.39 (1H, d), 5.79 (1H, d), 4.26 (1H, s), 4.08 (1H, m), 3.81 (3H, s), 1.90 (8H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 536, 538

**Example 155**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.54 (1H, s), 8.37 (1H, d), 8.08 (1H, s), 7.87 (1H, d), 7.24 (1H, m), 7.14 (2H, d), 6.93 (1H, m), 6.46 (1H, s), 6.40 (1H, d), 5.84 (1H, d), 4.28 (1H, m), 4.09 (1H, m), 3.82 (3H, s), 1.91 (8H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 538

**Example 156**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.53 (1H, s), 8.37 (1H, d), 8.06 (1H, s), 7.87 (1H, d), 7.24 (2H, m), 7.10 (2H, m), 6.46 (1H, s), 6.39 (1H, d), 5.84 (1H, d), 4.28 (1H, m), 4.11 (1H, m), 3.82 (3H, s), 1.90 (8H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 554, 556

**Example 157**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.59 (1H, s), 8.38 (1H, d), 8.08 (1H, d), 8.08 (1H, s), 7.39 (1H, t), 7.17 (1H, d), 6.99 (3H, m), 6.44 (1H, s), 6.38 (1H, d), 5.70 (1H, d), 4.29 (1H, s), 4.08 (1H, m), 3.82 (3H, s), 2.70(2H, q), 1.90 (8H, m) 1.25 (3H, t).

LCMS (electrospray): *m/z* $[M+Na]^+$ 530

**Example 158**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.59 (1H, s), 8.34 (1H, d), 8.08 (2H, m), 7.07 (1H, d), 6.88 (1H, d), 6.71 (1H, s), 6.64 (1H, d), 6.46 (1H, s), 6.39 (1H, d), 6.03 (2H, s), 5.78 (1H, d), 4.30 (1H, m), 4.08 (1H, m), 3.83 (3H, s), 1.93 (8H, m).

LCMS (electrospray): *m/z* 546 $[M+Na]^+$

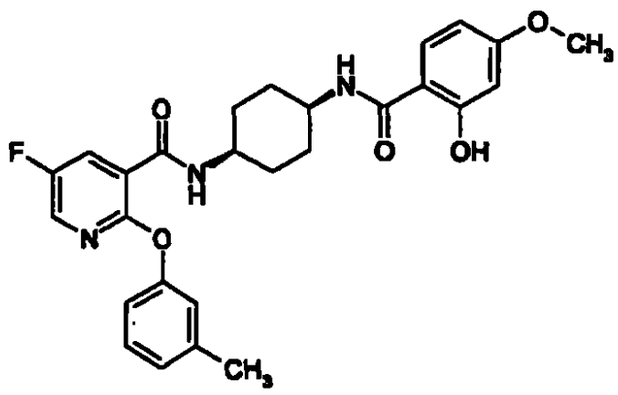
**Example 159**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.59 (1H, s), 8.37 (1H, d), 8.19 (1H, d), 8.07 (1H, s), 7.30 (1H, d), 7.02 (2H, m), 6.94 (1H, d), 6.46 (1H, s), 6.38 (1H, d), 5.74 (1H,

d), 4.30 (1H, m), 4.08 (1H, m), 3.83 (3H, s), 2.94 (4H, m), 2.17 (2H, m) 1.93 (8H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 542

**Example 160: Syn-5-Fluoro-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-2-m-tolyloxy-nicotinamide**



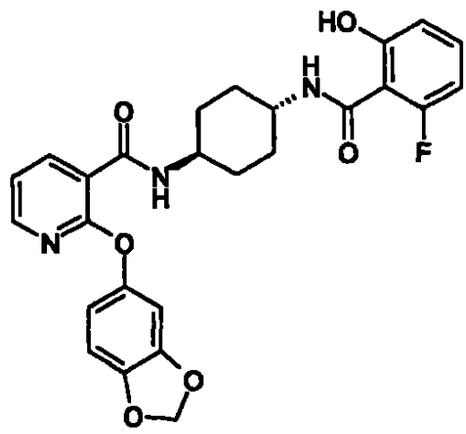
Caesium carbonate (116 mg, 0.36 mmol) was added to a solution of *syn*-2-chloro-5-fluoro-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-nicotinamide (100 mg, 0.24 mmol, see Preparation 45) and 3-hydroxytoluene (28 mg, 0.26 mmol) in N,N-dimethylformamide (3 ml) and was stirred at 55°C for 18 hours. A further portion of caesium carbonate (30 mg, 0.16 mmol) and 3-hydroxytoluene (10 mg, 0.9 mmol) were added and the mixture was heated to 65°C for 3 hours. The reaction mixture was cooled to room temperature and partitioned between ethyl acetate and water. The ethyl acetate layer was washed with water and then a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate in pentane (50:50) as eluant to give *syn*-5-fluoro-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-2-m-tolyloxy-nicotinamide (36 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 12.56 (1H, s), 8.37 (1H, d), 8.16 (1H, d), 8.10 (1H, s), 7.36 (1H, m), 7.14 (1H, d), 6.97 (3H, d), 7.07 (2H, m), 6.48 (1H, s), 6.39 (1H,

d), 5.70 (1H, d), 4.30 (1H, s), 4.06 (1H, m), 3.83 (3H, s), 2.40 (3H, s), 1.90 (8H, m).

LCMS (electrospray): *m/z* [M-H]⁻ 493

**Example 161: *Anti*-2-(Benzo[1,3]dioxol-5-yloxy)-N-[4-(2-fluoro-6-hydroxy-benzoylamino)-cyclohexyl]-nicotinamide**

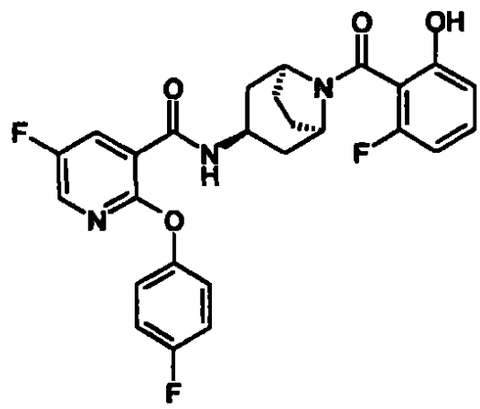


2-Fluoro-6-hydroxy-benzoic acid (119 mg, 0.77 mmol) was added to 1-hydroxybenzotriazole hydrate (155 mg 0.77 mmol) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (220 mg, 0.77 mmol) in N,N-dimethylformamide (5 ml) and the mixture was stirred for 1.5 hours. Anti-N-(4-Amino-cyclohexyl)-2-(benzo[1,3]dioxol-5-yloxy)-nicotinamide hydrochloride (300 mg, 0.77 mmol, see Preparation 39) and 4-methylmorpholine (167 µl, 0.77 mmol) were added and the mixture was stirred for 18 hours and then partitioned between dichloromethane and 10% citric acid solution (10 ml). The organic layer was separated, passed through a hydrophobic frit and evaporated *in-vacuo*. The residue was triturated with methanol and the solid obtained isolated by filtration to give *anti*-2-(benzo[1,3]dioxol-5-yloxy)-N-[4-(2-fluoro-6-hydroxy-benzoylamino)-cyclohexyl]-nicotinamide (26 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 13.36 (1H, s), 8.60 (1H, d), 8.21 (1H, d), 7.73 (1H, d), 7.27 (1H, m), 7.14 (1H, m), 6.93 (1H, m), 6.88 (1H, d), 6.79 (1H, d), 6.72 (1H, s), 6.60 (2H, m), 6.61 (2H, s), 4.02 (2H, m), 2.20 (4H, m), 1.46 (4H, m).

LCMS (electrospray): *m/z* [M-H]⁻ 492

**Example 162: *Exo*-5-Fluoro-N-[8-(2-fluoro-6-hydroxy-benzoyl)-8-aza-bicyclo[3.2.1]oct-3-yl]-2-(4-fluoro-phenoxy)-nicotinamide**

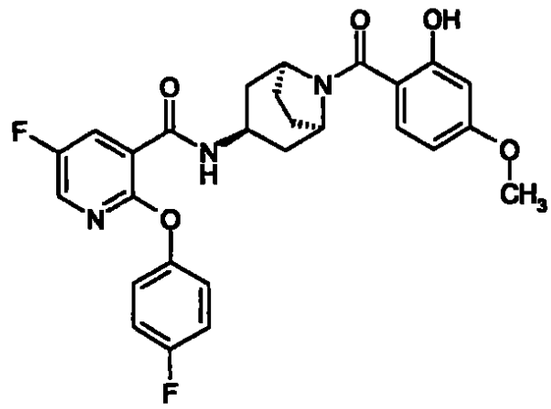


*Exo*-N-(8-Aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (155 mg, 0.43 mmol, see Preparation 35) was added to 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (101 mg, 0.52 mmol), 2-fluoro-6-hydroxybenzoic acid (69 mg, 0.43 mmol) and 1-hydroxybenzotriazole hydrate (70 mg, 0.52 mmol) in dichloromethane (5 ml) containing 4-methylmorpholine (57 µl, 0.52 mmol) and the mixture was stirred at room temperature for 24 hours. Water was added and the mixture was concentrated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane (5:95) as eluant, to give *exo*-5-fluoro-N-[8-(2-fluoro-6-hydroxy-benzoyl)-8-aza-bicyclo[3.2.1]oct-3-yl]-2-(4-fluoro-phenoxy)-nicotinamide (85 mg).

$^1$H NMR (400MHz, DMSO-d$^6$): δ 10.10 (1H, s), 8.19 (1H, d), 8.18 (1H, s), 7.92 (1H, d), 7.19 (5H, m), 6.86 (2H, m), 4.67 (1H, s), 4.33 (1H, m), 3.72 (1H, s), 1.79 (7H, m), 1.46 (1H, m).

LCMS: *m/z* AP$^+$ 498 [M+H]$^+$

**Example 163: *Exo*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[8-(2-hydroxy-4-methoxy-benzoyl)-8-aza-bicyclo[3.2.1]oct-3-yl]-nicotinamide**

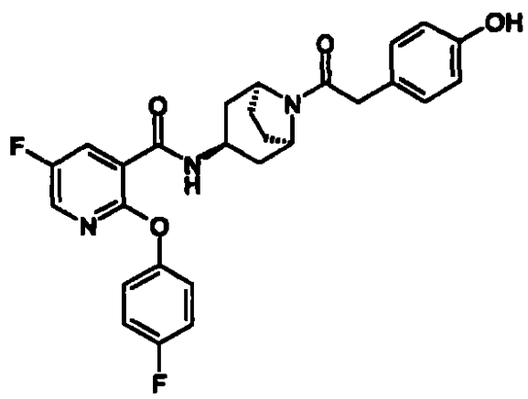


*Exo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (155 mg, 0.43 mmol, see Preparation 35) was added to 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (101 mg, 0.52 mmol), 2-hydroxy-4-methoxybenzoic acid (73 mg, 0.43 mmol) and 1-hydroxybenzotriazole hydrate (70 mg, 0.52 mmol) in dichloromethane (5 ml) containing 4-methylmorpholine (57 µl, 0.52 mmol) and the mixture was stirred at room temperature for 24 hours. Water was added and the mixture was concentrated *in-vacuo*, the residue was purified by chromatography on silica gel using methanol in dichloromethane (5:95) as eluant, to give *exo*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[8-(2-hydroxy-4-methoxy-benzoyl)-8-aza-bicyclo[3.2.1]oct-3-yl]-nicotinamide (165 mg).

$^1$H NMR (400MHz, DMSO-d$^6$): δ 10.13 (1H, s), 8.34 (1H, d), 8.19 (1H, s), 7.92 (1H, m), 7.19 (5H, m), 6.40 (2H, m), 4.36 (3H, m), 3.74 (3H, s), 1.79 (8H, m).

LCMS: *m/z* AP$^+$ 510 $[M+H]^+$

**Example 164: *Exo*-5-fluoro-2-(4-fluoro-phenoxy)-N-{8-[2-(4-hydroxy-phenyl)-acetyl]-8-aza-bicyclo[3.2.1]oct-3-yl}-nicotinamide**

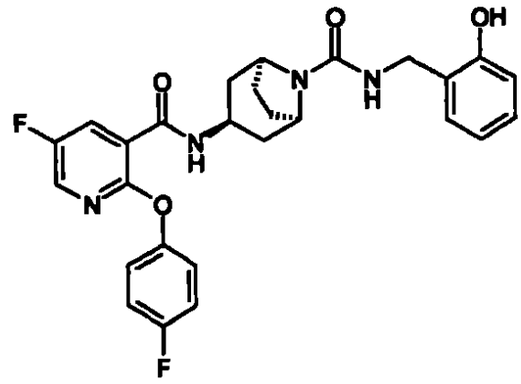


*Exo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (310 mg, 0.86 mmol, see Preparation 35) was added to 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (185 mg, 0.95 mmol), 4-hydroxyphenylacetic acid (134 mg, 0.86 mmol) and 1-hydroxybenzotriazole hydrate (128 mg, 0.95 mmol) in dichloromethane (5 ml) containing 4-methylmorpholine (104 µl, 0.95 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with water and the organic phase was concentrated *in-vacuo* and then purified by chromatography on silica gel using methanol in dichloromethane containing ammonium hydroxide solution as eluant (gradient from 1:99:0.1 to 5:95:0.5). The material obtained was triturated with methanol and isolated by filtration then dried *in-vacuo* to give *exo*-5-fluoro-2-(4-fluoro-phenoxy)-N-{8-[2-(4-hydroxy-phenyl)-acetyl]-8-aza-bicyclo[3.2.1]oct-3-yl}-nicotinamide (270 mg)

$^1$H NMR (400MHz, DMSO-d$^6$): δ 9.21 (1H, s), 8.31 (1H, d), 8.19 (1H, s), 7.94 (1H, d), 7.20 (4H, m), 7.00 (2H, d), 6.66 (2H, d), 4.46 (1H, m), 4.35 (2H, m), 3.56 (1H, d), 3.40 (1H, d), 1.79 (6H, m), 1.48 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 516

**Example 165: *Exo*-3-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid 2-hydroxy-benzyl-amide**



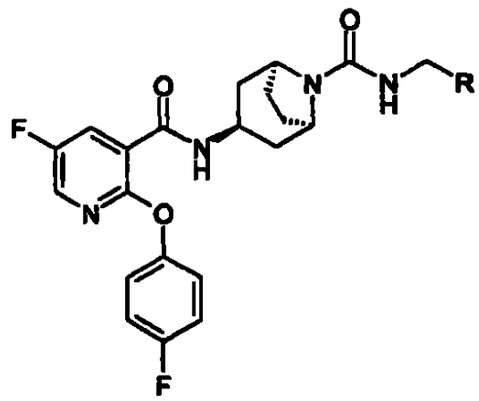
A solution of *exo*-3-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-aza-bicyclo[3.2.1]octane-8-carbonyl chloride was freshly prepared by adding *exo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (625 mg, 1.74 mmol, see Preparation 35) portionwise over 10 minutes to a solution of triphosgene (175 mg, 0.56 mmol) in dichloromethane (10 ml) and stirring for 18 hours at room temperature. Triethylamine (218 µl, 1.5 mmol) and 2-aminomethylphenol hydrochloride (96 mg, 0.6 mmol, see Tet. Lett. 2001, 41(49), 8665) were added to the above solution (3 ml, 0.52 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was washed with a saturated solution of sodium chloride and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 5:95) the material isolated was triturated with diethylether and dried *in-vacuo* to give *exo*-3-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid 2-hydroxy-benzylamide as an off white solid (22 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.30 (1H, m), 8.01 (1H, s), 7.60 (1H, d), 7.10 (7H, m), 6.90 (1H, d), 6.80 (1H, m), 5.03 (1H, s), 4.54 (2H, m), 4.34 (1H, s), 4.21 (1H, s), 4.19 (2H, s), 1.86 (8H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 531

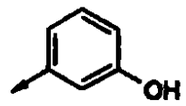
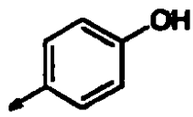
**Examples 166-167**

The compounds of the following tabulated examples (Table 11) of the general formula :



were prepared by a similar method to that of example 165 using the same carbamoyl chloride and the appropriate amine.

**Table 12**

| Example N° | R group |
|---|---|
| 166[1] |  |
| 167[2] |  |

[1] For the amine, see reference Tet. Lett. 1995, 36(8), 1279

[2] For the amine, see reference DE 2552423

**Example 166**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.31 (1H, d) 8.02 (1H, s), 7.80 (1H, d), 7.13 (7H, m), 6.92 (1H, s), 6.80 (1H, m), 6.74 (1H, d), 4.41 (3H, m), 4.26 (2H, m), 2.10 (2H, m), 1.19 (4H, m), 1.88 (2H, m).

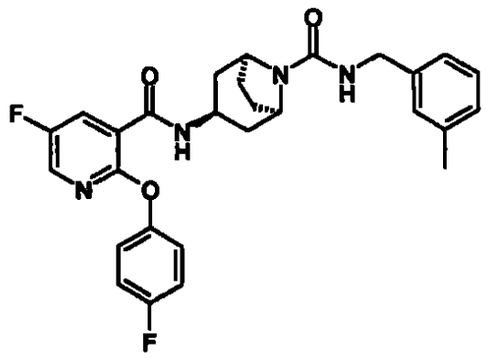
LCMS (electrospray): *m/z* $[M+Na]^+$ 531

**Example 167**

$^1H$ NMR (400MHz, DMSO-$d_6$): δ 9.13 (1H, s), 8.32 (1H, d), 8.14 (1H, s), 7.93 (1H, m), 7.19 (4H, m), 7.03 (2H, d), 6.87 (1H, m), 6.67 (2H, m) 4.33 (1H, m), 4.24 (2H, s), 4.13 (2H, m), 1.86 (2H, m), 1.72 (4H, m), 1.60 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 531

**Example 168: *Exo*-3-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid 3-methyl-benzyl-amide**



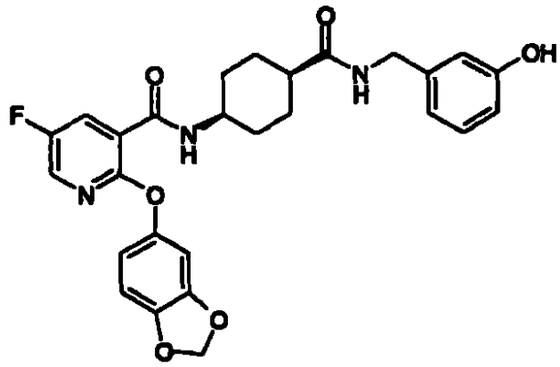
*Syn*-4-{[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid (150 mg 0.37 mmol, see Preparation 58), 2-aminomethylphenol hydrochloride (65 mg, 0.41 mmol, see Tet. Lett. 2001, 41(49), 8665), O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (156 mg, 0.41 mmol ) and 4-methylmorpholine (50 µl, 0.41 mmol) were mixed in N,N-dimethylformamide (4 ml) and were stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned between water (10 ml) and dichloromethane (10 ml). The dichloromethane layer was dried over magnesium sulphate and evaporated *in-vacuo* and the residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 2:98). The material isolated was triturated with ethyl acetate in pentane (10:90) to give

*syn*-2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[4-(2-hydroxy-benzylcarbamoyl)-cyclohexyl]-nicotinamide as a white powder (61 mg)

$^1$H NMR (400MHz, $CD_3OD$): δ 8.04 (1H, m), 8.01 (1H, m), 7.04 (2H, m), 6.79 (1H, d), 6.72 (3H, m), 6.61 (1H, d), 5.96 (2H, s), 4.27 (2H, s), 4.13 (1H, m), 2.33 (1H, m), 1.89 (2H, m), 1.71 (6H, m)

LCMS (electrospray): *m/z* $[M+Na]^+$ 530

**Example 169: *Syn*-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[4-(3-hydroxy-benzylcarbamoyl)-cyclohexyl]-nicotinamide**



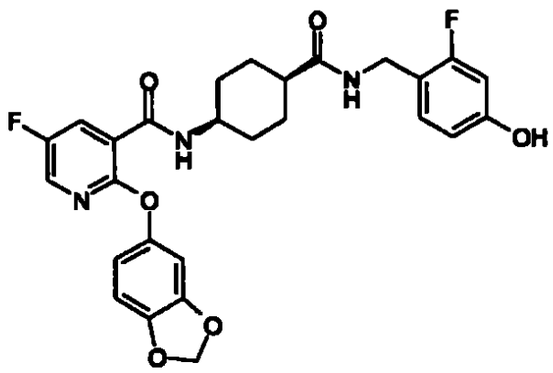
*Syn*-4-[[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino]-cyclohexanecarboxylic acid (144 mg 0.36 mmol, see Preparation 58), 3-aminomethylphenol hydrochloride (225 mg 0.39 mmol, see reference Tet. Lett. 1995, 36(8), 1279), O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (149 mg, 0.39 mmol ) and 4-methylmorpholine (50 µl, 0.39 mmol) were mixed in N,N-dimethylformamide (4 ml) and were stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned between water (10 ml) and ethyl acetate (10 ml). The ethyl acetate layer was washed with a saturated solution of sodium chloride, dried over magnesium sulphate and evaporated *in-vacuo*. The residue was triturated with ethyl acetate in pentane (10:90) the solid formed was isolated by filtration and triturated with diethylether. This material was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 2:98 to 3:97) to give *syn*-2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-

[4-(3-hydroxy-benzylcarbamoyl)-cyclohexyl]-nicotinamide as a white foam (83 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.08 (2H, m), 7.09 (1H, t), 6.80 (1H, d), 6.76 (1H, m), 6.66 (4H, m), 5.98 (2H, s), 4.27 (2H, s), 4.19 (1H, m), 2.38 (1H, m), 1.93 (2H, m), 1.75 (6H, m).

LCMS (electrospray): *m/z* $[M+H]^+$ 508

**Example 170: *Syn*-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[4-(2-fluoro-4-hydroxy-benzylcarbamoyl)-cyclohexyl]-nicotinamide**

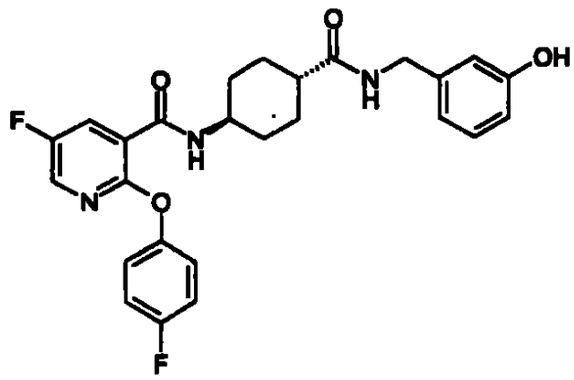


*Syn*-4-{[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid (200 mg 0.50 mmol, see Preparation 58), 4-aminomethyl-3-fluoro-phenol hydrochloride (97 mg, 0.55 mmol, see Preparation 49), O-(7-Azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (189 mg, 0.55 mmol ) and 4-methylmorpholine (60 µl, 0.55 mmol) were mixed in N,N-dimethylformamide (5 ml) and were stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned between water (10 ml) and dichloromethane (10 ml). The dichloromethane layer was dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 2:98). The material isolated was triturated with ethyl acetate in pentane (10:90) *syn*-2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-N-[4-(2-fluoro-4-hydroxy-benzylcarbamoyl)-cyclohexyl]-nicotinamide as a white solid (83 mg)

$^1$H NMR (400MHz, $CD_3OD$): δ 8.01 (2H, m), 7.04 (1H, m), 6.80 (1H, d), 6.74 (1H, m), 6.62 (1H, d), 6.48 (2H, m), 5.97 (2H, s), 4.23, (2H, s), 4.17 (1H, m), 2.13 (1H, m), 1.90 (2H, m), 1.72 (6H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 548

**Example 171 : *Anti*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[4-(3-hydroxy-benzyl-carbamoyl)-cyclohexyl]-nicotinamide**



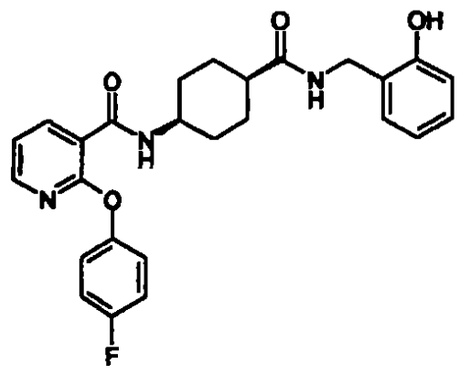
*Anti*-4-[[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino]-cyclo-hexanecarboxylic acid (200 mg 0.53 mmol, see Preparation 52), 3-aminomethylphenol hydrochloride (334 mg 0.58 mmol, see reference Tet. Lett. 1995, 36(8), 1279), O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (222 mg, 0.58 mmol ) and 4-methylmorpholine (70 µl, 0.58 mmol) were mixed in N,N-dimethylformamide (5 ml) and were stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned between water (10 ml) and dichloromethane (10 ml). The dichloromethane layer was dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 2:98). The material isolated was dried *in-vacuo* to give *anti*-5-fluoro-2-(4-fluoro-phenoxy)-N-[4-(3-hydroxy-benzylcarbamoyl)-cyclohexyl]-nicotinamide as a white powder (127 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.21 (1H, m), 8.07 (1H, d), 8.00 (1H, m), 7.13

(5H, m), 6.70 (3H, m), 4.29, (2H, d), 3.89 (1H, m), 2.26 (1H, m), 2.12 (2H, m), 1.95 (2H, m) 1.68 (2H, m), 1.39 (2H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 504

**Example 172 : *Syn*-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-benzyl-carbamoyl)-cyclohexyl]-nicotinamide**

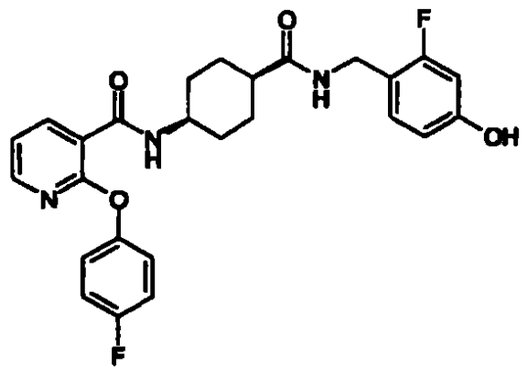


*Syn*-4-[[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino]-cyclohexane-carboxylic acid (164 mg 0.46 mmol, see Preparation 55), 2-aminomethylphenol hydrochloride (80 mg 0.50 mmol, see reference Tet. Lett. 1995, 36(8), 1279), O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (149 mg, 0.50 mmol ) and 4-methylmorpholine (60 µl, 0.50 mmol) were mixed in N,N-dimethylformamide (4 ml) and were stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned between water (10 ml) and ethyl acetate (10 ml). The ethyl acetate layer was washed with a saturated solution of sodium chloride, dried over magnesium sulphate and evaporated *in-vacuo*. The residue was triturated with diethylether, the solid formed was isolated by filtration and washed with diethylether. This material was purified by chromatography on silica gel using methanol in dichloromethane as eluant (2:98) to give *syn*-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-benzylcarbamoyl)-cyclohexyl]-nicotinamide as a white foam (77 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.26 (1H, d), 8.18 (1H, m), 7.21 (3H, m), 7.11 (4H, m), 6.78 (2H, m), 4.32 (2H, s), 4.20 (1H, m), 2.38 (1H, m), 1.92 (2H, m), 1.76 (6H, m).

LCMS (thermospray): *m/z* $[M+H]^+$ 464

**Example 173 : *Syn*-N-[4-(2-Fluoro-4-hydroxy-benzylcarbamoyl)-cyclohexyl]-2-(4-fluoro-phenoxy)-nicotinamide**



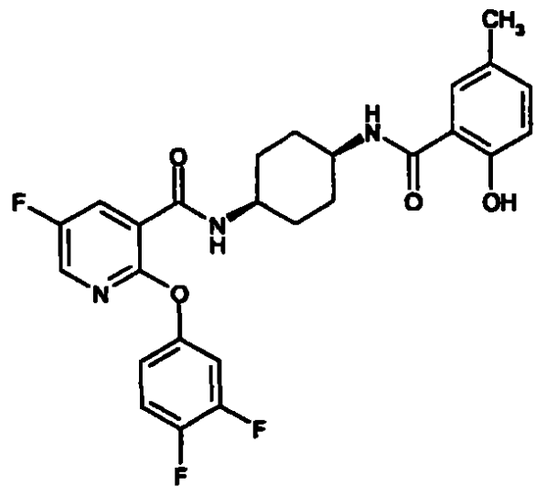
*Syn* -4-[[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid (200 mg 0.56 mmol, see Preparation 55), 4-aminomethyl-3-fluoro-phenol hydrochloride (109 mg, 0.61 mmol, see Preparation 49), O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (189 mg, 0.61 mmol ) and 4-methylmorpholine (70 µl, 0.61 mmol) were mixed in N,N-dimethylformamide (5 ml) and were stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned between water (10 ml) and dichloromethane (10 ml). The dichloromethane layer was dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 2:98). The material isolated was triturated with diethylether in pentane (20:80) to give *syn*-N-[4-(2-fluoro-4-hydroxy-benzylcarbamoyl)-cyclohexyl]-2-(4-fluoro-phenoxy)-nicotinamide as a white powder (83 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.40 (1H, d), 8.21 (1H, d), 8.14 (1H, d), 7.19 (3H, m), 7.09 (3H, m), 6.48 (2H, m), 4.22 (2H, s), 4.16 (1H, m), 2.31 (1H, m), 1.89 (2H, m), 1.70 (6H, m).

LCMS (electrospray): *m/z* $[M+Na]^+$ 505

89
90

**Example 174 : syn-2-(3,4-Difluoro-phenoxy)-5-fluoro-N-[4-(2-hydroxy-5-methyl-benzoylamino)-cyclohexyl]-nicotinamide**

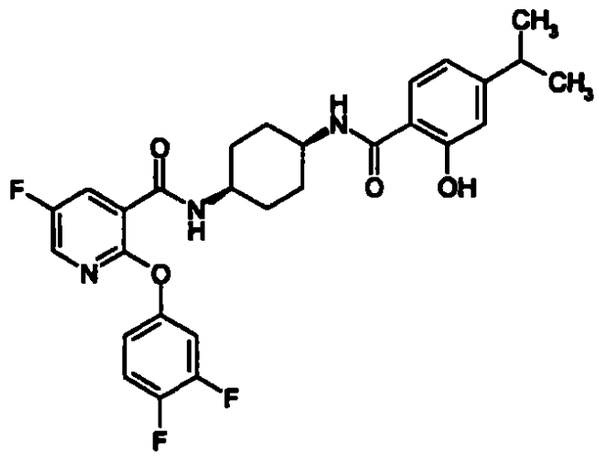


1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.45 g, 50 mmol) was added to a solution of the acid from preparation 60 (10.3 g, 38 mmol) and 1-hydroxybenzotriazole hydrate (5.65 g, 42 mmol) in 1-methyl-2-pyrrolidinone (150 ml) and the solution stired for 10 minutes. A solution of the amine from preparation 62 (11.8 g, 40 mmol) and Hünig's base (17.5 ml, 100 mmol) in 1-methyl-2-pyrrolidinone (50 ml) was then added and the reaction stirred at room temperature for 18 hours. The mixture was concentrated *in vacuo*, and the residue partitioned between ethyl acetate (1.25 L) and 1N hydrochloric acid (800 ml). The layers were separated, the organic phase washed with 2N hydrochloric acid (2-fold), water (2-fold) and brine, then dried over magnesium sulphate and evaporated *in vacuo*. The crude product was recrystallised from methanol, to afford the title compound as a white crystalline solid (15.6 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 1.56-1.66 (2H, m), 1.80-2.02 (6H, m), 2.26 (3H, s), 4.05 (1H, m), 4.25 (1H, m), 6.06 (1H, m), 6.90 (1H, d), 6.95 (1H, m), 6.99 (1H, s), 7.08 (1H, m), 7.19-7.30 (2H, m), 7.89 (1H, m), 8.05 (1H, s), 8.40 (1H, d), 11.98 (1H, s).

LCMS (APCI): m/z $[M+H]^+$ 500

**Example 175: *syn*-2-(3,4-Difluoro-phenoxy)-5-fluoro-N-[4-(2-hydroxy-4-isopropyl-benzoylamino)-cyclohexyl]-nicotinamide**



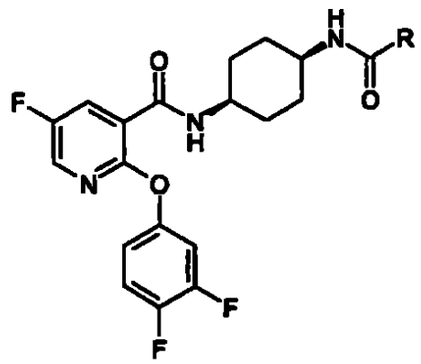
*syn*-N-(4-Amino-cyclohexyl)-2-(3,4-difluoro-phenoxy)-5-fluoro-nicotinamide (200 mg, 0.55 mmol, see preparation 64) was added to 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (115 mg, 0.6 mmol), 1-hydroxybenzotriazole hydrate (81 mg, 0.6 mmol), 4-methylmorpholine (120 µl, 1.1 mmol) and 2-hydroxy-4-isopropyl-benzoic acid (109 mg, 0.6 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature for 16 hours. Dichloromethane was added and the mixture was washed with saturated sodium hydrogen carbonate solution. The phases were separated and the organic phase was filtered through Whatman® phase separation tubes and concentrated *in-vacuo*. The residue was triturated with diethyl ether and dichloromethane to give *syn*-2-(3,4-difluoro-phenoxy)-5-fluoro-N-[4-(2-hydroxy-4-isopropyl-benzoylamino)-cyclohexyl]-nicotinamide as a white solid (145 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8.33 (m, 2H), 8.25 (d, 1H), 8.00 (m, 1H), 7.80 (d, 1H), 7.45 (m, 3H), 7.08 (m, 1H), 6.75 (m, 1H), 3.94 (m, 1H), 3.88 (m, 1H), 2.82 (m, 1H), 1.70 (m, 8H), 1.16 (d, 6H)

LCMS (electrospray): *m/z* [M-H]$^-$ 526

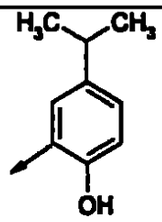
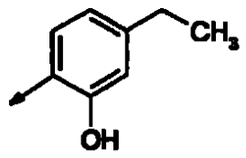
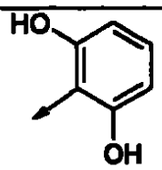
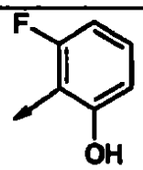
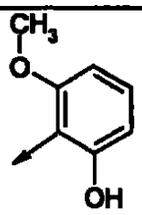
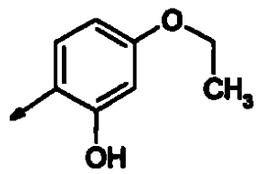
**Examples 176-194**

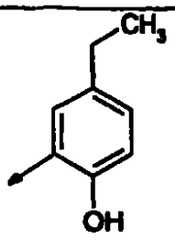
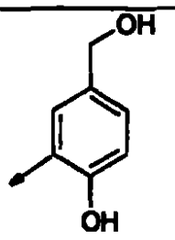
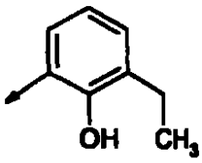
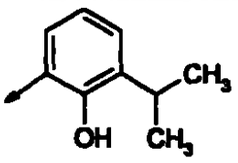
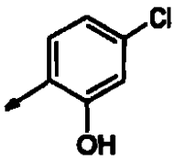
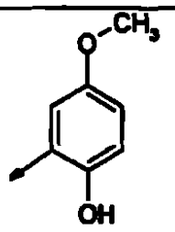
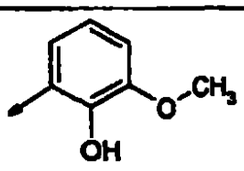
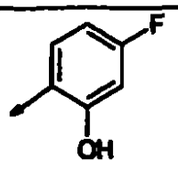
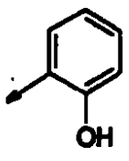
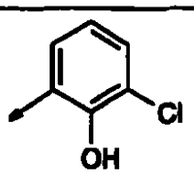
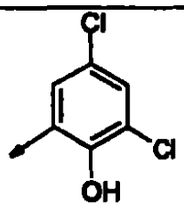
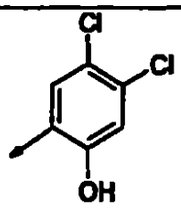
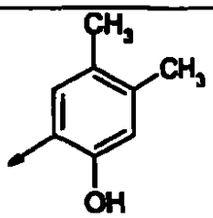
The compounds of the following tabulated examples (Table 13) of the general formula:



were prepared by a similar method to that of example 175 using the amine of preparation 64 and the appropriate carboxylic acid.

**Table 13**

| Example N° | R | Example N° | R |
|---|---|---|---|
| 176 |  | 177 |  |
| 178 |  | 179 |  |
| 180 |  | 181 |  |

| | | | |
|---|---|---|---|
| 182 |  | 183 |  |
| 184 |  | 185 |  |
| 186 [A] |  | 187 [A] |  |
| 188 [A] |  | 189 [A] |  |
| 190 [A] |  | 191 [A] |  |
| 192 [A] |  | 193 [AB] |  |
| 194 [AC] |  | | |

[A] Diisopropylethylamine was used as the base

[B] See reference Chem. And Pharm. Bull, 1996, 44(4), 734 for the starting carboxylic acid.

[c] See reference Synthesis 1984, (9), 758 for the starting carboxylic acid.

**Example 176**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8.35 (m, 3H), 8.00 (m, 1H), 7.70 (s, 1H), 7.45 (m, 3H), 7.25 (d, 1H), 7.08 (m, 1H), 6.83 (d, 1H), 3.90 (m, 2H), 2.81 (m, 1H), 1.70 (m, 8H), 1.15 (d, 6H)

LCMS (electrospray): *m/z* $[M-H]^-$ 526

**Example 177**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.26 (s, 1H), 8.32 (m, 2H), 8.25 (d, 1H), 8.00 (m, 1H), 7.79 (d, 1H), 7.43 (m, 2H), 7.07 (m 1H), 6.72 (m, 2H), 3.90 (m, 2H), 2.55 (q, 2H), 1.73 (m, 8H), 1.14 (t, 3H)

LCMS (electrospray): *m/z* $[M-H]^-$ 512

**Example 178**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.55 (s, 2H), 8.88 (d, 1H), 8.41 (d, 1H), 8.22 (d, 1H), 8.22 (d, 1H), 7.45 (m, 1H), 7.18 (m, 1H), 7.16 (m, 1H), 7.04 (m, 1H), 6.35 (d, 2H), 3.94 (m, 2H), 1.70 (m, 8H)

LCMS (electrospray): *m/z* $[M-H]^-$ 500

**Example 179**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 9.95 (s, 1H), 8.29 (d, 1H), 8.22 (d, 1H), 7.99 (m, 2H), 7.41 (m, 2H), 7.22 (m, 1H), 7.06 (m, 1H), 6.68 (m, 2H), 3.88 (m, 2H), 1.66 (m, 8H)

LCMS (electrospray): *m/z* $[M-H]^-$ 502

**Example 180**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 1.60 (m, 2H), 1.73 (m, 6H), 3.75 (s, 3H), 3.95 (m, 2H), 6.51 (d, 1H), 6.58 (d, 1H), 7.09 (m, 1H), 7.31 (m, 1H), 7.45 (m, 2H), 8.00 (m, 1H), 8.23 (m, 1H), 8.39 (d, 1H), 8.48 (d, 1H), 13.59 (s, 1H)

LCMS (electrospray): *m/z* $[M-H]^-$ 514

**Example 181**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8.84 (d, 1H), 8.24 (m, 2H), 8.00 (d, 1H), 7.80 (d, 1H), 7.46 (m, 3H), 7.09 (m, 1H), 6.44 (d, 1H), 3.98 (m, 5H), 1.71 (m, 8H), 1.30 (t, 3H)

LCMS (electrospray): *m/z* $[M-H]^-$ 528

**Example 182**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8.39 (m, 2H), 8.26 (s, 1H), 8.02 (d, 1H), 7.71 (s, 1H), 7.45 (m, 3H), 7.20 (m, 1H), 7.06 (m, 1H), 6.81 (d, 1H), 3.90 (m, 2H), 2.50 (q, 2H), 1.72 (m, 8H), 1.15 (t, 3H)

LCMS (electrospray): *m/z* $[M-H]^-$ 512

**Example 183**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.40 (m, 1H), 8.12 (s, 1H), m 8.03 (m, 1H), 7.79 (s, 1H), 7.30 (m, 3H), 6.86 (d, 1H), 4.52 (s, 2H), 4.13 (m, 1H), 4.05 (m, 1H), 1.83 (8H)

LCMS (APCI): *m/z* $[M-H]^-$ 514

**Example 184**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.11 (d, 1H), 8.07 (m, 1H), 7.48 (d, 1H), 7.30 (m, 3H), 7.04 (m, 1H), 6.78 (m, 1H), 4.15 (m, 1H), 3.98 (m, 1H), 2.63 (q, 2H), 1.88 (m, 8H), 1.09 (t, 3H)

LCMS (APCI): *m/z* $[M-H]^-$ 514

**Example 185**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.13 (s, 1H), 8.08 (d, 1H), 7.48 (d, 1H), 7.34 (d, 2H), 7.26 (m, 1H), 7.05 (m, 1H), 6.80 (m, 1H), 4.18 (m, 1H), 3.98 (m, 1H), 3.36 (m, 1H), 1.90 (m, 8H), 1.20 (d, 6H)

LCMS (APCI): *m/z* $[M+H]^+$ 528

**Example 186**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.58 (s, 1H), 8.40 (d, 1H), 8.33 (d, 1H), 8.23 (d, 1H), 8.00 (m, 1H), 7.92 (d, 1H), 7.43 (m, 2H), 7.07 (m, 1H), 6.98 (m, 2H), 3.90 (m, 2H), 1.72 (m, 8H)

LCMS (electrospray): *m/z* $[M-H]^-$ 518

**Example 187**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.60 (s, 1H), 8.45 (d, 1H), 8.39 (d, 1H), 8.23 (d, 1H), 7.99 (m, 1H), 7.41 (m, 3H), 7.06 (m, 1H), 6.99 (m, 1H), 6.84 (d, 1H), 3.96 (m, 1H), 3.87 (m, 1H), 3.72 (s, 3H), 1.72 (m, 8H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 538

**Example 188**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.42 (s, 1H), 8.39 (d, 1H), 8.37 (d, 1H), 8.26 (d, 1H), 8.01 (m, 1H), 8.46 (m, 3H), 7.10 (d, 2H), 6.80 (m, 1H), 3.97 (m, 1H), 3.88 (m, 1H), 3.79 (s, 3H), 2.73 (m, 8H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 538

**Example 189**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.84 (s, 1H), 8.40 (d, 1H), 8.36 (d, 1H), 8.25 (s, 1H), 7.99 (m, 2H), 7.45 (m, 2H), 7.08 (d, 1H), 6.73 (m, 2H), 3.97 (m, 1H), 3.85 (m, 1H), 1.72 (m, 8H)

LCMS (APCI): *m/z* $[M+H]^+$ 504

**Example 190**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.22 (s, 1H), 8.40 (d, 1H), 8.35 (d, 1H), 8.22 (d, 1H), 8.00 (m, 1H), 7.89 (d, 1H), 7.40 (m, 3H), 7.08 (m, 1H), 6.90 (m, 2H), 3.93 (m, 2H), 1.75 (m, 8H)

LCMS (electrospray): *m/z* $[M-H]^-$ 484

**Example 191**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 13.55 (s, 1H), 8.63 (s, 1H), 8.31 (d, 1H), 8.23 (d, 1H), 8.00 (m, 1H), 7.89 (d, 1H), 7.59 (d, 1H), 7.41 (m, 2H), 7.08 (m, 1H), 6.88 (m, 1H), 3.98 (m, 1H), 3.84 (m, 1H), 1.74 (m, 8H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 542

**Example 192**

$^1$H NMR (400MHz, $CDCl_3$): δ (rotamers) 12.68 (s, 1H), 8.36 (m, 1H), 8.05 (d, 1H), 7.86, 7.80 (2xd, 1H), 7.48 (d, 1H), 7.20 (m, 2H), 7.06 (m, 1H), 6.92 (d, 1H), 6.21, 6.10 (2xd, 1H), 4.22 (m, 1H), 4.10 (m, 1H), 1.93 (m, 6H), 1.62 (m, 2H)

LCMS (electrospray): *m/z* $[M-H]^-$ 552

**Example 193**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.28 (s, 1H), 8.35 (m, 1H), 8.05 (d, 1H), 7.88 (d, 1H), 7.27 (m, 2H), 7.05 (m, 2H), 6.96 (d, 1H), 6.07 (d, 1H), 4.23 (m, 1H), 4.12 (m, 1H), 1.90 (m, 6H), 1.62 (m, 2H)

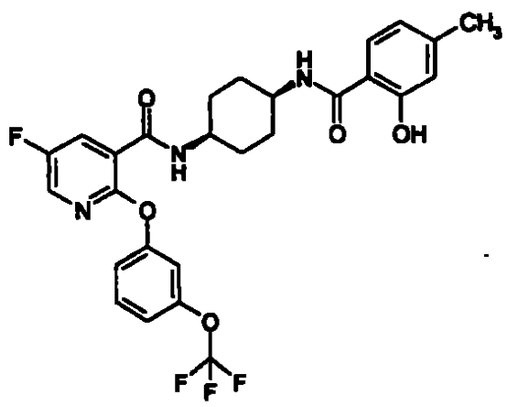
LCMS (electrospray): *m/z* $[M-H]^-$ 552

**Example 194**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.04 (s, 1H), 8.36 (d, 1H), 8.26 (m, 2H), 8.00 (d, 1H), 7.62 (s, 1H), 7.45 (m, 2H), 7.07 (m, 1H), 6.68 (s, 1H), 3.96 (m, 1H), 3.85 (m, 1H), 2.18 (s, 3H), 2.14 (s, 3H), 1.71 (m, 8H)

LCMS (electrospray): *m/z* $[M-H]^-$ 512

**Example 195: *syn*-5-Fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamin )-cyclohexyl]-2-(3-trifluoromethoxy-phenoxy)-nicotinamide**



*syn*-2-Chloro-5-fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide (150 mg, 0.37 mmol, see preparation 67) was mixed with caesium carbonate (602 mg, 1.85 mmol) and 3-trifluoromethoxyphenol (240µl, 1.85 mmol) in N,N-dimethylformamide (5 ml) and the reaction mixture was heated at 65°C under a nitrogen atmosphere for 16 hours. The reaction mixture was cooled to room temperature and was partitioned between ethyl acetate and water. The aqueous layer was adjusted to pH 4 by addition of citric acid and the layers were separated. The organic layer was washed with water and dried over magnesium sulphate and concentrated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 1:99). The material isolated was further purified by chromatography on silica gel using methanol in dichloromethane (0.5:99.5).

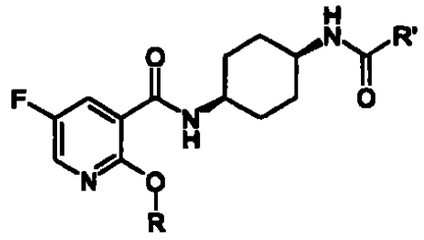
The material obtained was re-suspended in diethyl ether and the solid formed was isolated by filtration to give *syn*-5-fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-2-(3-trifluoromethoxy-phenoxy)-nicotinamide as a white solid (54 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 1.70 (m, 8H), 2.26 (s, 3H), 3.90 (m, 2H), 6.70 (m, 2H), 7.24 (m, 3H), 7.52 (m, 1H), 7.77 (d, 1H), 8.01 (d, 1H), 8.28 (s, 1H), 8.34 (m, 2H), 12.32 (s, 1H)

LCMS (electrospray): *m/z* $[M-H]^-$ 546

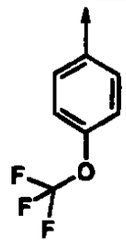
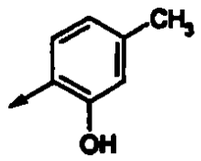
**Examples 196-215**

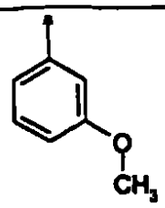
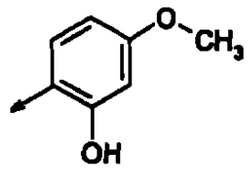
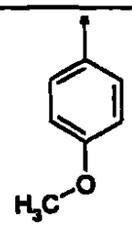
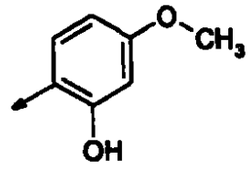
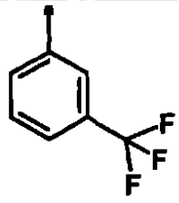
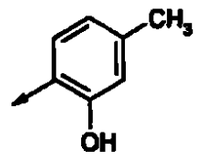
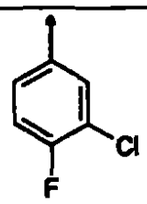
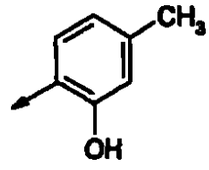
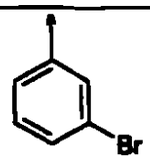
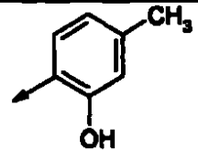
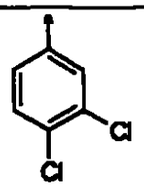
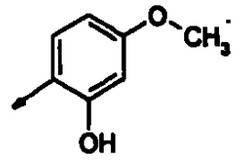
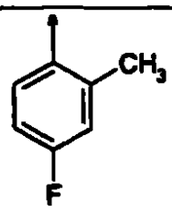
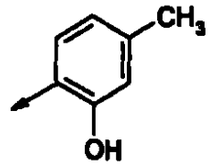
The compounds of the following tabulated examples (Table 14) of the general formula:

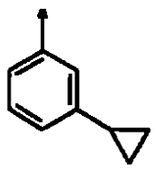
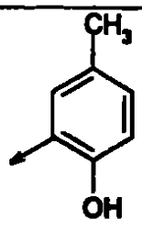
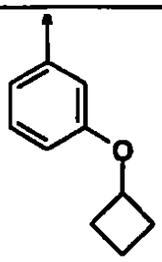
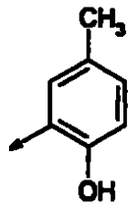
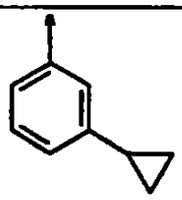
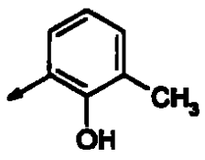
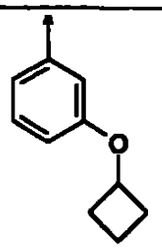
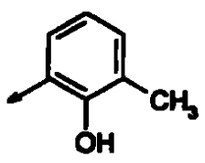
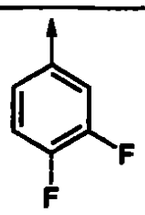
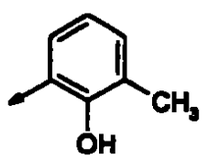
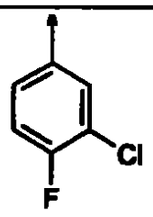
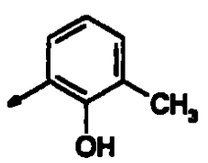


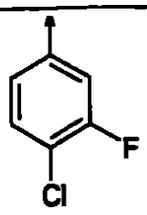
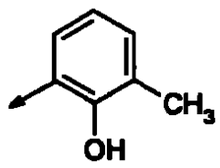
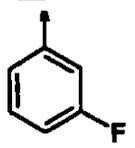
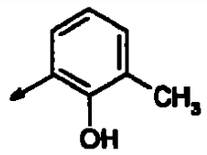
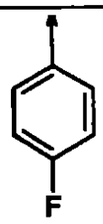
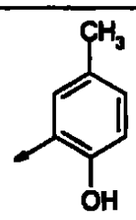
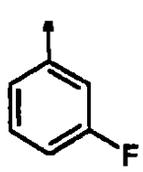
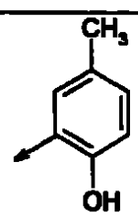
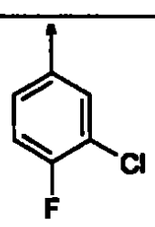
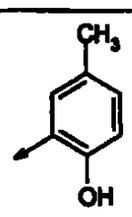
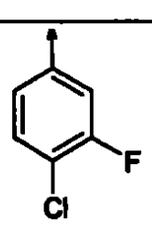
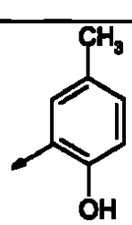
were prepared by a similar method to that of example 195 using the appropriate aryl chloride and phenol.

**Table 14**

| Example N° | R | R' |
|---|---|---|
| 196 |  |  |

| | | |
|---|---|---|
| 197 |  |  |
| 198 |  |  |
| 199 |  |  |
| 200 |  |  |
| 201 |  |  |
| 202 |  |  |
| 203 |  |  |

| | | |
|---|---|---|
| 204[A] |  |  |
| 205[A] |  |  |
| 206[A] |  |  |
| 207[A] |  |  |
| 208[A] |  |  |
| 209[AB] |  |  |

| | | |
|---|---|---|
| 210 [AB] |  |  |
| 211 [AB] |  |  |
| 212 [AB] |  |  |
| 213 [AB] |  |  |
| 214 [AB] |  |  |
| 215 [AB] |  |  |

[A] Acetonitrile was used as solvent

[B] Purified by chromatography on silica gel using ethyl acetate in cyclohexane as eluant

**Example 196**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.31 (s, 1H), 8.35 (m, 2H), 8.25 (d, 1H), 8.00 (m, 1H), 7.78 (d, 1H), 7.40 (d, 2H), 7.31 (d, 2H), 6.69 (m, 2H), 3.90 (m, 2H), 2.26 (s, 3H), 1.70 (m, 8H)

LCMS (electrospray): *m/z* $[M-H]^-$ 546

**Example 197**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.35 (m, 1H), 8.08 (m, 2H), 7.36 (m, 1H), 7.03 (d, 1H), 6.85 (d, 1H), 6.76 (m, 2H), 6.44 (s, 1H), 6.39 (d, 1H), 7.74 (d, 1H), 4.28 (m, 1H), 4.06 (m, 1H), 3.80 (2xs, 6H), 1.90 (m, 6H), 1.50 (m, 2H)

LCMS (APCI): *m/z* $[M-H]^-$ 508

**EXAMPLE 198**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.35 (d, 1H), 8.20 (d, 1H), 8.08 (d, 1H), 7.12 (d, 2H), 6.98 (m, 3H), 6.45 (s, 1H), 6.39 (d, 1H), 5.72 (d, 1H), 4.30 (m, 1H), 4.07 (m, 1H), 3.82 (2xs, 6H), 1.90 (m, 6H), 1.53 (m, 2H)

LCMS (APCI): *m/z* $[M-H]^-$ 508

**Example 199**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.28 (s, 1H), 8.40 (d, 1H), 8.32 (d, 1H), 8.26 (s, 1H), 8.01 (m, 1H), 7.76 (d, 1H), 7.60 (m, 4H), 6.69 (m, 2H), 3.95 (m, 1H), 3.46 (m, 1H), 2.50 (s, 3H), 1.72 (m, 8H)

LCMS (electrospray): *m/z* $[M-H]^-$ 530

**Example 200**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.30 (s, 1H), 8.33 (m, 2H), 8.23 (d, 1H), 8.00 (d, 1H), 7.77 (d, 1H), 7.53 (d, 1H), 7.46 (m, 1H), 7.24 (m, 1H), 6.70 (m, 2H), 3.97 (m, 1H), 3.86 (m, 1H), 2.28 (s, 3H), 1.74 (m, 8H)

LCMS (electrospray): *m/z* [M-H]$^-$ 514

**Example 201**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.30 (s, 1H), 8.37 (m, 2H), 8.24 (d, 1H), 8.00 (d, 1H), 7.78 (d, 1H), 7.45 (s, 1H), 7.38 (m, 2H), 7.20 (d, 1H), 6.70 (m, 2H), 3.91 (m, 2H), 2.26 (s, 3H), 1.70 (m, 8H)

LCMS (electrospray): *m/z* [M-H]$^-$ 542

**Example 202**

$^1$H NMR (400MHz, $CDCl_3$): δ 7.32 (m, 5H), 7.13 (d, 1H), 7.04 (d, 1H), 6.44 (s, 1H), 6.39 (d, 1H), 6.14 (m, 1H), 4.42 (m, 1H), 4.29 (m, 1H), 3.79 (s, 3H), 1.90 (m, 8H)

LCMS (APCI): *m/z* $[M+H]^+$ 548

**Example 203**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.38 (d, 1H), 8.10 (m, 1H), 8.00 (s, 1H), 7.02 (m, 4H), 6.79 (s, 1H), 6.62 (m, 1H), 5.92 (s, 1H), 4.26 (m, 1H), 4.08 (m, 1H), 2.38 (s, 3H), 2.20 (s, 3H), 2.02-1.80 (m, 6H), 1.59 (m, 2H).

**Example 204**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.00 (s, 1H), 8.35 (m, 1H), 8.13 (d, 1H), 8.08 (d, 1H), 7.35 (m, 1H), 7.20 (d, 1H), 7.00 (d, 1H), 6.95 (m, 2H), 6.86 (m, 2H), 5.91 (d, 1H), 4.28 (m, 1H), 4.07 (m, 1H), 2.31 (s, 3H), 1.90 (m, 6H), 1.52 (m, 3H), 0.97 (m, 2H), 0.68 (m, 2H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 526

**Example 205**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.00 (s, 1H), 8.18 (m, 1H), 8.09 (s, 1H), 7.33 (m, 1H), 7.20 (d, 1H), 6.95 (s, 1H), 6.87 (d, 1H), 6.72 (m, 2H), 6.61 (s, 1H), 5.92 (d, 1H), 4.59 (m, 1H), 4.27 (m, 1H), 4.05 (m, 1H), 2.34 (m, 6H), 1.80 (m, 11H)

LCMS (electrospray): *m/z* $[M+H]^+$ 534

**Example 206**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.47 (s, 1H), 8.37 (m, 1H), 8.16 (d, 1H), 8.07 (s, 1H), 7.14 (m, 1H), 7.00 (d, 1H), 6.94 (m, 2H), 6.88 (s, 1H), 6.72 (m, 1H), 5.88 (d, 1H), 4.36 (m, 1H), 4.08 (m, 1H), 2.27 (s, 3H), 1.90 (m, 7H), 1.50 (m, 2H), 0.98 (m, 2H), 0.69 (m, 2H)

LCMS (electrospray): *m/z* $[M+H]^+$ 504

**Example 207**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.49 (s, 1H), 8.38 (m, 1H), 8.16 (m, 2H), 7.34 (m, 1H), 6.99 (d, 1H), 6.73 (m, 3H), 6.63 (s, 1H), 5.90 (d, 1H), 4.60 (m, 1H), 4.29 (m, 1H), 4.08 (m, 1H), 2.39 (m, 2H), 2.26 (s, 3H), 2.15 (m, 2H), 1.80 (m, 11H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 556

**Example 208**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.11 (s, 1H), 8.06 (d, 1H), 7.49 (d, 1H), 7.30 (m, 3H), 7.05 (d, 1H), 6.75 (m, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 2.20 (s, 3H), 1.86 (m, 8H)

LCMS (APCI): *m/z* $[M-H]^-$ 498

**Example 209**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.13 (d, 1H), 8.08 (d, 1H), 7.49 (d, 1H), 7.42 (m, 1H), 7.27 (m, 3H), 6.75 (m, 1H), 4.17 (m, 1H), 3.99 (m, 1H), 2.19 (s, 3H), 1.85 (m, 8H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 538

**Example 210**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.15 (d, 1H), 8.06 (d, 1H), 7.50 (m, 2H), 7.22 (m, 2H), 7.06 (d, 1H), 6.75 (m, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 2.20 (s, 3H), 1.85 (m, 8H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 538

**Example 211**

$^1$H NMR (400MHz, $CD_3OD$): δ 8.15 (d, 1H), 8.07 (m, 1H), 7.48 (d, 1H), 7.42 (m, 1H), 7.25 (d, 1H), 7.01 M, 3H), 6.75 (m, 1H), 4.16 (m, 1H), 3.99 (m, 1H), 2.19 (s, 3H), 1.83 (m, 8H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 504

**Example 212**

$^1$H NMR (400MHz, $CDCl_3$): δ 12.00 (s, 1H), 8.39 (m, 1H), 8.06 (m, 2H), 7.18 (m, 4H), 6.96 (s, 1H), 6.90 (m, 1H), 5.99 (d, 1H), 4.30 (m, 1H), 4.08 (m, 1H), 2.32 (s, 3H), 1.95 (m, 6H), 1.60 (m, 2H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 504

**Example 213**

$^1$H NMR (400MHz, $CDCl_3$): δ 8.39 (m, 1H), 8.06 (d, 1H), 7.98 (d, 1H), 7.42 (m, 1H), 7.20 (d, 1H), 6.98 (m, 3H), 6.89 (d, 1H), 5.99 (d, 1H), 4.29 (m, 1H), 4.08 (m, 1H), 2.31 (s, 3H), 1.92 (m, 6H), 1.57 (m, 2H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 504

**Example 214**

$^1H$ NMR (400MHz, $CDCl_3$): δ 8.38 (m, 1H), 8.06 (d, 1H), 7.88 (d, 1H), 7.22 (m, 3H), 7.10 (m, 1H), 7.00 (s, 1H), 6.89 (d, 1H), 6.07 (d, 1H), 4.24 (m, 1H), 4.09 (m, 1H), 2.29 (s, 3H), 1.90 (m, 6H), 1.62 (m, 2H)

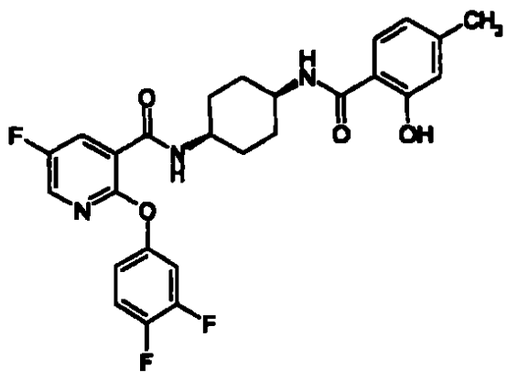
LCMS (electrospray): *m/z* $[M+Na]^+$ 538

**Example 215**

$^1H$ NMR (400MHz, $CDCl_3$): δ 8.38 (m, 1H), 8.06 (d, 1H), 7.80 (m, 1H), 7.49 (m, 1H), 7.21 (d, 1H), 7.00 (m, 3H), 6.05 (d, 1H), 4.23 (m, 1H), 4.06 (m, 1H), 2.32 (s, 3H), 1.90 (m, 6H), 1.56 (m, 2H)

LCMS (electrospray): *m/z* $[M+Na]^+$ 538

**Example 216: *syn*-2-(3,4-Difluoro-phenoxy)-5-fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide**




1-Hydroxybenzotriazole hydrate (6.06 g, 44.85 mmol) was added to 2-(3,4-difluoro-phenoxy)-5-fluoro-nicotinic acid (10.5 g, 39 mmol, see preparation 60) in 4-methylmorpholine (100 ml). 1-(3-Dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (9.71 g, 50.7 mmol) was added portionwise and the mixture was stirred for 20 minutes at room temperature. *Syn*-N-(4-Amino-cyclohexyl)-2-hydroxy-4-methyl-benzamide hydrochloride (11.66 g, 40.9 mmol, see

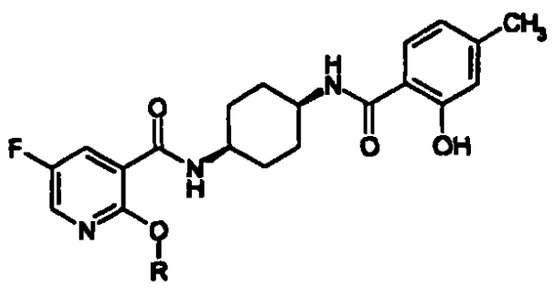
preparation 66) was dissolved in 4-methylmorpholine (100 ml) and diisopropylamine (12.6 g, 97.5 mmol) was added. The mixture was stirred at room temperature for 15 minutes and then was added to the mixture containing the carboxylic acid. The reaction mixture was stirred at room temperature for 17 hours and then was partitioned between ethyl acetate (1 l) and water (1.5 l). The phases were separated and the organic phase was washed with 10% citric acid solution (300 ml then 200 ml), saturated sodium hydrogen carbonate (3-fold 500 ml) and then was diluted with ethyl acetate (500 ml). The organic solution was washed with water (3-fold 500 ml) dried over magnesium sulphate and concentrated *in-vacuo*. The residue was triturated with methanol and the material obtained was isolated by filtration and was washed with methanol and diethyl ether. The material obtained was dried *in-vacuo* at 50°C for 17 hours and was recrystalised from ethyl acetate/ propan-2-ol. The material obtained was triturated with propan-2-ol and the residue was isolated by filtration and was washed with propan-2-ol and diethyl ether then dried *in-vacuo* at 50°C for 17 hours to give *syn*-2-(3,4-difluoro-phenoxy)-5-fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide as a white solid (15.3 g).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.25 (s, 1H), 8.33 (m, 2H), 8.23 (s, 1H), 7.99 (m, 1H), 7.75 (d, 1H), 7.42 (m, 2H), 7.08 (d, 1H), 6.68 (m, 2H), 3.97 (m, 1H), 3.86 (m, 1H), 2.26 (s, 3H), 1.72 (m, 8H)

LCMS (APCI): *m/z* $[M-H]^-$ 498

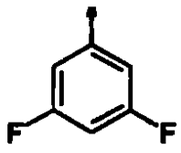
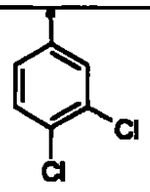
**Examples 217-218**

The compounds of the following tabulated examples (Table 15) of the general formula:



were prepared by a similar method to that of example 216 using *syn*-N-(4-Amino-cyclohexyl)-2-hydroxy-4-methyl-benzamide hydrochloride (see preparation 66) and the appropriate carboxylic acid.

**Table 15**

| Example N° | R Group | Example N° | R Group |
|---|---|---|---|
| 217 |  | 218 |  |

**Example 217**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.28 (s, 1H), 8.30 (m, 3H), 8.00 (m, 1H), 7.75 (d, 1H), 7.08 (m, 1H), 6.99 (m, 2H), 6.68 (m, 2H), 3.89 (m, 2H), 2.27 (s, 3H), 1.72 (m, 8H)

LCMS (electrospray): *m/z* [M-H]$^-$ 498

**Example 218**

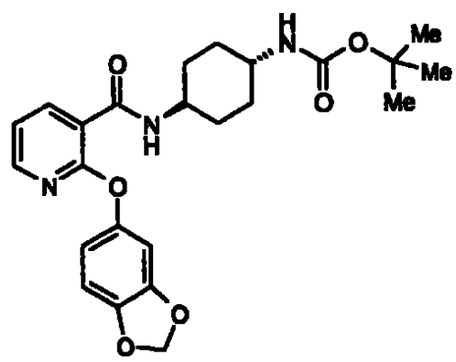
$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.28 (s, 1H), 8.31 (m, 2H), 8.27 (s, 1H), 8.00 (m, 1H), 7.75 (d, 1H), 7.67 (d, 1H), 7.57 (s, 1H), 7.22 (d, 1H), 6.68 (m, 2H), 3.90 (m, 2H), 2.26 (s, 3H), 1.73 (m, 8H)

LCMS (electrospray): *m/z* [M-H]$^-$ 530

99
100

## PREPARATIONS

**Preparation 1 : *anti*-(4-{[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester**



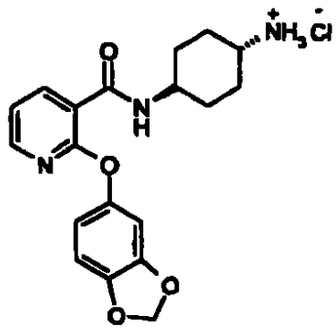
2-(4-Benzo[1,3]dioxol-5-yloxy)-nicotinic acid (5.0 g, 19.3 mmol, see reference WO 98/45268), *anti*-(4-amino-cyclohexyl)-carbamic acid tert-butyl ester (4.13 g, 19.3 mmol) (see Preparation 40), 1-hydroxybenzotriazole (3.91 g, 29 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.81 g, 25.1 mmol) and N-methyl morpholine (3.18 ml, 29 mmol) were stirred in N,N-dimethylformamide (50 ml) at room temperature under an atmosphere of nitrogen for 18 hours. The reaction mixture was then partitioned between dichloromethane (200 ml) and a 2 N aqueous solution of sodium carbonate (150 ml), and the organic layer separated. The aqueous phase was extracted with dichloromethane (2-fold 200 ml) and the combined organic extracts were washed with a saturated aqueous solution of sodium chloride (200 ml). The combined organic extracts were then dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (50 ml) giving *anti*-(4-{[2-(benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester (6.5 g) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8.06-8.12 (1H, m), 8.02-8.05 (1H, d), 7.94-7.98 (1H, d), 7.10-7.15 (1H, m), 6.82-6.87 (1H, d), 6.76-6.80 (1H, d), 6.50-6.70

(2H, m), 6.00 (2H, s), 3.50-370 (1H, m), 3.05-3.20 (1H, m), 1.70-1.90 (4H, m), 1.32 (9H, s), 1.10-1.30 (4H, m) ppm.

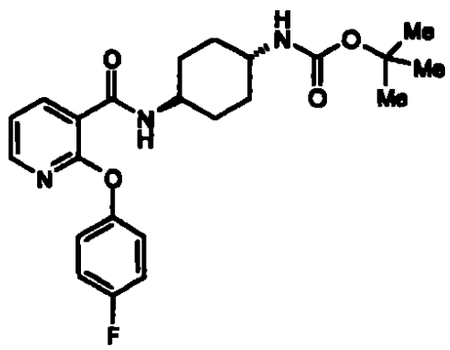
LRMS (electrospray) : m/z $[M-H]^+$ 454

**Preparation 2 : *anti*-N-(4-Amino-cyclohexyl)-2-(Benzo[1,3]dioxol-5-yloxy)-nicotinamide hydrochloride**



*anti*-(4-[[2-(Benzo[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino)-cyclohexyl)-carbamic acid tert-butyl ester (5.2 g, 11.4 mmol) (see Preparation 1) was dissolved in dichloromethane (20 ml) and 4M HCl in dioxan (20 ml) added. The reaction mixture was stirred for 2 hours. The solvent was then removed *in vacuo* and the residue azeotroped with toluene to give *anti*-N-(4-amino-cyclohexyl)-2-(Benzo[1,3]dioxol-5-yloxy)-nicotinamide hydrochloride (5.02g) as a colourless oil.

**Preparation 3 : *anti*-(4-[[2-(4-Fluorophenoxy)-pyridine-3-carbonyl]amino)-cyclohexyl)-carbamic acid tert-butyl ester**

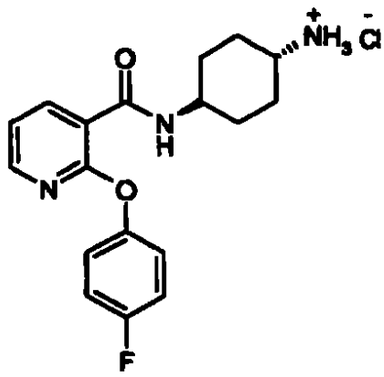


2-(4-Fluoro-phenoxy)-nicotinic acid (10.88 g, 0.046 mol) (see reference patent application WO 98/45268), 1-hydroxybenzotriazole (9.32 g, 0.069 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.46 g, 0.06 mol) were stirred in N,N-dimethylformamide (150ml) at room temperature and *anti*-(4-amino-cyclohexyl)-carbamic acid tert-butyl ester (10 g, 0.046 mol) (see Preparation 40) added followed by addition of N-methyl morpholine (7.59 ml, 0.069 mol). The reaction mixture was then stirred under an atmosphere of nitrogen at room temperature for 18 hours. The reaction mixture was then partitioned between ethyl acetate (400 ml) and water (400 ml), and the organic layer separated, washed with a saturated aqueous solution of sodium chloride (300 ml), dried over anhydrous sodium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (50 ml) giving *anti*-(4-{[2-(4-fluorophenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl)-carbamic acid tert-butyl ester (14.52 g) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$/$D_2O$): δ = 8.08-8.12 (1H, d), 7.94-7.98 (1H, d), 7.09-7.20 (5H, m), 3.58-3.63 (1H, m), 3.13-3.20 (1H, m), 1.79-1.83 (2H, m), 1.69-1.78 (2H, m), 1.30 (9H, s), 1.18-1.30 (4H, m) ppm.

LRMS (electrospray) : m/z $[M-H]^+$ 428

**Preparation 4 : *anti*-N-(4-Amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride**

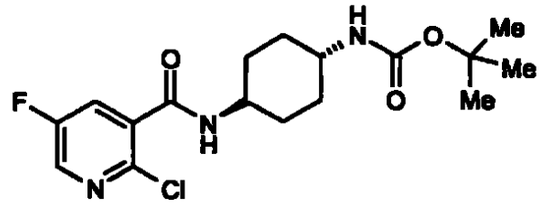


*anti*-(4-[[2-(4-Fluorophenoxy)-pyridine-3-carbonyl]amino)-cyclohexyl)-carbamic acid tert-butyl ester (14.81 g, 0.039 mol) (see Preparation 3) was dissolved in methanol (10 ml) and 4M HCl in dioxan (200 ml) added. The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 4 hours. The solvent was then removed *in vacuo* and the resultant white precipitate was triturated with ether (50 ml) giving *anti*-N-(4-amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (14.00 g) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8.20-8.26 (1H, d), 8.16-8.18 (1H, s), 8.04-8.15 (3H, brs), 7.98-8.02 (1H, d), 7.17-7.26 (4H, m), 3.42-3.57 (1H, m), 2.88-3.01 (1H, m), 1.88-2.03 (4H, m), 1.23-1.50 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 330

**Preparation 5 : *anti*-{4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)amino]-cyclo hexyl}-carbamic acid tert-butyl ester**

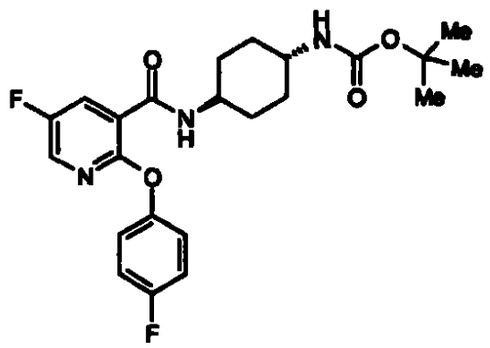


2-Chloro-5-fluoro nicotinic acid (3.95 g, 0.022 mol) (see Preparation 41), 1-hydroxybenzotriazole (4.56 g, 0.034 mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.61 g, 0.029 mol) were stirred in N,N-dimethylformamide (50 ml) at room temperature for 30 minutes. N-methyl morpholine (4.95 ml, 0.045 mol) was then added followed by *anti*-(4-amino-cyclohexyl)-carbamic acid tert-butyl ester (4.82 g, 0.022 mol) (see Preparation 43) and the reaction mixture stirred under an atmosphere of nitrogen at room temperature for 18 hours. The mixture was then partitioned between ethyl acetate (100 ml) and water (100 ml), the organic phase separated, washed with a saturated aqueous solution of sodium chloride (100 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (3-fold 10 ml) giving *anti*-{4-[(2-chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexyl}-carbamic acid tert-butyl ester (7.56 g) as a white solid.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8.32-8.35 (1H, d), 7.82-7.88 (1H, m), 6.32-6.41 (1H, d), 4.38-4.51 (1H, m), 3.87-4.02 (1H, m), 2.03-2.21 (4H, m), 1.45 (9H, s), 1.26-1.41 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 389.

**Preparation 6 : *anti*-(4-{[5-Fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl] amino}-cyclohexyl)-carbamic acid tert-butyl ester**

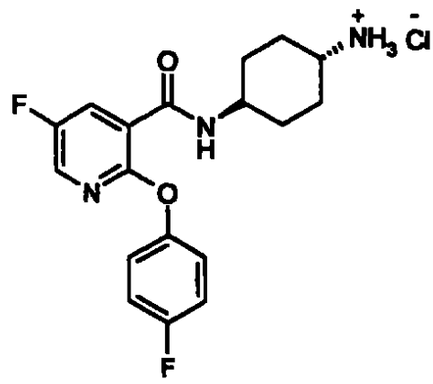


*Anti*-{4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)amino]-cyclohexyl}-carbamic acid tert-butyl ester (7.64 g, 0.02 mol) (see Preparation 5), 4-fluorophenol (2.30 g, 0.02 mol) and caesium carbonate (13.35 g, 0.04 mol) were stirred in N,N-dimethylformamide (50 ml) at 60°C under an atmosphere of nitrogen for 18 hours. The mixture was then partitioned between ethyl acetate (100 ml) and water (100 ml), the organic layer separated, washed with a saturated aqueous solution of sodium chloride (100 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with a solvent gradient of 100 % dichloromethane changing to 98:2, by volume, dichloromethane : methanol giving *anti*-(4-{[5-fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl]amino}-cyclo hexyl)-carbamic acid tert-butyl ester (4.93 g) as a white solid.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8.31-8.37 (1H, m), 8.02-8.05 (1H, d), 7.65-7.72 (1H, d), 7.10-7.20 (4H, m), 4.38-4.48 (1H, m), 3.88-4.02 (1H, m), 2.01-2.20 (4H, m), 1.43 (9H, s), 1.23-1.40 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+NH_4]^+$ 465

**Preparation 7 : *anti*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride**

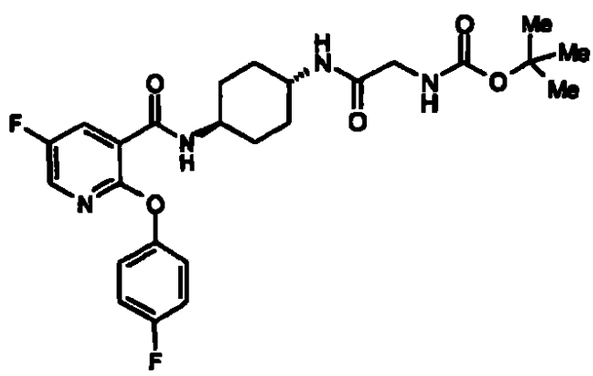


*Anti*-(4-{[5-Fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl)-carbamic acid tert-butyl ester (4.93 g, 0.011 mol) (see Preaparation 6) was dissolved in dichloromethane (50 ml) and hydrogen chloride gas bubbled through the solution at 0°C until the solution became saturated (30 minutes). The reaction mixture was then stirred under an atmosphere of nitrogen at room temperature for a further 2 hours and the solvent then removed *in vacuo*. The resultant white precipitate was triturated with ether (3-fold 10 ml) giving *anti*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (3.64 g) as a white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.32-8.38 (1H, d), 8.18-8.22 (1H, m), 7.92-8.08 (4H, m), 7.16-7.28 (4H, m), 3.60-3.77 (1H, m), 2.95-3.07 (1H, m), 1.83-2.03 (4H, m), 1.23-1.52 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 348

**Preparation 8 : *anti*-[(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl] amino}-cyclohexylcarbamoyl)-methyl]-carbamic acid tert-butyl ester**



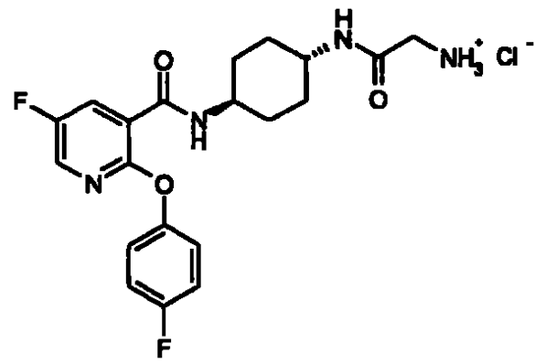
*Anti*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (1.13 g, 2.94 mmol) (see Preparation 7), 1-hydroxybenzotriazole (597 mg, 4.42 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (734 mg, 3.83 mmol), N-methyl morpholine (0.65 ml, 5.89 mol) and tert-butoxycarbonylamino-acetic acid (516 mg, 2.94 mmol) were stirred in N,N-dimethylformamide (10 ml) at room temperature for 18 hours. The reaction mixture was then partitioned between ethyl acetate (50 ml) and water (50 ml), the organic layer separated, washed with a saturated aqeous solution of sodium chloride (50 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* giving *anti*-[(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]amino}-cyclohexylcarbamoyl)-methyl]-carbamic acid tert-butyl ester (1.48 g) as a white solid.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8.30-8.40 (1H, m), 8.00-8.04 (1H, d), 7.67-7.77 (1H, d), 7.08-7.21 (4H, m), 6.00-6.11 (1H, m), 5.09-5.21 (1H, brs), 3.92-4.06 (1H, m), 3.75-3.84 (3H, m), 2.00-2.25 (4H, m), 1.28-1.60 (13H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 505, $[M+H\text{-}Boc]^+$ 405.

103
104

**Preparation 9 : *anti*-N-[4-(2-Amino-acetylamino)-cyclohexyl]-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride**

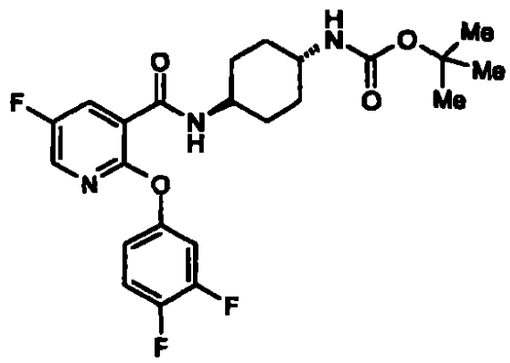


*anti*-[(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl carbamoyl)-methyl]-carbamic acid tert-butyl ester (1.47 g, 2.91 mmol) (see Preparation 8) was dissolved in dichloromethane (20 ml) and hydrogen chloride gas bubbled into the solution at 0°C until the solution became saturated (30 minutes). The reaction was then stirred under an atmosphere of nitrogen at room temperature for a further 18 hours, and the solvent then removed *in vacuo*. The resultant white precipitate was triturated with ether (3-fold 10 ml) giving *anti*-N-[4-(2-amino-acetylamino)-cyclohexyl]-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (1.24 g) as a white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.34-8.43 (2H, m), 8.19-8.21 (1H, d), 8.10-8.18 (3H, brs), 7.92-7.99 (1H, dd), 7.18-7.32 (4H, m), 3.66-3.82 (1H, m), 3.42-3.60 (3H, m, partially masked by solvent), 1.78-1.99 (4H, m), 1.22-1.50 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 405.

**Preparation 10 : *anti*-(4-{[5-Fluoro-2-(3,4-difluorophenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl)-carbamic acid tert-butyl ester**



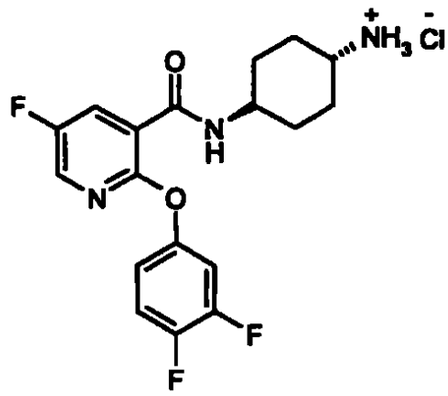
*Anti*-(4-{(2-Chloro-5-fluoro-pyridine-3-carbonyl)amino]-cyclohexyl}-carbamic acid tert-butyl ester (675 mg, 1.81 mmol) (see Preparation 5), 3,4-difluorophenol (236 mg, 1.81 mmol) and caesium carbonate (1.18 g, 3.63 mmol) were stirred in N,N-dimethylformamide (10 ml) at 60°C under an atmosphere of nitrogen for 18 hours. The mixture was then partitioned between ethyl acetate (20 ml) and water (20 ml), the organic layer separated, washed with a saturated aqueous solution of sodium chloride (20 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (3-fold 5 ml) giving *anti*-(4-{[5-fluoro-2-(3,4-difluorophenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl)-carbamic acid tert-butyl ester (490 mg) as a white solid.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8.31-8.38 (1H, m), 8.03-8.06 (1H, d), 7.68-7.77 (1H, d), 7.17-7.28 (1H, m, partially masked by solvent), 7.00-7.08 (1H, m), 6.86-6.93 (1H, m), 4.34-4.45 (1H, m), 3.86-4.04 (1H, m), 2.01-2.20 (4H, m), 1.45 (9H, s), 1.24-1.40 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+NH_4]^+$ 483

104
105

**Preparation 11 : *anti*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(3,4-difluoro-phenoxy)-nicotinamide hydrochloride**

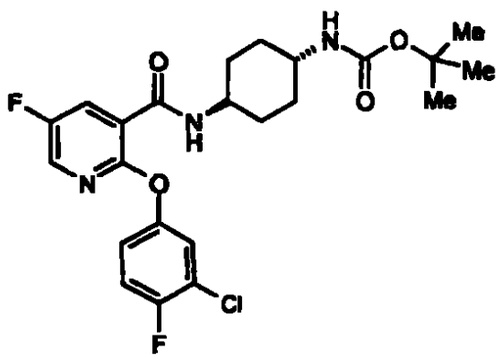


*Anti*-(4-[[5-Fluoro-2-(3,4-difluorophenoxy)-pyridine-3-carbonyl]amino)-cyclo hexyl)-carbamic acid tert-butyl ester (480 mg, 1.03 mmol) (see Preparation 10) was dissolved in dichloromethane (10 ml) and hydrogen chloride gas bubbled into the solution at 0°C until the solution became saturated (30 minutes). The reaction mixture was then stirred under an atmosphere of nitrogen at room temperature for 18 hours and the solvent then removed *in vacuo*. The resultant white precipitate was triturated with ether (3-fold 5 ml) giving *anti*-N-(4-amino-cyclohexyl)-5-fluoro-2-(3,4-difluoro-phenoxy)-nicotinamide hydrochloride (360 g) as a white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.36-8.41 (1H, d), 8.21-8.26 (1H, d), 7.93-8.11 (4H, m), 7.35-7.60 (2H, m), 7.01-7.13 (1H, m), 3.60-3.83 (1H, m), 2.88-3.12 (1H, m), 1.85-2.10 (4H, m), 1.25-1.58 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 366

**Preparation 12 : *anti*-(4-[[5-Fluoro-2-(3-chloro-4-fluorophenoxy)-pyridine-3-carbonyl]amino)-cyclohexyl)-carbamic acid tert-butyl ester**

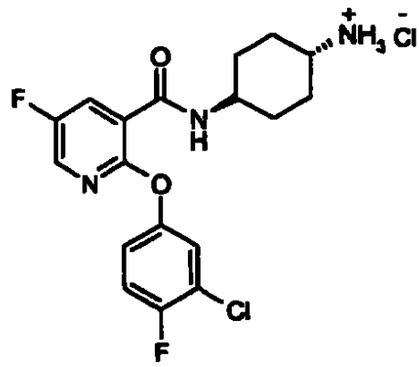


*Anti*-(4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)amino]-cyclohexyl)-carbamic acid tert-butyl ester (675 mg, 1.81 mmol) (see Preparation 5), 3-chloro-4-fluorophenol (266 mg, 1.81 mmol) and caesium carbonate (1.18 g, 3.63 mmol) were stirred in N,N-dimethylformamide (10 ml) at 60°C under an atmosphere of nitrogen for 18 hours. The reaction mixture was then partitioned between ethyl acetate (20 ml) and water (20 ml), and the organic layer separated, washed with a saturated aqueous solution of sodium chloride (20 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was triturated with diethylether (3-fold 5 ml) giving *anti*-(4-[[5-fluoro-2-(3-chloro-4-fluorophenoxy)-pyridine-3-carbonyl]amino)-cyclohexyl)-carbamic acid tert-butyl ester (540 mg) as a white solid.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8.31-8.38 (1H, m), 8.03-8.06 (1H, d), 7.50-7.58 (1H, d), 7.18-7.30 (1H, m, partially masked by solvent), 7.02-7.10 (1H, m), 4.36-4.45 (1H, m), 3.80-4.05 (1H, m), 2.01-2.20 (4H, m), 1.44 (9H, s), 1.28-1.41 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+NH_4]^+$ 499, 501.

**Preparation 13 : *anti*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(3-chloro-4-fluoro-phenoxy)-nicotinamide hydrochloride**

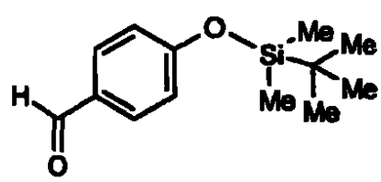


*anti*-(4-{[5-Fluoro-2-(3-chloro-4-fluorophenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl)-carbamic acid tert-butyl ester (530 mg, 1.10 mmol) (see Preparation 12) was dissolved in dichloromethane (10 ml) and hydrogen chloride gas bubbled into the solution at 0°C until the solution became saturated (30 minutes). The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours, and the solvent then removed *in vacuo*. The resultant white precipitate was triturated with ether (3-fold 5 ml) giving *anti*-N-(4-amino-cyclohexyl)-5-fluoro-2-(3-chloro-4-fluoro-phenoxy)-nicotinamide hydrochloride (390 g) as a white solid.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8.32-8.40 (1H, d), 8.22-8.26 (1H, d), 7.93-8.11 (3H, brs), 7.90-8.02 (1H, m), 7.40-7.52 (2H, m), 7.16-7.24 (1H, m), 3.60-3.81 (1H, m), 2.90-3.08 (1H, m), 1.85-2.00 (4H, m), 1.23-1.60 (4H, m) ppm.

LRMS (thermospray) : m/z [M+H]$^+$ 382.

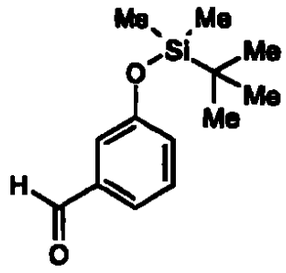
**Preparation 14 : 4-(tert-Butyl-dimethyl-silanyloxy)-benzaldehyde**



4-Hydroxybenzaldehyde (5.14 g, 42.1 mmol) was added to a suspension of tert-butyl-dimethyl-silyl chloride (6.7 g, 44.4 mmol) and imidazole (3.03 g, 44.5 mmol) in dichloromethane (100 ml) under an atmosphere of nitrogen at room temperature. The reaction mixture was stirred at room temperature for 18 hours, and then washed sequentially with 1 M hydrochloric acid (2-fold 50 ml) followed by a saturated aqueous solution of sodium hydrogen carbonate (50 ml). The organic phase was separated, dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residual yellow oil was passed through a plug of silica gel eluting with 1:1, by volume, dichloromethane : pentane giving 4-(tert-butyl-dimethyl-silanyloxy)-benzaldehyde (7.5 g) as a golden yellow oil.

$^1$H NMR (400MHz, $CDCl_3$): δ= 9.88 (1H, s), 7.74-7.81 (2H, d), 6.87-6.95 (2H, d), 1.00 (9H, s), 0.25 (6H, s) ppm.

**Preparation 15 : 3-(tert-Butyl-dimethyl-silanyloxy)-benzaldehyde**

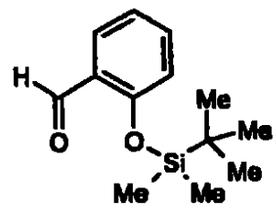



3-Hydroxybenzaldehyde (5.14 g, 42.1 mmol) was added to a suspension of tert-butyl-dimethyl-silyl chloride (6.7 g, 44.4 mmol) and imidazole (3.03 g, 44.5 mmol) in dichloromethane (100 ml) under an atmosphere of nitrogen at room temperature. The reaction mixture was stirred at room temperature for 18 hours, and the mixture washed sequentially with 1 M hydrochloric acid (2-fold 50 ml) followed by a saturated aqueous solution of sodium hydrogen carbonate (50 ml). The organic phase was separated, dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residual yellow oil was passed through a plug of silica gel eluting with 1:1, by volume, dichloromethane :

pentane giving 3-(tert-butyl-dimethyl-silanyloxy)-benzaldehyde (9.2 g) as a golden yellow oil.

$^1$H NMR (400MHz, $CDCl_3$): δ = 9.98 (1H, s), 7.42-7.46 (1H, m), 7.35-7.41 (1H, t), 7.28-7.34 (1H, m), 7.05-7.11 (1H, m), 0.98 (9H, s), 0.22 (6H, s) ppm.

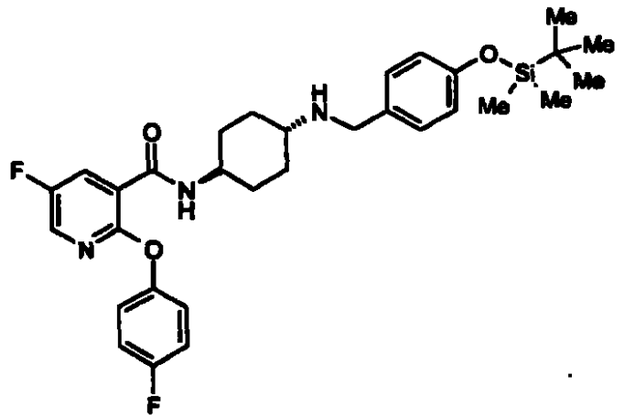
**Preparation 16 : 2-(tert-Butyl-dimethyl-silanyloxy)-benzaldehyde**




2-Hydroxybenzaldehyde (5.14 g, 42.1 mmol) was added to a suspension of tert-butyl-dimethyl-silyl chloride (6.7 g, 44.4 mmol) and imidazole (3.03 g, 44.5 mmol) in dichloromethane (100 ml) under an atmosphere of nitrogen at room temperature. The reaction mixture was stirred at room temperature for 18 hours, and then washed sequentially with 1 M hydrochloric acid (2-fold 50 ml) followed by a saturated aqueous solution of sodium hydrogen carbonate (50 ml). The organic phase was separated, dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residual yellow oil was passed through a plug of silica gel eluting with 1:1, by volume, dichloromethane : pentane giving 2-(tert-butyl-dimethyl-silanyloxy)-benzaldehyde (8.6 g) as a golden yellow oil.

$^1$H NMR (400MHz, $CDCl_3$): δ = 10.48 (1H, s), 7.78-7.83 (1H, d), 7.42-7.47 (1H, t), 6.96-7.04 (1H, t), 6.86-6.91 (1H, d), 1.01 (9H, s), 0.29 (6H, s) ppm.

**Preparation 17 : *anti*-N-{4-[4-(tert-Butyl-dimethyl-silanyloxy)-benzylamino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**

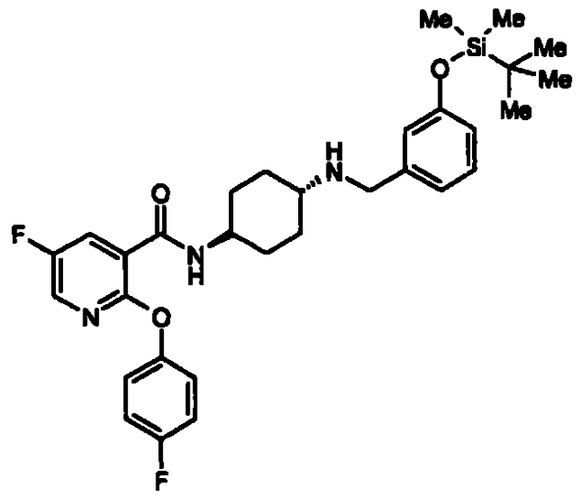


*Anti*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (500 mg, 2.15 mmol) (see Preparation 7) was dissolved in dichloromethane (15 ml) and diisopropylethylamine (0.44 ml, 2.54 mmol) added. The reaction mixture was stirred for 1 hour and 4-(tert-butyl-dimethyl-silanyloxy)-benzaldehyde (750 mg, 3.173 mmol) (see Preparation 14), sodium triacetoxyborohydride (673 mg, 3.173 mmol) and acetic acid (0.3 ml, 5.08 mmol) then added sequentially. The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours. The reaction mixture was then washed with a saturated aqueous solution of sodium hydrogen carbonate (15 ml) and the organic phase dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel, eluting with a solvent gradient of 100:2, changing to 100:4, by volume, dichloromethane : methanol giving *anti*-N-{4-[4-(tert-butyl-dimethyl-silanyloxy)-benzylamino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (270 mg) as an off-white solid.

$^1$H NMR (400MHz, $CDCl_3$): $\delta$ = 8.28-8.34 (1H, m), 7.97-7.99 (1H, d), 7.61-7.65 (1H, d), 7.16-7.19 (2H, d), 7.03-7.15 (4H, m), 6.72-6.78 (2H, d), 3.90-4.03 (1H, m), 3.71 (2H, s), 2.46-2.57 (1H, m), 2.07-2.18 (2H, d), 1.97-2.06 (2H, d), 1.17-1.29 (4H, m), 0.95 (9H, s), 0.17 (6H, s) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 568.

**Preparation 18 : *anti*-N-{4-[3-(tert-Butyl-dimethyl-silanyloxy)-benzylamino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**



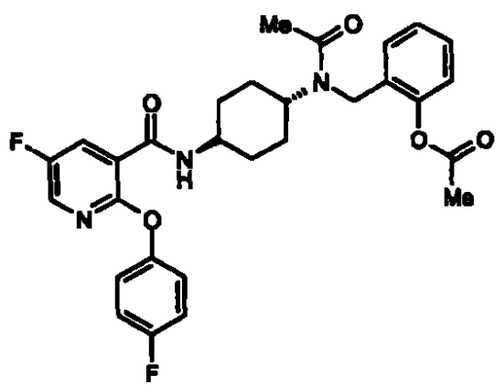
*Anti*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (500 mg, 2.14 mmol) (see Preparation 7) was dissolved in dichloromethane (10 ml) and diisopropyl ethylamine (0.56 ml, 3.21 mmol) added. The reaction mixture was stirred at room temperature for 1 hour and 3-(tert-butyl-dimethyl-silanyloxy)-benzaldehyde (766 mg, 3.21 mmol) (see Preparation 15), sodium triacetoxyborohydride (681 mg, 3.21 mmol) and acetic acid (0.19 ml, 3.21 mmol) were added sequentially. The reaction mixture was stirred under an atmosphere nitrogen at room temperature for a further 18 hours. The reaction mixture was then washed with a saturated aqueous solution of sodium hydrogen carbonate (15 ml), the organic phase separated and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel, eluting with 100:2, by volume, dichloromethane : methanol giving *anti*-N-{4-[3-(tert-butyl-dimethyl-silanyloxy)-benzylamino]-cyclohexyl}-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (937 mg) as an off-white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.32-8.36 (1H, m), 8.00-8.03 (1H, d), 7.65-7.70 (1H, d), 7.10-7.20 (5H, m), 6.86-6.94 (1H, d), 6.81 (1H, s), 6.68-6.74 (1H, d),

3.94-4.02 (1H, m), 3.78 (2H, s), 2.47-2.55 (1H, m), 2.07-2.15 (2H, m), 1.96-2.05 (2H, m), 1.20-1.42 (4H, m), 0.98 (9H, s), 0.19 (6H, s) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 568.

**Preparation 19 : *anti*-Acetic acid 2-{[acetyl-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-amino]-methyl}-phenyl ester**



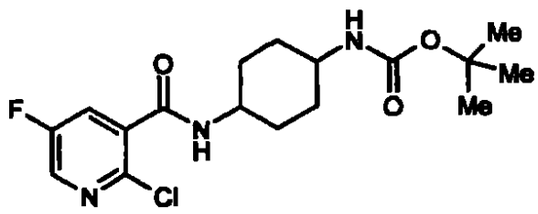
*Anti*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-benzylamino)-cyclohexyl]-nicotinamide (350 mg, 0.772 mmol) (see Preparation 26) and diisopropyl ethylamine (0.38 ml, 2.16 mmol) were dissolved in dichloromethane (10 ml) and acetyl chloride (0.14 ml, 1.85 mmol) added. The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 18 hours. The reaction mixture was then washed sequentially with a saturated aqueous solution of sodium hydrogen carbonate (10 ml), a 10 % solution of citric acid in water (10 ml) and water (10 ml) before drying the organic phase over anhydrous magnesium sulphate giving *anti*-acetic acid 2-{[acetyl-(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-amino]-methyl}-phenyl ester (277 mg) as a cream foam.

$^1H$ NMR (400MHz, $CDCl_3$): $\delta$ = 8.27-8.42 (1H, m), 7.99-8.14 (1H, m), 7.58-7.75 (1H, m), 7.00-7.42 (7H, m), 4.43-4.67 (1H, m), 4.37 (2H, s), 3.81-3.98 (1H, m), 2.00-2.50 (10H, m), 1.74-1.86 (2H, m), 1.24-1.60 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 538, $[M+Na]^+$ 560

LRMS (electrospray) $[M-H-OAc]^+$ 568.

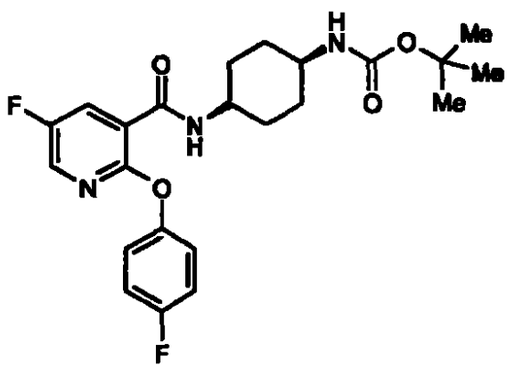
**Preparation 20 : {4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)amin ]-cyclohexyl}-carbamic acid tert-butyl ester**



2-Chloro-5-fluoro nicotinic acid (3.00 g, 0.017 mol) (see Preparation 41), was dissolved in dichloromethane (100 ml) and N,N-dimethylformamide (1 drop) was added, followed by oxalyl chloride (3.0 ml, 0.034 mol). The reaction mixture was held at room temperature for 4 hours, after which time the solvent was removed *in vacuo*. The residue was suspended in dichloromethane (100 ml) and triethylamine (5 ml) added followed by addition of (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (5.40 g, 0.026 mol) (Preparation 42a). The reaction mixture was then held under an atmosphere of nitrogen at room temperature for a further 18 hours. The reaction mixture was then washed with water (100 ml) and the organic phase dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo*, and the residue triturated with ethyl acetate/pentane (1:1, by volume, 10 ml) giving {4-[(2-chloro-5-fluoro-pyridine-3-carbonyl)amino]-cyclohexyl}-carbamic acid tert-butyl ester (2.5 g, 80:20 syn:anti) as a white solid.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8.32-8.38 (1H, d), 7.95-8.00 (0.8H, m), 7.81-7.88 (0.2H, d), 6.58-6.75 0.8H, m), 6.29-6.37 (0.2H, m), 4.38-4.62 (1H, m), 4.12-4.25 (0.8H, m), 3.95-4.03 (0.2H, m), 3.58-3.73 (0.8H, m), 3.38-3.56 (0.2H, m), 2.03-2.2 (0.8H, m), 1.66-1.95 (6.4H, m), 3.87-4.02 (1H, m), 1.58 (9H, s), 1.23-1.44 (0.8H, m, partially masked by solvent) ppm.

**Preparation 21 : *syn*-(4-{[5-Fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl] amino}-cyclohexyl)-carbamic acid tert-butyl ester**

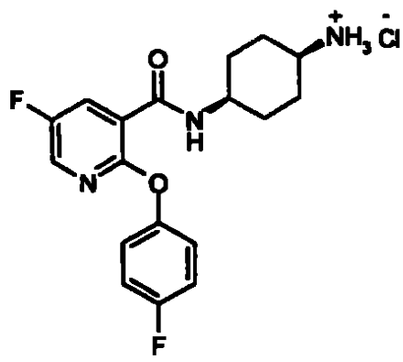


{4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)amino]-cyclohexyl}-carbamic acid tert-butyl ester (2.4 g, 6.46 mmol) (80:20 *syn/anti* mixture) (see Preparation 20), 4-fluorophenol (800 mg, 7.11 mmol) and caesium carbonate (4.2 g, 12.02 mmol) were stirred in N,N-dimethylformamide (40ml) at 50°C under an atmosphere of nitrogen for 18 hours. The reaction mixture was then partitioned between ethyl acetate (100 ml) and water (100 ml), and the organic layer separated, washed with a saturated aqueous solution of sodium chloride (100 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with a solvent gradient of 100 % dichloromethane changing to 98:2, by volume, dichloromethane : methanol giving *syn*-(4-{[5-fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl)-carbamic acid tert-butyl ester (2.4 g) as a white solid.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8.32-8.39 (1H, m), 8.01-8.04 (1H, d), 7.90-7.99 (1H, d), 7.10-7.22 (4H, m), 4.25-4.47 (1H, m), 4.15-4.23 (1H, m), 3.56-3.68 (1H, m), 1.63-1.91 (6H, m), 1.38-1.60 (11H, m, partially masked by solvent) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 448

**Preparation 22 : *syn*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride**

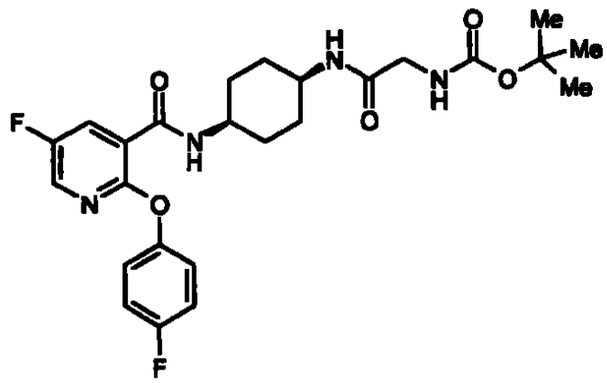


*Syn*-(4-{[5-Fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl)-carbamic acid tert-butyl ester (2.4 g, 5.4 mmol) (see Preparation 21) was dissolved in 4 M HCl in dioxan (100 ml) and stirred under an atmosphere of nitrogen at room temperature for 4 hours. The solvent was removed *in vacuo* and the resultant white precipitate triturated with dichloromethane (20 ml), ethyl acetate (20 ml) and diethylether (20 ml) giving *syn*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (1.7 g) as a white solid.

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.01-8.10 (2H, m), 7.08-7.23 (4H, m), 4.10-4.18 (1H, m), 3.18-3.33 (1H, m, partially masked by solvent), 1.78-2.00 (6H, m), 1.61-1.77 (2H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 348.

**Preparation 23 : *syn*-[(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl] amino}-cyclohexylcarbamoyl)-methyl]-carbamic acid tert-butyl ester**

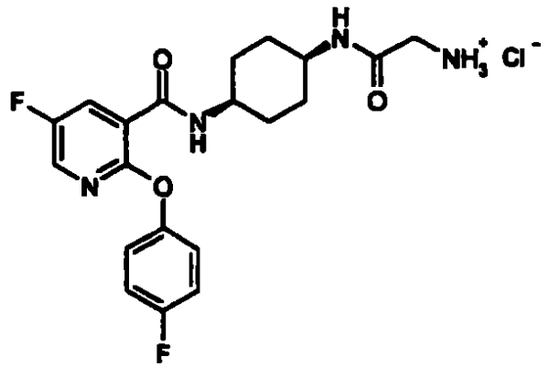


*Syn*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (200 mg, 0.521 mmol) (see Preparation 22), 1-hydroxybenzotriazole (106 mg, 0.782 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (130 mg, 0.677 mmol), N-methyl morpholine (0.12 ml, 1.04 mmol) and tert-butoxycarbonylamino-acetic acid (100 mg, 0.573 mmol) were stirred in N,N-dimethylformamide (5 ml) at room temperature for 18 hours. The reaction mixture was then partitioned between ethyl acetate (10 ml) and water (10 ml) and the organic layer separated, washed with a saturated aqueous solution of sodium chloride (10 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was then triturated with diethylether (5 ml) giving *syn*-[(4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]amino}-cyclohexylcarbamoyl)-methyl]-carbamic acid tert-butyl ester (182 mg) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.32-8.38 (1H, dd), 8.02-8.04 (1H, d), 7.89-7.97 (1H, d), 7.10-7.19 (4H, m), 6.08-6.23 (1H, brs), 5.03-5.17 (1H, brs), 4.13-4.21 (1H, m), 3.89-3.98 (1H, m), 3.64-3.71 (2H, d), 1.74-1.91 (4H, m), 1.62-1.73 (2H, m), 1.47-1.60 (2H, m), 1.36 (9H, s) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 527.

**Preparation 24 : *syn*-N-[4-(2-Amino-acetylamino)-cyclohexyl]-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride**

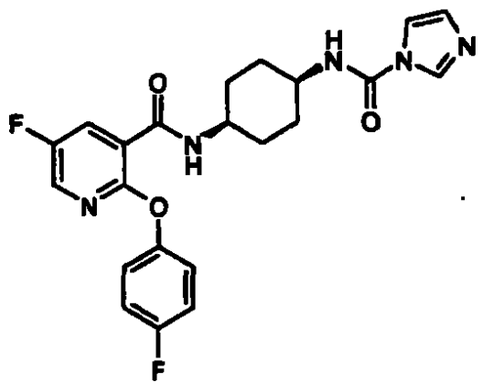


*Syn*-[(4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]amino}-cyclohexyl carbamoyl)-methyl]-carbamic acid tert-butyl ester (1.47 g, 2.91 mmol) (see

preparation 23) was dissolved in dichloromethane (20 ml) and hydrogen chloride gas bubbled into the solution at 0°C until the solution became saturated (15 minutes). The reaction mixture was then stirred under an atmosphere of nitrogen at room temperature for a further 45 minutes, and the solvent then removed *in vacuo*. The resultant white precipitate was triturated with ether (3-fold 10 ml) giving *syn*-N-[4-(2-amino-acetylamino)-cyclohexyl]-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (2.07 g) as a white solid.

LRMS (thermospray) : m/z $[M+H]^+$ 405.

**Preparation 25 : *syn*-5-Fluoro-2(4-fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclohexyl}-nicotinamide**



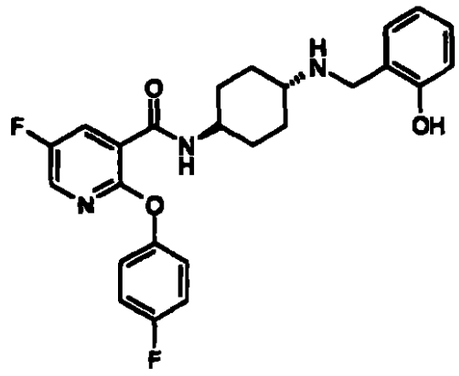
A solution of *syn*-N-(4-amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (220 mg, 0.52 mmol) (see Preparation 22) in dichloromethane (5 ml) was added dropwise to a suspension of carbonyldiimidazole (253 mg, 1.563 mmol) and triethylamine (0.08 ml, 0.521 mmol) in dichloromethane (5 ml) over a 35 minute period. The reaction mixture was then washed sequentially with water (10 ml) followed by a saturated aqueous solution of sodium chloride (10 ml). The organic phase was separated and dried over anhydrous magnesium sulphate. The solvent was then removed *in vacuo*, and the residue purified by flash column chromatography on silica gel eluting with a solvent gradient of 100 % dichloromethane changing to 99:1 then 98:2, by volume, dichloromethane : methanol giving *syn*-5-fluoro-2(4-fluoro-phenoxy)-N-{4-

[(imidazole-1-carbonyl)-amino]-cyclohexyl)-nicotinamide (147 mg) as a white foam.

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.32-8.39 (1H, m), 7.95-8.06 (3H, m), 7.19 (1H, s), 7.08-7.17 (4H, m), 7.05 (1H, s), 4.18-4.26 (1H, m), 3.92-4.02 (1H, m), 1.78-2.02 (6H, m), 1.57-1.77 (2H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 442, $[M+Na]^+$ 464

**Preparation 26 : *anti*-5-Fluoro-2-(4-fluoro-phenoxy)-N-[4-(2-hydroxy-benzylamino)-cyclohexyl]-nicotinamide**



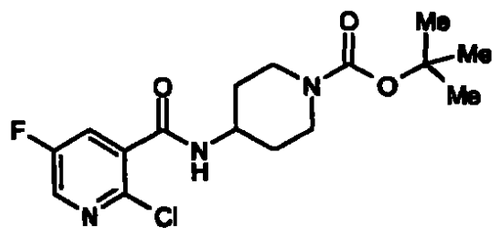
2-(tert-Butyl-dimethyl-silanyloxy)-benzaldehyde (769 mg, 3.21 mmol) (see Preparation 16) and *anti*-N-(4-Amino-cyclohexyl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (900 mg, 2.14 mmol) (see Preparation 7) were dissolved in dichloromethane (10 ml) and diisopropylethylamine (0.56 ml, 3.21 mmol) added. The reaction mixture was stirred at room temperature for 30 minutes and acetic acid (0.19 ml, 3.21 mmol) added followed by addition of sodium triacetoxyborohydride (0.681 g, 3.21 mmol). The reaction mixture was then held at room temperature for 18 hours. The mixture was then quenched with water (10 ml), the organic phase separated and dried over anhydrous magnesium sulphate. The solvent was then removed *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with 100:2, by volume, dichloromethane : methanol giving *anti*-5-fluoro-2-(4-fluoro-phenoxy)-

N-[4-(2-hydroxy-benzylamino)-cyclohexyl]-nicotinamide (800 mg) as a white solid (acetate salt).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.32-8.38 (1H, m), 8.01-8.04 (1H, d), 7.64-7.72 (1H, d), 7.05-7.21 (5H, m), 6.95-6.99 (1H, d), 6.81-6.84 (1H, d), 6.73-6.80 (1H, t), 3.92-4.04 (3H, m), 2.50-2.62 (1H, m), 2.02-2.20 (7H, s + m), 1.20-1.40 (4H, m) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 454

**Preparation 27 : 4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester**



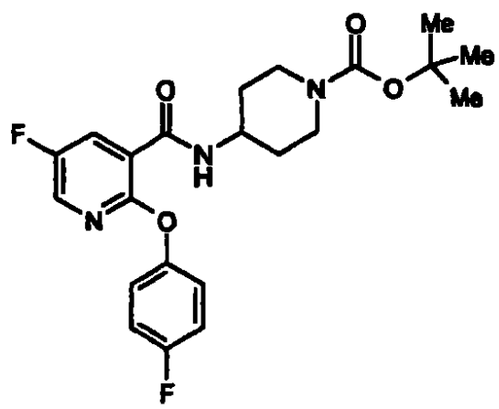

2-Chloro-5-fluoro nicotinic acid (5.00 g, 28.48 mmol) (see Preparation 41), was dissolved in dichloromethane (200 ml) and N,N-dimethylformamide (1 drop) was added, followed by addition of oxalyl chloride (7.45 ml, 85.44 mmol). The reaction mixture was held at room temperature for 18 hours, after which the solvent was removed *in vacuo*. The residue was th en suspended in dichloromethane (150 ml) and triethylamine (11.91 ml, 85.44 mmol) added followed by addition of 4-amino-piperidine-1-carboxylic acid tert-butyl ester (6.85 g, 34.18 mmol). The reaction mixture was then stirred under an atmosphere of nitrogen at room temperature for 64 hours before being washed sequentially with water (2-fold 100 ml), a saturated aqueous solution of sodium chloride (100 ml) and a 10 % solution of citric acid in water (50 ml). The organic phase was separated, dried over anhydrous magnesium sulphate and the solvent was removed *in vacuo* giving 4-[(2-chloro-5-fluoro-pyridine-3-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (8.7 g) as an off-white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.28-8.30 (1H, d), 7.78-7.83 (1H, m), 6.46-6.52 (1H, m), 4.04-4.13 (1H, m), 3.96-4.03 (1H, m), 2.83-2.98 (2H, t), 1.97-2.03 (2H, d), 1.38-1.50 (11H, m) ppm.

LRMS (thermospray) : m/z $[M+Na]^+$ 380

LRMS (electrospray) : m/z $[M-H]^+$ 356.

**Preparation 28 : 4-{[5-Fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester**

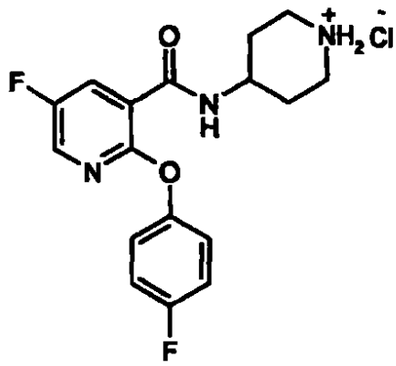



4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (4.0 g, 11.18 mmol) (see Preparation 27), 4-fluorophenol (1.378 g, 12.3 mmol) and caesium carbonate (7.29 g, 33.54 mmol) were stirred in N,N-dimethylformamide (40 ml) at 55°C under an atmosphere of nitrogen for 18 hours. The reaction mixture was then partitioned between ethyl acetate (50 ml) and water (30 ml) and the organic layer separated. The organic layer was then washed with a saturated aqueous solution of sodium chloride (40 ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with dichloromethane. The product was finally triturated with diethylether (25 ml) giving 4-{[5-fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (2.59 g) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.30-8.33 (1H, m), 7.78-8.00 (1H, d), 7.73-7.80 (1H, d), 7.02-7.13 (4H, m), 4.07-4.20 (1H, m), 3.90-4.04 (1H, m), 2.87-3.03 (2H, d), 1.37-1.45 (11H, m) ppm.

LRMS (thermospray) : m/z $[M+Na]^+$ 456, $[M-H]^+$ 432.

**Preparation 29 : 5-Fluoro-2-(4-fluoro-phenoxy)-N-piperidin-4-yl-nicotinamide hydrochloride**

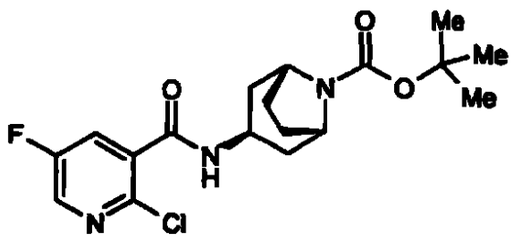


4-{[5-Fluoro-2-(4-fluorophenoxy)-pyridine-3-carbonyl]-amino}-piperidine-1-carboxylic acid tert-butyl ester (2.58 g, 5.95 mmol) (see Preparation 28) was dissolved in dichloromethane (15 ml) and hydrogen chloride gas bubbled through the solution at 0°C for 10 minutes. The reaction mixture was then held under an atmosphere of nitrogen at room temperature for a further 45 minutes and the solvent tremoved *in vacuo*. The resultant white precipitate was triturated with diethylether (2-fold 10 ml) giving 5-fluoro-2-(4-fluoro-phenoxy)-N-piperidin-4-yl-nicotinamide hydrochloride (2.14 g) as a white solid.

$^1$H NMR (400MHz, $CD_3OD$): δ = 8.04-8.07 (1H, d), 7.96-8.01 (1H, m), 7.10-7.21 (4H, m), 4.13-4.22 (1H, m), 3.39-3.44 (2H, d), 3.11-3.20 (2H, t), 2.18-2.26 (2H, d), 1.77-1.90 (2H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 334.

**Preparation 30 : *endo*-3-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester**

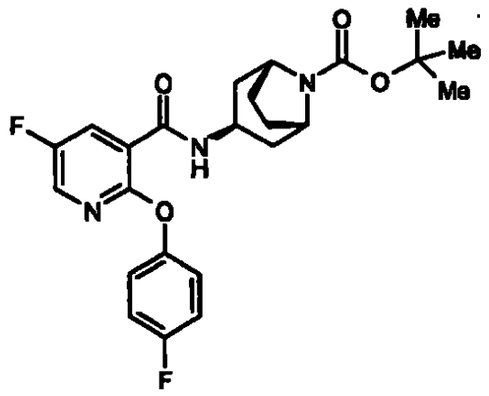


2-Chloro-5-fluoro nicotinic acid (1.75 g, 10 mmol) (see Preparation 44) was dissolved in dichloromethane (250 ml) and N,N-dimethylformamide (0.4 ml) added followed by addition of oxalyl chloride (4.4 ml, 50 mmol). The reaction mixture was then held at room temperature for 18 hours after which time the solvent was removed *in vacuo*. The residue was azeotroped with toluene, then suspended in dichloromethane (200 ml) and 3-amino-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (2.26 g, 10 mmol) (see reference Patent application WO 00/38680) added followed by addition of triethylamine (2.82 ml, 20 mmol). The reaction mixture was then was held under an atmosphere of nitrogen at room temperature for 3 hours before being washed with a saturated aqueous solution of sodium chloride (3-fold 100 ml) aqnd the organic layer separated. The solvent was then removed *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 90:10, by volume, dichloromethane : methanol giving *endo*-3-[(2-chloro-5-fluoro-pyridine-3-carbonyl)-amino]-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (1.12 g) as a white foam.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.31-8.34 (1H, d), 7.97-8.02 (1H, dd), 7.18-7.23 (1H, m, partially masked by solvent), 4.34-4.39 (1H, m), 4.15-4.32 (2H, brs), 2.19-2.38 (2H, brs), 2.07-2.13 (2H, m), 1.82-1.90 (2H, m), 1.71-1.79 (2H, d), 1.45 (9H, s) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 406, $[M-H]^+$ 382.

**Preparation 31 : *endo*-3-{[(5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester**

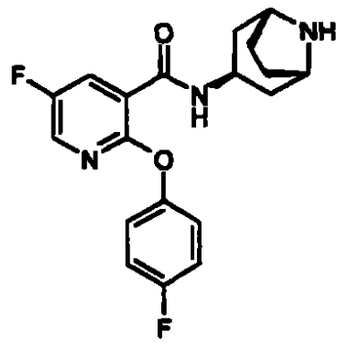



*Endo*-3-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-8-aza-bicyclo[3.2.1] octane-8-carboxylic acid tert-butyl ester (119 mg, 0.31 mmol) (see Preparation 30), 4-fluorophenol (39 mg, 0.34 mmol) and caesium carbonate (202 mg, 0.62 mmol) were stirred in N,N-dimethylformamide (2 ml) at 60°C under an atmosphere of nitrogen for 18 hours. The reaction mixture was then partitioned between ethyl acetate (10 ml) and water (10 ml), and the organic layer separated. The organic layer was then washed with a saturated aqueous solution of sodium chloride (3-fold 10 ml) and concentrated *in vacuo* to give a residue which was purified by flash column chromatography on silica gel eluting with a solvent gradient of 10:90 changing to 50:50, by volume, ethyl acetate : pentane. The product was finally triturated with pentane (5 ml) giving *endo*-3-{[(5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-aza-bicyclo[3.2.1] octane-8-carboxylic acid tert-butyl ester (100 mg) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ= 8.51-8.56 (1H, d), 8.32-8.36 (1H, dd), 7.98-8.00 (1H, d), 7.01-7.15 (4H, m), 4.37-4.43 (1H, m), 4.11-4.30 (2H, brs), 2.14-2.36 (2H, brs), 1.91-1.98 (2H, m), 1.70-1.84 (4H, m), 1.43 (9H, s) ppm.

LRMS (electrospray) : m/z $[M+Na]^+$ 482, $[M-H]^+$ 458.

**Preparation 32 ; *endo*-N-(8-Aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**

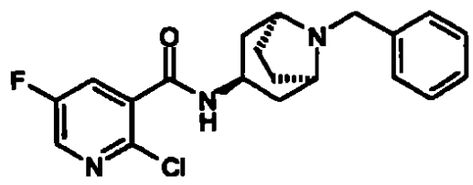


*Endo*-3-[[(5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (1.92 g, 4.2 mmol) (see Preparation 31) was dissolved in 2.2 M acetyl chloride in methanol (20 ml) and the reaction stirred at room temperature under an atmosphere of nitrogen for 1hour. The reaction mixture was then heated at 50°C for 3 hours before removal of the solvent *in vacuo*. The residue was then partitioned between dichloromethane (50 ml) and water (50 ml), the pH of the aqueous phase adjusted to pH>8 by addition of sodium hydrogen carbonate and the organic layer separated. The aqueous phase was then further extracted with ethyl acetate (50 ml) followed by 10 % methanol in dichloromethane (5-fold 50 ml). The combined organic extracts were then concentrated under reduced pressure. The residue was azeotroped with toluene giving *endo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (1.40 g) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8.34-8.39 (1H, d), 8.16-8.18 (1H, d), 7.97-8.01 (1H, dd), 7.18-7.23 (4H, d), 3.99-4.06 (1H, m), 3.33-3.40 (2H, brs, partially masked by solvent), 1.85-1.99 (4H, m), 1.64-1.72 (2H, d), 1.49-1.57 (2H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 360.

**Preparation 33 : exo-N-(8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-2-chloro-5-fluoro-nicotinamide**

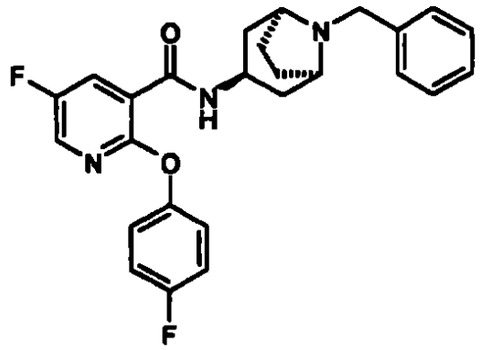


2-Chloro-5-fluoro nicotinic acid (8.78 g, 50 mmol) (see Preparation 41), was dissolved in dichloromethane (1 l) and N,N-dimethylformamide (0.4 ml) added, followed by addition of oxalyl chloride (22.3 ml, 250 mmol). The reaction mixture was then held at room temperature for 18 hours after which time the solvent was removed *in vacuo*. The residue was azeotroped with toluene, then suspended in dichloromethane (300ml) and *exo*-8-benzyl-8-aza-bicyclo[3.2.1]oct-3-ylamine reference Patent application WO 00/38680) (10.82 g, 50 mmol) added followed by addition of triethylamine (14 ml, 100 mmol) in dichloromethane (100 ml). The reaction mixture was then held under an atmosphere of nitrogen at room temperature for 5 hours and then washed with a saturated aqueous solution of sodium chloride (3-fold 300 ml). The organic phase was separated, concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with a solvent gradient of 100:0 changing to 90:10, by volume, dichloromethane : methanol giving *exo*-N-(8-benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-2-chloro-5-fluoro-nicotinamide (17 g) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ= 8.30-8.32 (1H, d), 7.81-7.85 (1H, dd), 7.20-7.38 (5H, m, partially masked by solvent), 6.28-6.31 (1H, d), 4.30-4.42 (1H, m), 3.55 (2H, s), 3.22-3.30 (2H, brs), 2.02-2.13 (2H, m), 1.91-1.99 (2H, m), 1.72-1.80 (2H, quart), 1.60-1.70 (2H, t) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 374, $[M-H]^+$ 372.

**Preparation 34 : exo-N-(8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**



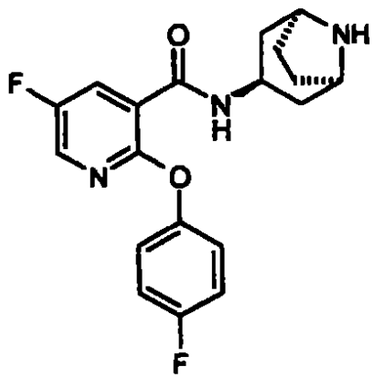
*Exo*-N-(8-Benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-2-chloro-5-fluoro-nicotinamide (7.9 g, 21 mmol) (see Preparation 33), 4-fluorophenol (2.6 g, 23 mmol) and caesium carbonate (13.8 g, 42 mmol) were stirred in N,N-dimethylformamide (200ml) at 70°C under an atmosphere of nitrogen for 20 hours. The reaction mixture was then partitioned between ethyl acetate (300 ml) and water (300 ml) and the organic layer separated. The organic phase was then washed with a saturated aqueous solution of sodium chloride (3-fold 200 ml), concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with a solvent gradient of 20:80 changing to 100:0, by volume, ethyl acetate : pentane. The product was triturated with pentane (30 ml) giving exo-N-(8-benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (6.3 g) as a white solid.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.26-8.30 (1H, dd), 7.96-7.98 (1H, d), 7.58-7.64 (1H, d), 7.17-7.33 (5H, m), 7.04-7.16 (4H, m), 4.30-4.42 (1H, m), 3.48 (2H, s), 3.20-3.25 (2H, brs), 2.03-2.11 (2H, m), 1.88-1.96 (2H, m), 1.72-1.80 (2H, quartet), 1.55-1.62 (2H, m, partially masked by solvent) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 450, $[M-H]^+$ 448.

45
116

**Preparation 35 : exo-N-(8-Aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide**

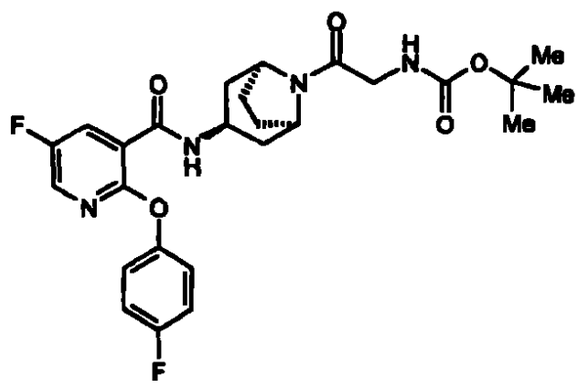


10 % Palladium on carbon (0.5 g) and ammonium formate (7.5 g, 115 mmol) were added to a solution of *exo*-N-(8-benzyl-8-aza-bicyclo[3.2.1]oct-3-yl-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide (5.15 g, 11.5 mmol) (see Preparation 34) in ethanol (35 ml) under an atmosphere of nitrogen and the reaction mixture heated at reflux for 25 minutes. The reaction mixture was then cooled, filtered through a short column of arbocel (washing with ethanol) and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with 90:10:1, by volume, dichloromethane : methanol : ammonia giving *exo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluooro-phenoxy)-nicotinamide (3.4 g) as a white foam.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8.26-8.31 (1H, dd), 7.97-7.99 (1H, d), 7.56-7.70 (1H, d), 7.00-7.14 (4H, m), 4.33-4.43 (1H, m), 3.52-3.60 (2H, brs), 1.97-2.06 (2H, m), 1.73-1.88 (4H, m), 1.41-1.50 (2H, t) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 360.

**Preparation 36 : exo-[2-(3-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-aza-bicyclo[3.2.1]-oct-8-yl)-2-oxo-ethyl]-carbamic acid-tert-butyl ester**



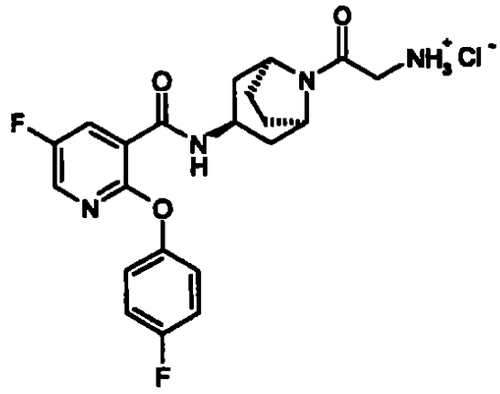
N-tert-Butoxycarbonyl-glycine (284 mg, 1.6 mmol), 1-hydroxybenzotriazole (257 mg, 1.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (375 mg, 1.9 mmol) were stirred in dichloromethane (10 ml) at room temperature and *exo*-N-(8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluooro-phenoxy)-nicotinamide (570 mg, 1.6 mmol) (see Preparation 35) added followed by addition of N-methyl morpholine (0.21 ml, 1.9 mmol). The reaction mixture was then stirred under an atmosphere of nitrogen at room temperature for 4 hours before being washed with water (10 ml). The organic phase was separated, concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with 100:0 changing to 98:2, by volume, dichloromethane : methanol giving *exo*-[2-(3-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-azo-bicyclo[3.2.1]-oct-8-yl)-2-oxo-ethyl]-carbamic acid-tert-butyl ester (760 mg) as an oil.

$^1$H NMR (400MHz, $CDCl_3$): δ= 8.28-8.34 (1H, m), 8.0-8.02 (1H, m), 7.59-7.65 (1H, d), 7.05-7.16 (4H, m), 5.37-5.43 (1H, brs), 4.72-4.78 (1H, brs), 4.57-4.70 (1H, m), 4.15-4.20 (1H, brs), 3.89-3.94 (2H, brs), 2.16-2.23 (1H, m), 1.94-2.15 (2H, m), 1.82-1.92 (1H, m), 1.58-1.68 (1H, t), 1.40-1.56 (10H, m), 0.90-0.96 (2H, d) ppm.

LRMS ( lectrospray) : m/z $[M+Na]^+$ 539, $[M-H]^+$ 515.

116
117

**Preparation 37 : exo-N-[8-(2-Amino-acetyl)-8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride**

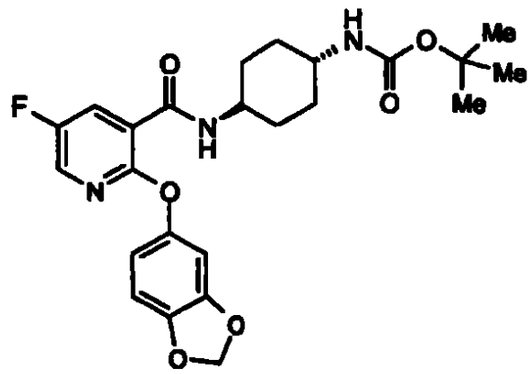


*Exo*-[2-(3-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-8-azo-bicyclo[3.2.1]-oct-8-yl)-2-oxo-ethyl]-carbamic acid-tert-butyl ester (760 g, 1.5 mmol) (see Preparation 36) was dissolved in 2 M acetyl chloride in methanol (10 ml). The reaction mixture was stirred 50°C under an atmosphere of nitrogen for 3 hours and the solvent then removed *in vacuo*. The residue was azeotroped with methanol (5 ml) and dried *in vacuo* giving *exo*-N-[8-(2-amino-acetyl)-8-aza-bicyclo[3.2.1]oct-3-yl)-5-fluoro-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (600 mg) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8.29-8.33 (1H, d), 8.13-8.23 (3H, m), 7.92-7.96 (1H, dd), 7.16-7.25 (4H, m), 4.50-4.58 (1H, brs), 4.28-4.41 (1H, m), 4.21-4.27 (1H, m), 3.80-3.90 (1H, m), 3.60-3.72 (1H, m), 1.70-2.06 (6H, m), 1.49-1.64 (2H, m) ppm.

LRMS (thermospray) : m/z $[M+H]^+$ 417.

**Preparation 38 : *anti*-(4-{[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester**

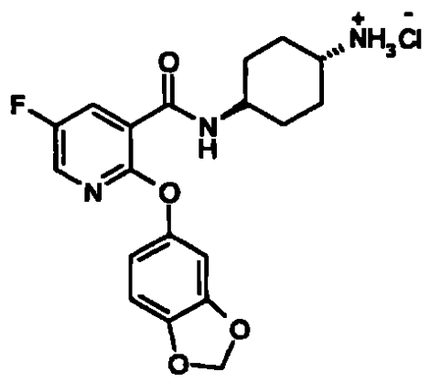


2-(4-Benzo[1,3]dioxol-5-yloxy)-5-fluoro-nicotinic acid (5.0 g, 18.04 mmol) (see reference patent application WO 98/45268), 1-hydroxybenzotriazole (3.66 g, 27.06 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.50 g, 23.45 mmol) were stirred in N,N-dimethylformamide (40 ml) at room temperature under an atmosphere of nitrogen for 45 minutes. *anti*-(4-Amino-cyclohexyl)-carbamic acid tert-butyl ester (3.87 g, 18.04 mmol) (see Preparation 40) was then added followed by addition of N-methyl morpholine (4 ml, 36.08 mmol) and the reaction mixture stirred for a further 16 hours. The solvent was then removed in vacuo, the residue dissolved in ethyl acetate and the solution washed sequentially with water and a saturated aqueous solution of sodium chloride. The organic layer was separated, dried over anhydrous sodium sulphate and the solvent removed in vacuo. The residue was then triturated with diethyl ether and dried in vacuo to give *anti*-(4-{[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester (6.695 g) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8.15 (1H, m), 7.88 (1H, m), 6.85 (1H, d), 6.78 (1H, d), 6.64 (1H, d), 6.58 (2H, m), 5.99 (2H, s), 3.62 (1H, m), 3.15 (1H, m), 1.70-1.90 (4H, m), 1.32 (9H, s), 1.10-1.30 (4H, m) ppm.

LRMS (thermospray) : m/z $[M+Na]^+$ 496

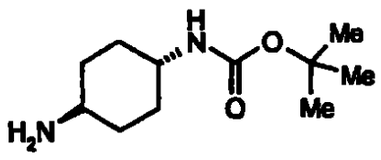
**Preparation 39 : *anti*-N-(4-Amino-cyclohexyl)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-nicotinamide hydrochloride**



*Anti*-(4-[[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester (6.7 g, 14.15 mmol) (see Preparation 38) was treated with 4M HCl in dioxan (40 ml) and the reaction mixture stirred for 90 minutes. The solvent was then reduced *in vacuo* and a solid precipitated. The precipitate was suspended in diethyl ether, filtered and then dried in vacuo to give *anti*-N-(4-amino-cyclohexyl)-2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-nicotinamide hydrochloride (6.13 g) as a white solid.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8.24 (1H, d), 8.20 (1H, d), 7.86-7.99 (4H, m), 6.86 (1H, d), 6.80(1H, d), 6.58 (1H, m), 5.99 (2H, s), 3.60-3.70 (1H, m), 2.90-2.95 (1H, m), 1.85-1.98 (4H, m), 1.25-1.45 (4H, m) ppm.

**Preparation 40 : *anti*-(4-Amino-cyclohexyl)-carbamic acid tert-butyl ester**



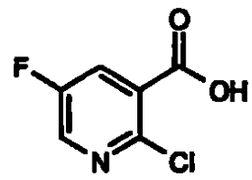
*Anti* 1,4-Diamino cyclohexane (18.27 g, 0.16 mol) was dissolved in dichloromethane (80 ml) and the solution cooled at 0°C under an atmosphere of nitrogen. The reaction mixture was maintained at 0°C and a solution of di-*tert*-butyl dicarbonate (6.98 g, 0.032 mol) in dichloromethane (70 ml) added

dropwise over a period of 5 hours. The reaction mixture was stirred at room temperature for a further 16 hours and then washed with water (200 ml). The organic layer was separated, extracted with a 10 % aqueous solution of citric acid (200 ml) and the organic phase disgarded. The pH of the aqueous phase was then increased to pH>8 by the addition of 0.88 ammonia and extracted with dichloromethane (3-fold 150 ml). The organic extracts were combined, dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to give *anti* (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (4.83 g) as a solid.

$^1$H NMR (400MHz, CDCl3): δ = 4.35 (br s, 1H), 4.55 (br s, 1H), 3.40 (br S, 1H), 2.60-2.65 (m, 1H), 1.80-2.00 (m, 4H), 1.10-1.50 (m, ~14H) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 215.

**Preparation 41 : 2-Chloro-5-fluoro nicotinic acid**

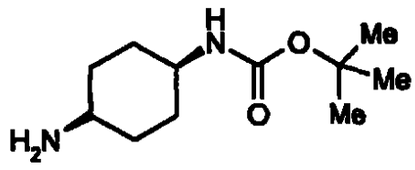



Ethyl-2-chloro-5-fluoro-nicotinoate (50.4 g, 0.247 mol) (see reference *J. Med. Chem.*, 1993, 36(18), 2676-88) was dissolved in tetrahydrofuran (350 ml) and a 2 M aqueous solution of lithium hydroxide (247 ml, 0.495 mol) added. The reaction mixture was stirred at room temperature for 3 days. The pH of the solution was reduced to pH1 by addition of 6 N hydrochloric acid and then extracted with dichloromethane (3 fold). The combined extracts were dried over anhydrous magnesium sulphate and the solvent removed *in vacuo* to give a solid which was triturated with diethyl ether and then dried *in vacuo* to give 2-chloro-5-fluoro nicotinic acid (40.56 g) as a white solid.

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 8.20 (1H, s), 8.62 (1H, s) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 174.

**Preparation 42a : 80:20 *syn: anti* (4-Amino-cyclohexyl)-carbamic acid tert-butyl ester**

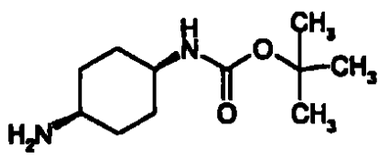


80:20 *syn:anti* 1,4-Diamino cyclohexane (20 g, 0.175 mol) was dissolved in dichloromethane (160 ml) and the solution cooled at 0°C under an atmosphere of nitrogen. The reaction mixture was maintained at 0°C and a solution of di-*tert*-butyl dicarbonate (7.65 g, 0.035 mol) in dichloromethane (40 ml) added dropwise over a period of 5 hours. The reaction mixture was stirred at room temperature for a further 16 hours and then washed with water (200 ml). The organic layer was separated, extracted with a 10 % aqueous solution of citric acid (200 ml) and the organic phase disgarded. The pH of the aqueous phase was then increased to pH>8 by the addition of .88 ammonia and extracted with dichloromethane (2-fold 150 ml). The organic extracts were combined, dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. The residue was then triturated with pentane to give 80:20 *syn: anti* (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (5.143 g) as a solid.

$^1$H NMR (400MHz, CDCl3): δ = 4.60 (br s, 0.8H), 4.36 (br s, 0.2H), 3.63 (br S, 0.8H), 3.39 (br s, 0.2H), 3.80-3.86 (m, 0.8H), 2.60-2.65 (m, 0.2H), 1.96-2.00 (m, 0.2H), 1.80-1.86 (m, 0.2H), 1.10-2.75 (m, ~17H) ppm.

LRMS (electrospray) : m/z $[M+H]^+$ 215.

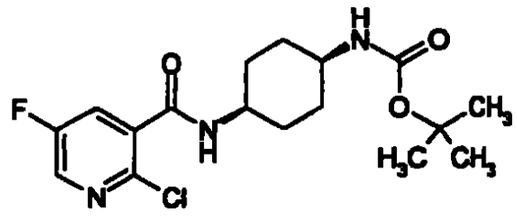
**Preparation 42b : *Syn*-(4-Amino-cyclohexyl)-carbamic acid tert-butyl ester**



5% Palladium on charcoal (5 g) was mixed with toluene (10 ml) and was added to (4-azido-cyclohexyl)-carbamic acid tert-butyl ester (170 g, 0.71 mol, see WO 99/54284) in methanol (400 ml). The mixture was hydrogenated (80 atmospheres) at room temperature for 18 hours and then filtered. The solvent was evaporated *in-vacuo* and the residue was triturated with ethyl acetate (50 ml) and then with hexane (200 ml). The solid obtained was isolated by filtration, dissolved in ethyl acetate (600 ml) and filtered through Celite . The filtrate was concentrated *in-vacuo* to give a slush that was diluted with hexane (300 ml). The solid obtained was isolated by filtration and was washed with ethyl acetate in hexane (20:80). The mother liquors were combined and evaporated *in-vacuo*, the residue was purified by chromatography on silica gel using ethyl acetate and then methanol as eluant. The material obtained was crystallised from ethyl acetate and hexane and combined with the first crop to give *syn*-(4-amino-cyclohexyl)-carbamic acid tert-butyl ester as a white solid (76 g).

Mp 88-90°C

**Preparation 43 : *Syn*-[4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexyl]-carbamic acid tert-butyl ester**



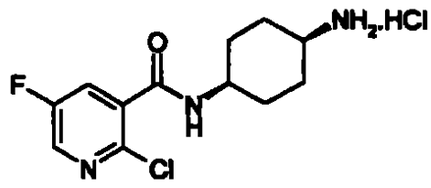
2-Chloro-5-fluoro nicotinic acid (1 g, 5.7 mmol, see Preparation 41), 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (1.2 g, 6.27 mmol) and 1-hydroxybenzotriazole hydrate (0.847 g, 6.27 mmol) were added to (4-amino-cyclohexyl)-carbamic acid tert-butyl ester (1.28 g, 5.98 mmol, see Preparation 42b) in N,N-dimethylformamide (20 ml) containing triethylamine (2.38 ml, 17 mmol). The mixture was stirred for 18 hours and then partitioned between ethyl acetate and water. The organic solution was washed with water and then with

saturated solution of sodium chloride, dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using cyclohexane in ethyl acetate (40:60) to give syn-{4-[(2-chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexyl}-carbamic acid tert-butyl ester (1.01 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.33 (1H, d), 7.80 (1H, m), 6.67 (1H, s), 4.54 (1H, m), 4.16 (1H, m), 3.64 (1H, s), 1.86 (6H, m), 1.76 (2H, m), 1.27 (9H, s).

LCMS (electrospray): m/z $[M+Na]^+$ 394, 396

**Preparation 44 : *Syn*-N-(4-amino-cyclohexyl)-2-chloro-5-fluoro-nicotinamide hydrochloride**

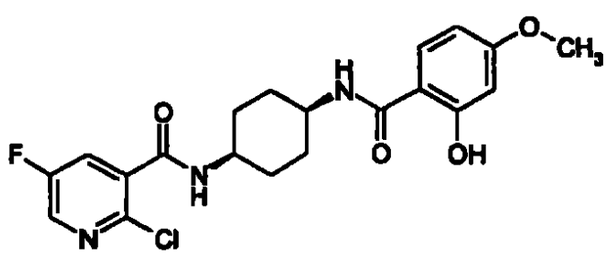



Hydrogen chloride (4M in 1,4-dioxane, 20 ml) was added to syn-{4-[(2-chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexyl}-carbamic acid tert-butyl ester (1.01 g, 2.72 mmol, see Preparation 43) in 1,4-dioxane (10 ml) and was stirred for 1 hour. The solvent was evaporated *in-vacuo* and the residue triturated with diethylether. The resulting material was dried *in-vacuo* to give syn-N-(4-amino-cyclohexyl)-2-chloro-5-fluoro-nicotinamide hydrochloride as an off white solid (1.11g).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.41 (1H, d), 7.79 (1H, m), 4.07 (1H, m), 3.25 (1H, m), 1.88 (8H, m).

LCMS (electrospray): m/z $[M+H]^+$ 372, 274

**Preparation 45 : *Syn*-2-Chloro-5-fluoro-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-nicotinamide**

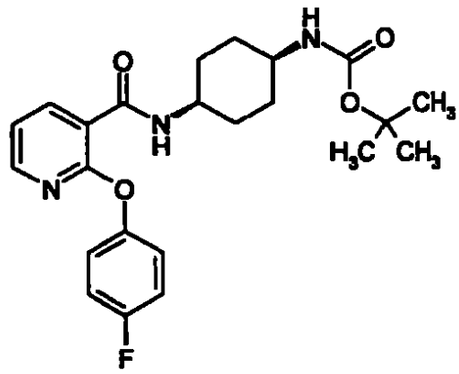


1-(3-Dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (3.27 g, 17 mmol) was added to syn-N-(4-amino-cyclohexyl)-2-chloro-5-fluoro-nicotinamide hydrochloride (3.5 g, 11.3 mmol, see Preparation 44), 1-hydroxybenzotriazole hydrate (1.69 g, 12.5 mmol) and 2-hydroxy-4-methoxybenzoic acid (1.91 g, 11.31 mmol) in N,N-dimethylformamide (50 ml) containing triethylamine (8 ml, 57 mmol). The mixture was stirred 18 hours and then was evaporated *in-vacuo*. The residue was partitioned between ethyl acetate and water and the organic phase was dried and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate in pentane (30:70) then changing the eluant for the column to ammonium hydroxide and methanol in dichloromethane (1:10:90). The material obtained was triturated with methanol in dichloromethane (5:95) to give *syn*-2-chloro-5-fluoro-N-[4-(2-hydroxy-4-methoxy-benzoylamino)-cyclohexyl]-nicotinamide as a white solid (940 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12.78 (1H, s), 8.53 (2H, s), 8.23 (1H, d), 7.94 (1H, m), 7.84 (1H, d), 6.43 (1H, d), 6.38 (1H, s), 3.88 (2H, m), 3.74 (3H, s), 1.73 (8H, m).

LCMS (electrospray): m/z $[M+H]^+$ 444, 446

**Preparation 46 : *Syn*-(4-{[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester**

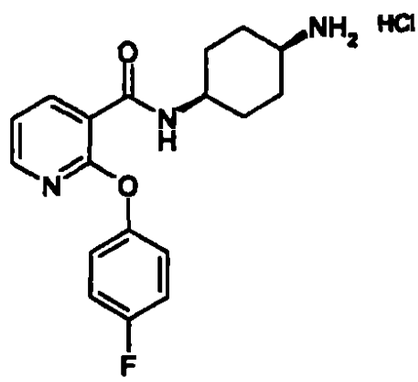


O-(7-Azabenzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (2.24 g, 5.89 mmol) was added to 2-(4-fluoro-phenoxy)-nicotinic acid (0.916 g, 3.93 mmol), Hünig's base (1.37 ml, 7.86 mmol) and to *syn*-(4-amino-cyclohexyl)-carbamic acid tert-butyl ester (1.01 g, 4.71 mmol, see Preparation 42-B) in N,N-dimethylformamide (26.2 ml) and was stirred for 18 hours. The reaction mixture was partitioned between water (100 ml) and a mixture of diethylether (200 ml) and ethyl acetate (50 ml). The aqueous layer was separated and extracted with ethyl acetate (50ml) and the combined organic layers were washed with a saturated solution of sodium chloride, dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate in cyclohexane as eluant (gradient from 25:73 to 50:50) to give *syn*-(4-{[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester as white solid (1.07 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.60 (1H, d), 8.20 (1H, d), 1.91 (1H, d), 1.17 (5H, m), 4.40 (1H, m), 4.19 (1H, s), 3.61 (1H, s), 1.77 (8H, m), 1.42 (9H, s).

LCMS (electrospray): m/z $[M+Na]^+$ 452

**Preparation 47 : *Syn*-N-(4-Amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride**

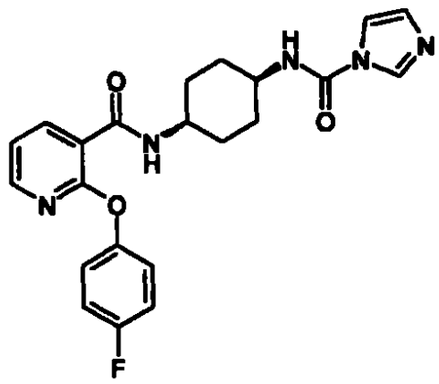


*Syn*-(4-{[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester (989 mg, 2.3 mmol, see Preparation 46) was suspended in a solution of hydrogen chloride in 1,4-dioxane (4M, 20 ml) and was stirred for 3.5 hours at room temperature after which the solvent was evaporated *in-vacuo* to give *syn*-N-(4-amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride as a white solid (1.04 g).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.29 (1H, d), 8.19 (1H, d), 7.22 (5H, m), 4.19 (1H, m), 3.28 (1H, m), 2.94 (6H, m), 1.73 (2H, m).

LCMS (electrospray): m/z $[M+H]^+$ 330

**Preparation 48 : *Syn*-2-(4-Fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclohexyl}-nicotinamide**

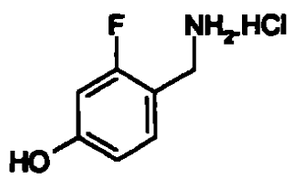


A solution of *syn*-N-(4-amino-cyclohexyl)-2-(4-fluoro-phenoxy)-nicotinamide hydrochloride (300 mg, 0.82 mmol) (see Preparation 47) and triethylamine (110 µl, 0.82 mmol) in dichloromethane (10 ml) was added over 1 hour to a solution of 1,1'-carbonyldiimidazole (399 mg, 2.46 mmol) in dichloromethane (5 ml) under a nitrogen atmosphere. The mixture was stirred for 18 hours and then diluted with water (10 ml). The organic solution was washed with saturated solution of sodium chloride (10 ml) dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane (5:95) to give *syn*-2-(4-Fluoro-phenoxy)-N-{4-[(imidazole-1-carbonyl)-amino]-cyclohexyl}-nicotinamide as a white foam (269 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.61 (1H, d), 8.39 (1H, m), 8.21 (1H, d), 7.99 (1H, d), 7.13 (7H, m), 5.78 (1H, m), 4.23 (1H, m), 4.00 (1H, m), 1.88 (8H, m)

LCMS (electrospray): m/z $[M+H]^+$ 426

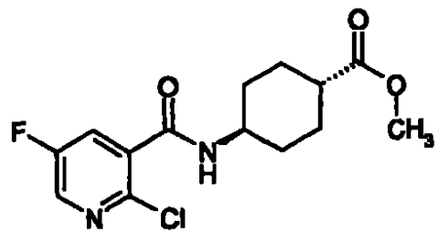
**Preparation 49 : 4-Aminomethyl-3-fluorophenol hydrochloride**




A mixture of 2-fluoro-4-hydroxy-benzonitrile (6 g, 43.8 mmol), palladium hydroxide (600 mg), ethanol (60 ml) and 2N hydrochloric acid (6 ml) was hydrogenated (60 psi) for 18 hours. The mixture was filtered through Arbocel® and the filter cake was washed with methanol and the filtrates were evaporated *in-vacuo*. The residue was triturated with diethylether to give 4-aminomethyl-3-fluoro phenol hydrochloride (4.71 g).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 10.26 (1H, d), 8.30 (1H, s), 7.39 (1H, m), 6.63 (2H, m), 3.94 (2H, d).

**Preparation 50 : *Anti*-4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid methyl ester**



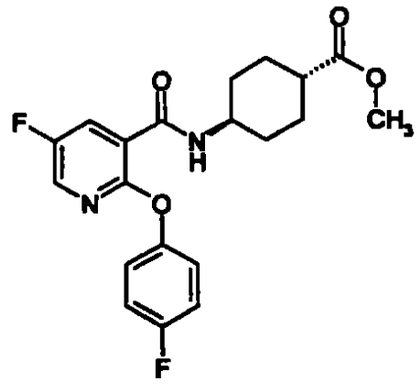
2-Chloro-5-fluoro nicotinic acid (3 g, 17 mmol, see Preparation 41), 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (4.26 g, 22 mmol) and 1-hydroxybenzotriazole hydrate (3.46 g, 26 mmol) were stirred in N,N-dimethylformamide(20 ml) for 30 minutes. *Anti*-4-amino-cyclohexanecarboxylic acid methyl ester hydrochloride (3.31 g, 17 mmol, see Reference J. Med. Chem. 1977, 20(2), 279) and 4-methyl morpholine (3.76 ml, 34 mmol) were added and the mixture was stirred at room temperature for 18 hours. The mixture was partitioned between water and ethyl acetate and the organic solution was washed with a saturated solution of sodium chloride, dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 3:97) the material isolated was dried *in-vacuo* to give *anti*-4-[(2-chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid methyl ester as a solid (4.23 g).

$^1$H NMR (300MHz, $CDCl_3$): δ 8.32 (1H, d), 7.83 (1H, m), 6.44 (1H, d), 3.96 (1H, m), 3.69 (3H, s), 2.16 (5H, m), 1.63 (2H, m), 1.33 (2H, m).

LCMS (electrospray): m/z $[M-H]^-$ 313

122
123

**Preparation 51 : *Anti*-4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid methyl ester**

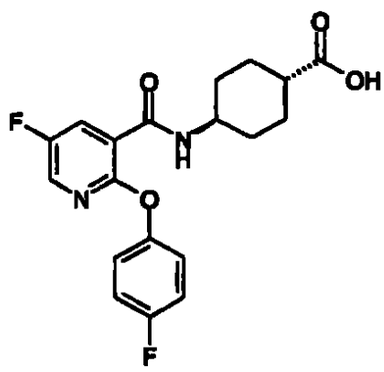


*Anti*-4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid methyl ester (4.22 g, 13 mmol, see Preparation 50) was added to a mixture of 4-fluorophenol (1.5 g, 13 mmol) and caesium carbonate (8.71 g, 27 mmol) in N,N-dimethylformamide (30 ml) and was stirred under a nitrogen atmosphere at 60°C for 18 hours. The mixture was partitioned between water and ethyl acetate and the organic solution was washed with a saturated solution of sodium chloride, dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 2:98) the material isolated was dried *in-vacuo* to give *anti*-4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid methyl ester as a solid (3.71 g).

$^1$H NMR (300MHz, $CDCl_3$): δ 8.36 (1H, m), 8.02 (1H, d), 7.72 (1H, d), 7.14 (4H, m), 4.00 (1H, m), 3.70 (3H, s), 2.22 (3H, m), 1.67 (2H, m), 1.30 (2H, m).

LCMS (thermospray): m/z $[M]^+$ 390

**Preparation 52 : *Anti*-4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid**

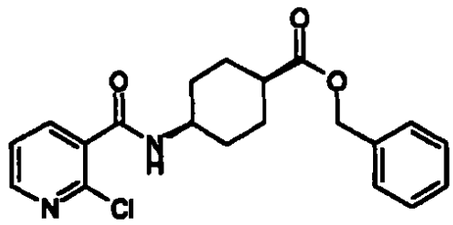


*Anti*-4-{[5-Fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexane-carboxylic acid methyl ester (3.7 g, 9.48 mmol, see Preparation 52) was dissolved in a mixture of tetrahydrofuran (40 ml) and 1M lithium hydroxide solution (19 ml, 19 mmol) and was stirred under a nitrogen atmosphere for 18 hours. 2N Hydrochloric acid (10 ml) was added and the mixture was extracted with dichloromethane (3 fold). The combined organic solutions were washed with saturated solution of sodium chloride dried over magnesium sulphate and evaporated *in-vacuo*. The residue was triturated with diethylether and the solid obtained was dried *in-vacuo* to give *anti*-4-{[5-fluoro-2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid (2.45g).

$^1$H NMR (300MHz, $CDCl_3$): δ 12.0 (1H, s), 8.29 (1H, d), 8.20 (1H, d), 7.95 (1H, d), 7.21 (4H, m), 3.70 (1H, m), 2.17 (1H, m), 1.91 (4H, m), 1.34 (4H, m).

LCMS (thermospray): m/z $[M]^+$ 376

**Preparation 53 : *Syn*-4-[(2-Chloro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid benzyl ester**

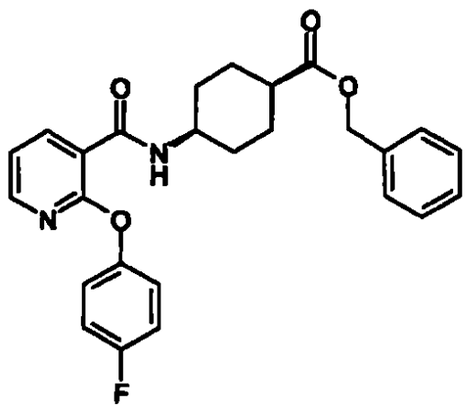


2-Chloronicotinic acid (2 g, 12.69 mmol) was suspended in dichloromethane (320 ml) under a nitrogen atmosphere, oxalyl chloride (3.32 ml, 38 mmol) was added and then one drop of N,N-dimethylformamide was added and the mixture was stirred for 3 hours. The solvent was evaporated *in-vacuo* and the residue was dissolved in dichloromethane (110 ml). A solution of *syn*-4-amino-cyclohexanecarboxylic acid benzyl ester tosylate (6.18 g, 15.23 mmol, see preparation 62) and triethylamine (5.31 ml, 38 mmol) in dichloromethane (50 ml) was added and the mixture was stirred under a nitrogen atmosphere for 18 hours. The reaction mixture was washed with water (2-fold 100 ml), then saturated solution of sodium chloride (100 ml), dried over magnesium sulphate and evaporated *in-vacuo*. The residue was dissolved in dichloromethane (50 ml), washed with citric acid solution (50 ml), dried with saturated solution of sodium chloride and evaporated *in-vacuo* to give *syn*-4-[(2-chloro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid benzyl ester as an orange solid (4.80 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.43 (1H, m), 8.06 (1H, m), 7.31 (6H, m), 6.44 (1H, m), 5.11 (2H, s), 4.16 (1H, m), 2.37 (1H, m), 1.94 (2H, m), 1.73 (6H, m).

LCMS (electrospray): m/z $[M+Na]^+$ 395, 397

**Preparation 54 : *Syn*-4-[[2-(4-Fluoro-phenoxy)-pyridine-3-carbonyl]-amino]-cyclohexanecarboxylic acid benzyl ester**

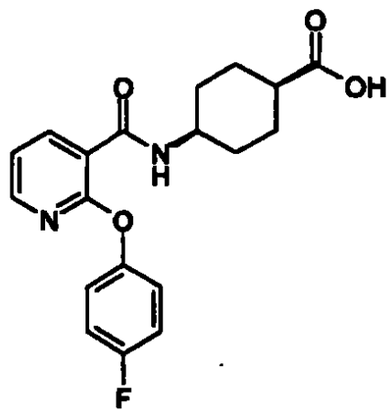


*Syn*-4-[(2-chloro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid benzyl ester (2 g, 5.36 mmol, see Preparation 53) was added to a mixture of 4-fluorophenol (661 mg, 5.90 mmol) and caesium carbonate (3.495 g, 10.72 mmol) in N,N-dimethylformamide (20 ml) and was stirred under a nitrogen atmosphere at 55°C for 18 hours. The mixture was partitioned between water (20 ml) and ethyl acetate (30 ml) the organic solution was washed with a saturated solution of sodium chloride (20 ml), dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 1:99) to give *syn*-4-{[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid benzyl ester as white solid (1.078 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.78 (1H, d), 8.17 (1H, d), 7.91 (1H, d), 7.28 (5H, m), 7.10 (5H, m), 5.04 (2H, s), 4.20 (1H, m), 2.52 (1H, m), 1.80 (8H, m).

LCMS (electrospray): m/z $[M+Na]^+$449

**Preparation 55 : *Syn*-4-{[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid**



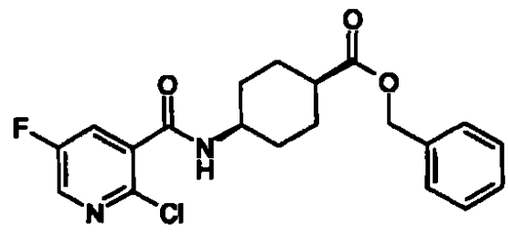
10% Palladium on carbon (250 mg) was added to *syn*-4-[(2-chloro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid benzyl ester (1.07 g, 5.36 mmol, see Preparation 54) in methanol (25 ml). The mixture was hydrogenated at 60 psi for 30 minutes and then was filtered through Arbocel®. The filter cake

was washed with methanol and the combined filtrates were evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane (gradient from 0:100 to 1:99) to give *syn*-4-[(2-chloro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid as a white powder (363 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.39 (1H, d), 8.24 (1H, d), 8.17 (1H, d), 7.16 (5H, m), 4.10 (1H, m), 2.48 (1H, m), 1.89 (2H, m), 1.77 (6H, m)

LCMS (thermospray): m/z $[M]^+$ 359

**Preparation 56 : *Syn*-4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid benzyl ester**



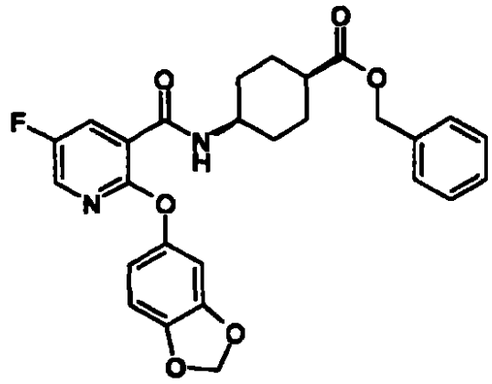
2-Chloro-5-fluoronicotinic acid (1 g, 5.7 mmol, see Preparation 41) was suspended in dichloromethane (80 ml) under a nitrogen atmosphere, oxalyl chloride (1.49 ml, 17.1 mmol) was added and then one drop of N,N-dimethylformamide was added and the mixture stirred for 1.25 hours. The solvent was evaporated *in-vacuo* and the residue was dissolved in dichloromethane (60 ml). A suspension of 4-amino-cyclohexanecarboxylic acid benzyl ester tosylate (2.77 g, 6.84 mmol, see preparation 62) and triethylamine (2.38 ml, 17.1 mmol) in dichloromethane (20 ml) was added and the mixture was stirred under a nitrogen atmosphere for 18 hours. The mixture was washed with water (2-fold 75 ml) a saturated solution of sodium chloride (100 ml), dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane as eluant (gradient from 0:100 to 1:99) to give *syn*-4-[(2-chloro-5-fluoro-pyridine-3-

carbonyl)-amino]-cyclohexanecarboxylic acid benzyl ester as an orange solid (2.18g).

$^1$H NMR (400MHz, $CD_3OD$): δ 8.30 (1H, d), 7.87 (1H, m), 7.33 (5H, m), 6.64 (1H, s), 5.12 (2H, s), 4.14 (1H, m), 2.55 (1H, m), 1.93 (2H, m), 1.79 (4H, m), 1.68 (2H, m).

LCMS (thermospray): m/z $[M+NH_4]^+$ 408

**Preparation 57 : *Syn*-4-[[2-(Benzo[1.3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid benzyl ester**

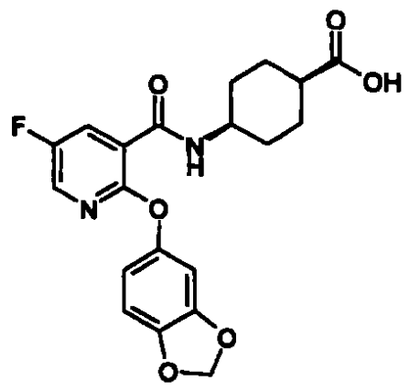


Caesium carbonate (3.38 g, 10.38 mmol) and 3,4-methylenedioxyphenol (78 mg, 5.71 mmol) were added to a solution of *syn*-4-[(2-chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexanecarboxylic acid benzyl ester (2.03 g, 5.19 mmol, see Preparation 56) in N,N-dimethylformamide (20 ml) and the mixture was stirred under a nitrogen atmosphere for 18 hours at 55°C. The mixture was partitioned between water (30 ml) and ethyl acetate (30 ml) the organic solution was washed with a saturated solution of sodium chloride (30 ml), dried over magnesium sulphate and evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using dichloromethane as eluant to give *syn*-4-[[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexane-carboxylic acid benzyl ester as an orange solid (2.07 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.34 (1H, m), 8.06 (1H, m),8.00 (1H, m), 7.31 (5H, m), 6.80 (1H, d), 6.65 (1H, m), 6.59 (1H, m), 6.00 (2H, s), 5.09 (2H, s), 4.19 (1H, m), 2.34 (1H, m),1.80 (8H, m).

LCMS (electrospray): m/z $[M+Na]^+$ 515

**Preparation 58 : *Syn*-4-{[2-(Benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid**

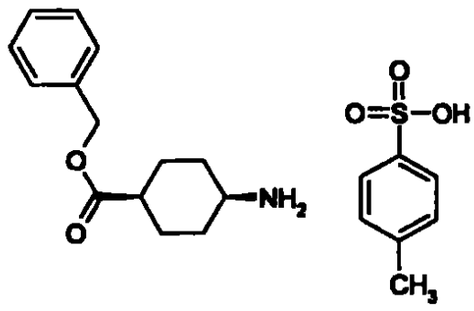


10% Palladium on carbon (50 mg) was added to *syn*-4-{[2-(4-fluoro-phenoxy)-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid benzyl ester (200 mg, 0.406 mmol, see Preparation 57) in methanol (5 ml). The mixture was hydrogenated at 60 psi for 2 hours and then was filtered through Arbocel®. The filter cake was washed with methanol and the combined filtrates were evaporated *in-vacuo*. The residue was purified by chromatography on silica gel using methanol in dichloromethane (2:98) to give *syn*-4-{[2-(benzo[1,3]dioxol-5-yloxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexanecarboxylic acid as a white solid (50 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8.30 (1H, m), 8.01 (2H, m), 6.79 (1H, d), 6.66 (1H, d), 6.57 (1H, m), 5.97 (2H, s), 4.18 (1H, m), 2.53 (1H, m), 1.79 (8H, m).

LCMS (electrospray): m/z $[M+Na]^+$ 425

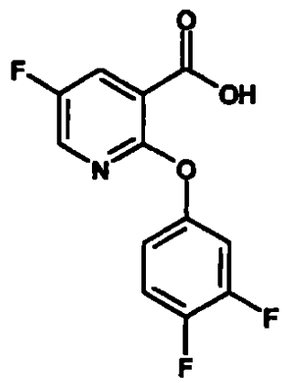
**Preparation 59 : *Syn*-4-Amino-cyclohexanecarboxylic acid benzyl ester tosylate**



4-Amino-cyclohexanecarboxylic acid (10 g, 69.9 mmol) was dissolved in 1N hydrochloric acid (70 ml, 70 mmol) and the mixture was evaporated *in-vacuo*. The residue was dried by toluene azeotrope (2-fold 50 ml). Benzyl alcohol (36 ml, 0.25 mol), toluene (220 ml) and p-toluenesulphonic acid hydrate (15.9 g, 83.6 mmol) were added and the mixture was heated at reflux for 24 hours using a Dean and Starke trap. The reaction mixture was cooled to room temperature and diethyl ether (100 ml) was added. The solid formed was isolated by filtration and washed with diethyl ether and then dried *in-vacuo* at 40°C to give the title compound (27.3g).

LCMS (electrospray): m/z $[M+Na]^+$ 283

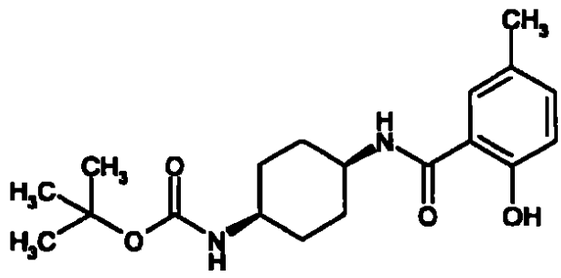
**Preparation 60: 2-(3,4-Difluoro-phenoxy)-5-fluoro-nicotinic acid**



A solution of 3,4-difluorophenol (29.25 g, 225 mmol) in dioxan (300 ml) was dried over magnesium sulphate, then filtered. Ethyl-2-chloro-5-fluoro-nicotinoate (J. Med. Chem., 1993, 36(18), 2676-88) (30.6 g, 150 mmol) and freshly dried cesium carbonate (73.2 g, 225 mmol) were added and the reaction stirred under reflux for 18 hours. The cooled mixture was concentrated in vacuo, the residue partitioned between water (1500 ml) and ether (1500 ml), and the layers separated. The aqueous phase was further extracted with ether and the combined organic solutions were washed with saturated sodium bicarbonate solution, water, then brine, dried over magnesium sulphate and evaporated in vacuo to give a brown oil (48.3 g). A mixture of this intermediate ester and 1N lithium hydroxide solution (450 ml), in tetrahydrofuran (450 ml), was stirred vigorously at room temperature for 18 hours. The tetrahydrofuran was removed in vacuo and the residual aqueous solution was acidified to pH 5 using 2N hydrochloric acid (ca. 150 ml). The solution was washed with ether (2-fold) and then further acidified by the addition of more 2N hydrochloric acid (150 ml). The resulting precipitate was filtered off and dried to afford the title compound as a white solid (25.92 g).

1H NMR (400 MHz, $CD_3OD$): δ 6.94 (1H, m), 7.10 (1H, m), 7.25 (1H, dd), 8.14 (2H, m).

**Preparation 61: syn-[4-(2-Hydroxy-5-methyl-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester**



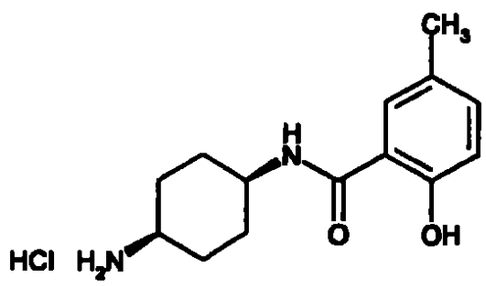
Hünig's base (8.72 g, 67.5 mmol) followed by 1-hydroxybenzotriazole hydrate (6.99 g, 51.75 mmol) were added to a solution of the amine from preparation 42B (9.64 g, 45 mmol) in dichloromethane (110 ml), and the suspension stirred

for 5 minutes. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.22 g, 58.5 mmol) followed by 5-methyl salicylic acid (6.33 g, 41.6 mmol) were then added portionwise, and the reaction stirred at room temperature for 48 hours. The mixture was diluted with dichloromethane (200 ml), and washed with water (250 ml). The aqueous layer was acidified to pH 3 using 2M hydrochloric acid and re-partitioned with the organic layer. This organic phase was separated, washed with water, dried over magnesium sulphate and evaporated *in vacuo*. The residual orange oil was triturated with ethyl acetate and then ether, the resulting solid filtered off, washed with ether and dried under vacuum to afford the title compound as a white crystalline solid, (9.95 g).

$^1$H NMR (400 MHz, DMSO$d_6$ ): δ 1.38 (9H, s), 1.55 (4H, m), 1.67 (4H, m), 2.22 (3H, s), 3.40 (1H, m), 3.82 (1H, m), 6.66 (1H, m), 6.75 (1H, s), 7.15 (1H, d), 7.69 (1H, s), 8.38 (1H, d), 12.08 (1H, s).

LCMS (electrospray): m/z $[M+Na]^+$ 371

**Preparation 62: syn- N-(4-Amino-cyclohexyl)-2-hydroxy-5-methyl-benzamide hydrochloride**

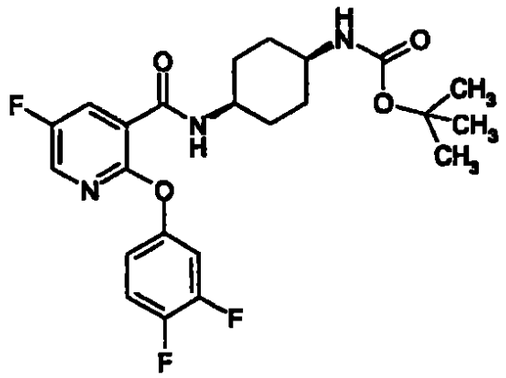



A solution of the protected amine from preparation 61 (9.8 g, 28.1 mmol) in dry dichloromethane (600 ml) was cooled to 4°C, and purged with nitrogen. This solution was saturated with hydrogen chloride gas, and then stirred for a further 3 hours. The mixture was concentrated *in vacuo*, and the residue azeotroped with dichloromethane. The product was triturated with ether, and the resulting solid filtered off, and dried to afford the title compound (7.6 g).

$^1$H NMR (400 MHz, DMSO$d_6$ ): δ 1.55-1.92 (8H, m), 2.10 (3H, s), 3.10 (1H, m), 3.90 (1H, m), 6.80 (1H, d), 7.15 (1H, d), 7.73 (1H, s), 8.00 (3H, s), 8.35 (1H, s), 11.35 (1H, s).

LCMS (electrospray): m/z $[M+H]^+$ 249

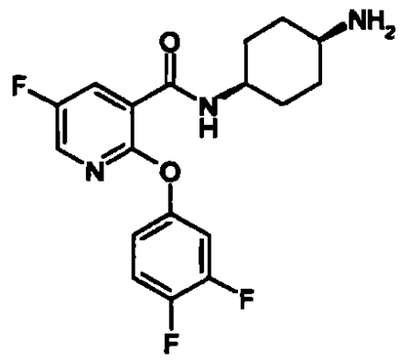
**Preparation 63: *syn*-(4-{[2-(3,4-Difluoro-phenoxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester**



*Syn*-[4-[(2-Chloro-5-fluoro-pyridine-3-carbonyl)-amino]-cyclohexyl]-carbamic acid tert-butyl ester (500 mg, 1.35 mmol, see preparation 43) was mixed with 3,4-difluorophenol (280 mg, 2 mmol) and caesium carbonate (2.2 g, 6.7 mmol) in N-methylpyrrolidinone (10 ml) and was heated to 80°C for 16 hours. The reaction mixture was cooled to room temperature and the solvent was concentrated *in-vacuo*. The residue was dissolved in 1N sodium hydroxide solution and the solution was extracted with ethyl acetate (4-fold 25 ml). The combined organic solutions were washed with 10% citric acid solution (2-fold 20 ml) and brine (20 ml), then dried over magnesium sulphate and concentrated *in-vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (50:50) to give *syn*-(4-{[2-(3,4-difluoro-phenoxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester as a white solid (340 mg).

LCMS (electrospray): *m/z* $[M+H]^+$ 466

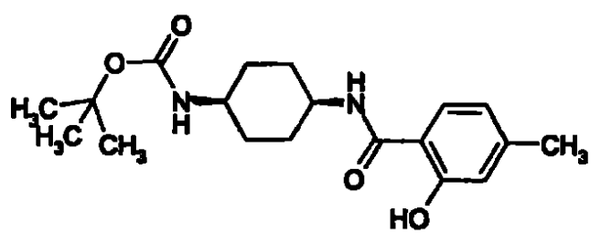
**Preparation 64: *syn*-N-(4-Amino-cyclohexyl)-2-(3,4-difluoro-phenoxy)-5-fluoro-nicotinamide**



*Syn*-(4-{[2-(3,4-Difluoro-phenoxy)-5-fluoro-pyridine-3-carbonyl]-amino}-cyclohexyl)-carbamic acid tert-butyl ester (11.25 g, 24.2 mmol, see preparation 63) was dissolved in dichloromethane (200 ml) at 0°C. Hydrogen chloride gas was bubbled into the solution with stirring for 45 minutes and the mixture was stirred at 0°C for a further 20 minutes. The reaction mixture was concentrated *in-vacuo* and the residue was dissolved in 1N sodium hydroxide solution. The aqueous solution was extracted with dichloromethane. The phases were separated and the organic solution was dried over magnesium sulphate and concentrated *in-vacuo* to give *syn*-N-(4-amino-cyclohexyl)-2-(3,4-difluoro-phenoxy)-5-fluoro-nicotinamide (7.36 g).

LCMS (electrospray): *m/z* $[M+H]^+$ 366

**Preparation 65: *syn*-[4-(2-Hydroxy-4-methyl-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester**

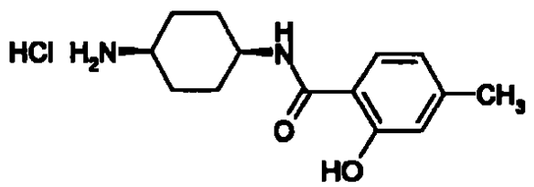


4-Methylsalycilic acid (3.5 g, 23 mmol) was added to a mixture of the *syn*-(4-amino-cyclohexyl)-carbamic acid tert-butyl ester (5.35 g, 25 mmol, see

preparation 42-b) 1-hydroxybenzotriazole hydrate (3.88 g, 28.8 mmol) 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (6.23 g, 32.5 mmol) and diisopropylethylamine (4.84 g, 37.5 mmol) in dichloromethane (65 ml). The mixture was stirred at room temperature for 72 hours and was diluted with dichloromethane (100 ml). Water (150 ml) was added and the aqueous layer was acidified to pH 3 by addition of 2M hydrochloric acid. The phases were separated and the organic phase was washed with water (2-fold 100 ml) and dried over magnesium sulphate. The organic solution was concentrated *in-vacuo* and the residue was triturated with hot ethyl acetate to give *syn*-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester (5.2 g).

LCMS (electrospray): *m/z* $[M+Na]^+$ 371

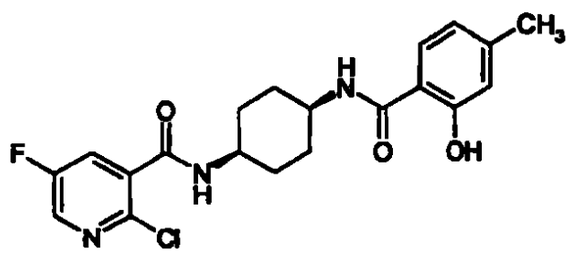
**Preparation 66: *syn*-N-(4-Amino-cyclohexyl)-2-hydroxy-4-methyl-benzamide hydrochloride**




*Syn*-[4-(2-Hydroxy-4-methyl-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester (5.1 g, 14.6 mmol, see Preparation 65) was suspended in dichloromethane (400 ml) and was cooled to 0°C. The mixture was purged under nitrogen and hydrogen chloride gas was bubbled into the mixture for 10 minutes to give a saturated solution. The reaction mixture was stirred at 4°C for 3 hours and then concentrated *in-vacuo*. The residue was co-evaporated with dichloromethane (2 fold) and triturated with diethyl ether. The material obtained was isolated by filtration and was washed with diethyl ether to give *syn*-N-(4-amino-cyclohexyl)-2-hydroxy-4-methyl-benzamide hydrochloride as a white solid (4.21 g).

LCMS (electrospray): *m/z* $[M+H]^+$ 249

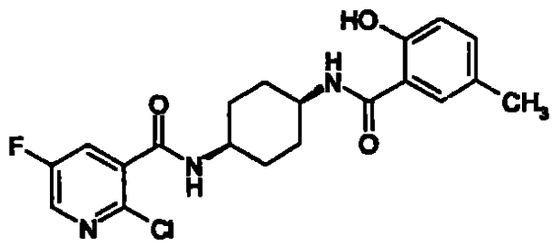
**Preparation 67: *syn*-2-Chloro-5-fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide**



1-(3-Dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (1.68 g, 5.85 mmol) was added to *syn*-N-(4-amino-cyclohexyl)-2-hydroxy-4-methyl-benzamide hydrochloride (2 g, 7.02 mmol)(see preparation 66), 2-chloro-5-fluoronicotinic acid (1.03 g, 5.85 mmol, see preparation 41), 1-hydroxybenzotriazole hydrate (0.95 g, 7.02 mmol) and diisopropylethylamine (4.6 ml, 26.3 mmol) in dichloromethane (50 ml) and the mixture was stirred at room temperature under a nitrogen atmosphere for 16 hours. Additional 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (0.56 g, 2.9 mmol) was added and the mixture was stirred for a further 2 hours. The reaction mixture was partitioned between 1N hydrochloric acid and dichloromethane. The phases were separated and the aqueous layer was extracted with dichloromethane (2 fold). The combined organic solutions were dried over magnesium sulphate and concentrated *in-vacuo*. The material obtained was recrystalised from isopropyl acetate to give *syn*-2-chloro-5-fluoro-N-[4-(2-hydroxy-4-methyl-benzoylamino)-cyclohexyl]-nicotinamide as a white solid (1.3 g).

LCMS (electrospray): *m/z* $[M+H]^+$ 406

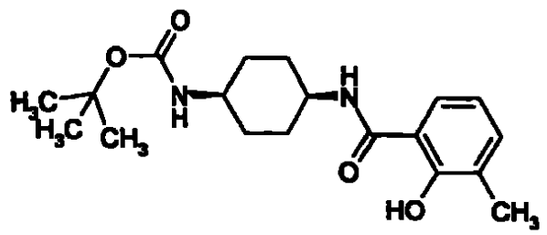
**Preparation 68: *syn*-2-Chloro-5-fluoro-N-[4-(2-hydroxy-5-methyl-benzoylamino)-cyclohexyl]-nicotinamide**



1-(3-Dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (245 mg, 3.9 mmol) was added to a mixture of *syn*-N-(4-amino-cylcohexyl)-2-hydroxy-5-methyl-benzamide hydrochloride (1 g, 3.5 mmol, see preparation 62), 1-hydroxybenzotriazole hydrate (492 mg, 3.7 mmol), 2-chloro-5-fluoronicotinic acid (0.65 g, 3.7 mmol, see preparation 41), and triethylamine (0.96 ml, 8.75 mmol) in N,N-dimethylformamide (20 ml) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in-vacuo* and the residue was partitioned between ethyl acetate and water. The layers were separated and the organic layer was dried over magnesium sulphate and concentrated *in-vacuo* to give *syn*-2-chloro-5-fluoro-N-[4-(2-hydroxy-5-methyl-benzoylamino)-cyclohexyl]-nicotinamide (1 g).

LCMS (electrospray): *m/z* $[M+H]^+$ 406

**Preparation 69: *syn*-[4-(2-Hydroxy-3-methyl-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester**

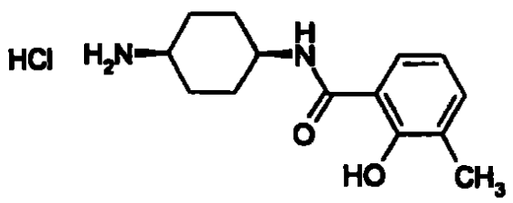


3-Methylsalycilic acid (2.74 g, 18 mmol) was added to a mixture of the *syn*-(4-amino-cyclohexyl)-carbamic acid tert-butyl ester (4.28 g, 20 mmol, see preparation 42-b) 1-hydroxybenzotriazole hydrate (3.19 g, 24 mmol) 1-(3-

dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (4.97 g, 26 mmol) and diisopropylethylamine (3.87 g, 30 mmol) in dichloromethane (45 ml). The mixture was stirred at room temperature for 40 hours and was partitioned between dichloromethane and water (75 ml). The aqueous layer was extracted with dichloromethane and the combined organic phases dried over magnesium sulphate and concentrated *in-vacuo*. The material obtained was isolated by filtration to give *syn*-[4-(2-hydroxy-3-methyl-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester (1.14 g)

LCMS (electrospray): *m/z* $[M+H]^+$ 349

**Preparation 70: *syn*-N-(4-Amino-cyclohexyl)-2-hydroxy-3-methyl-benzamide hydrochloride**

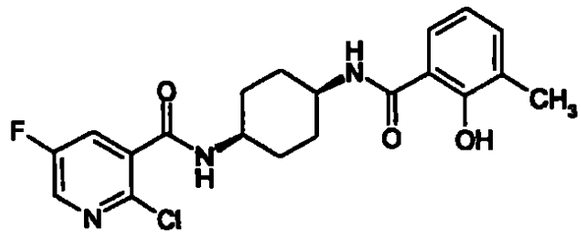



*syn*-[4-(2-Hydroxy-3-methyl-benzoylamino)-cyclohexyl]-carbamic acid tert-butyl ester (1.14 g, 3.3 mmol, see preparation 69) was suspended in dichloromethane (17 ml) and was cooled to 0°C. Hydrogen chloride gas was bubbled into the mixture for 20 minutes and the mixture was warmed to room temperature and was stirred for 16 hours. Hydrogen chloride was bubbled into the mixture for a further 15 minutes and the mixture was stirred at room temperature for 15 minutes. Methanol was added to the reaction mixture and the solvent was concentrated *in-vacuo* to give *syn*-N-(4-amino-cyclohexyl)-2-hydroxy-3-methyl-benzamide hydrochloride (0.96 g).

LCMS (electrospray): *m/z* $[M+H]^+$ 249

130
131

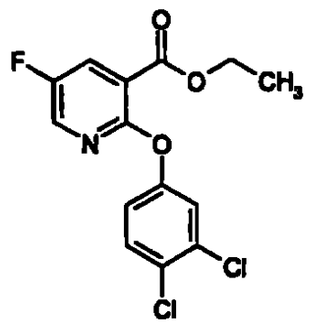
**Preparation 71: *syn*-2-Chloro-5-fluoro-N-[4-(2-hydroxy-3-methyl-benzoylamino)-cyclohexyl]-nicotinamide**



1-(3-Dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (0.81 g, 4.24 mmol) was added to a mixture of *syn*-N-(4-amino-cyclohexyl)-2-hydroxy-3-methyl-benzamide hydrochloride (0.96 g, 3.4 mmol, see preparation 70), 1-hydroxybenzotriazole hydrate (459 mg, 3.4 mmol), 2-chloro-5-fluoronicotinic acid (497 mg, 2.8 mmol, see preparation 41), and diisopropylamine (2.2 ml, 12.7 mmol) in dichloromethane (20 ml) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in-vacuo* and the residue was partitioned between dichloromethane and water. The layers were separated and the organic layer was washed with 10% citric acid solution, dried over magnesium sulphate and concentrated *in-vacuo* to give *syn*-2-chloro-5-fluoro-N-[4-(2-hydroxy-3-methyl-benzoylamino)-cyclohexyl]-nicotinamide (0.71 g).

LCMS (electrospray): *m/z* $[M+H]^+$ 406

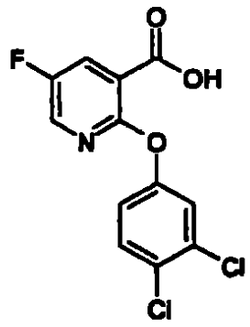
**Preparation 72: 2-(3,4-Dichloro-phenoxy)-5-fluoro-nicotinic acid ethyl ester**



Ethyl 2-chloro-5-fluoronicotinate (5.09 g, 25 mmol, see reference J. Med. Chem., 1993, 36(18) 267-88) and 3,4-dichlorophenol (6.11g, 37.5 mmol) were dissolved in 1,4-dioxane and the solution was purged with argon. Anhydrous caesium carbonate (12.21 g, 37.5 mmol) was added and the mixture was heated under reflux for 17 hours. The reaction mixture was partitioned between water (300 ml) and ethyl acetate (300 ml). The aqueous layer was acidified to pH 3 by addition of 2M hydrochloric acid and the phases were separated. The aqueous layer was extracted with ethyl acetate (2-fold 100 ml) and the combined organic solutions were dried over magnesium sulphate and concentrated *in-vacuo* to give a red oil. The material isolated was redissolved in ethyl acetate and was washed with 5% potassium carbonate solution (2-fold 200 ml), 0.5 M sodium hydroxide solution (2-fold 200 ml) and saturated sodium hydrogen carbonate solution (100 ml). The organic phase was dried over magnesium sulphate and concentrated *in-vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (4:96) to give 2-(3,4-dichloro-phenoxy)-5-fluoro-nicotinic acid ethyl ester as a colourless oil that crystallised on standing (4.95 g).

LCMS (electrospray): *m/z* $[M+Na]^+$ 352

**Preparation 73: 2-(3,4-Dichloro-phenoxy)-5-fluoro-nicotinic acid**

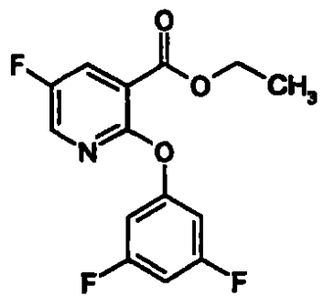



2-(3,4-Dichloro-phenoxy)-5-fluoro-nicotinic acid ethyl ester (4.9 g, 14.8 mmol, see preparation 72) was dissolved in tetrahydrofuran (50 ml). Water (27 ml) and lithium hydroxide (1.56 g, 37.1 mmol) were added and the mixture was stirred vigorously for 7 hours. The reaction mixture was acidified to pH5 by addition of

2 M hydrochloric acid and the mixture was partitioned between ethyl acetate (200 ml) and water (200 ml). The aqueous layer was acidified to pH 3 by addition of 2 M hydrochloric acid and the phases were separated. The aqueous phase was extracted with ethyl acetate (2-fold 50 ml) and the combined organic solutions were dried over magnesium sulphate and concentrated *in-vacuo* to give 2-(3,4-dichloro-phenoxy)-5-fluoro-nicotinic acid as a white solid (4.4 g).

LCMS (electrospray): *m/z* $[M+Na]^+$ 348

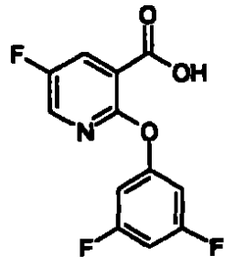
**Preparation 74: 2-(3,5-Difluoro-phenoxy)-5-fluoro-nicotinic acid ethyl ester**



The title compound was prepared from ethyl 2-chloro-5-fluoronicotinate and 3,5-difluorophenol in 23% yield following the procedure described in preparation 72.

LCMS (electrospray): *m/z* $[M+Na]^+$ 371

**Preparation 75: 2-(3,5-Difluoro-phenoxy)-5-fluoro-nicotinic acid**

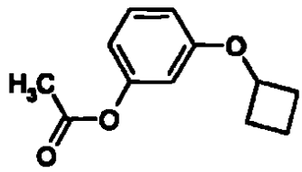


2-(3,4-Dichloro-phenoxy)-5-fluoro-nicotinic acid ethyl ester (0.68 g, 2.25 mmol, see Preparation 74) was dissolved in tetrahydrofuran (8 ml). Water (4.5 ml) and lithium hydroxide (239 mg, 5.7 mmol) were added and the mixture was stirred

vigorously for 7 hours. The reaction mixture was acidified to pH 5 by addition of 2 M hydrochloric acid and the mixture was partitioned between ethyl acetate (50 ml) and water (50 ml). The aqueous layer was acidified to pH 3 by addition of 2 M hydrochloric acid and the phases were separated. The aqueous phase was extracted with ethyl acetate (2-fold 25 ml) and the combined organic solutions were dried over magnesium sulphate and concentrated *in-vacuo* to give 2-(3,5-difluoro-phenoxy)-5-fluoro-nicotinic acid as a white solid (0.57 g).

LCMS (electrospray): *m/z* $[M-H]^-$ 268

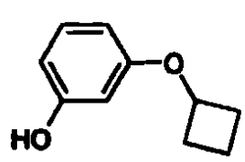
**Preparation 76: Acetic acid 3-cyclobutoxy-phenyl ester**



Acetic acid 3-hydroxy-phenyl ester (1 ml, 9 mmol) was mixed with cyclobutanol (0.58 g, 8 mmol), triphenylphosphine (2.1 g, 8 mmol) and diisopropyl azodicarboxylate (1.57 ml, 8 mmol) in tetrahydrofuran (20 ml) at 0°C under a nitrogen atmosphere. The mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was concentrated *in-vacuo* the residue was purified by chromatography on silica gel using ethyl acetate in pentane as eluant (gradient from 0:100 to 15:85) to give acetic acid 3-cyclobutoxy-phenyl ester (340 mg).

LCMS (electrospray): *m/z* $[M+H]^+$ 207

**Preparation 77: 3-Cyclobutoxy-phenol**



Acetic acid 3-cyclobutoxy-phenyl ester (340 mg, 1.65 mmol) was dissolved in methanol (6 ml) and 1 M sodium hydroxide solution (2 ml, 2 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours and then was acidified with 2 M hydrochloric acid. The reaction mixture was extracted with ethyl acetate and the organic solution was dried over magnesium sulphate and concentrated *in-vacuo* to give 3-cyclobutoxy-phenol (300 mg).

LCMS (electrospray): *m/z* $[M+H]^+$ 165

***In vitro* activity of the nicotinamide derivatives**

The PDE4 inhibitory activity of the nicotinamide derivatives of the formula (1) is determined by the ability of compounds to inhibit the hydrolysis of cAMP to AMP by PDE4 (see also reference 1). Tritium labelled cAMP is incubated with PDE4. Following incubation, the radiolabelled AMP produced is able to bind ytrium silicate SPA beads. These SPA beads subsequently produce light that can be quantified by scintillation counting. The addition of a PDE4 inhibitor prevents the formation of AMP from cAMP and counts are diminished. The $IC_{50}$ of a PDE4 inhibitor can be defined as the concentration of a compound that leads to a 50% reduction in counts compared to the PDE4 only (no inhibitor) control wells.

The anti-inflammatory properties of the nicotinamide derivatives of the formula (1) are demonstrated by their ability to inhibit TNFα release from human peripheral blood mononuclear cells (see also reference 2). Venous blood is collected from healthy volunteers and the mononuclear cells purified by centrifugation through Histopaque (Ficoll) cushions. TNFα production from these cells is stimulated by addition of lipopolysaccharide. After 18 hours incubation in the presence of LPS, the cell supernatant is removed and the concentration of TNFα in the supernatant determined by ELISA. Addition of PDE4 inhibitors reduces the amount of TNFα produced. An $IC_{50}$ is determined which is equal to the concentration of compound that gives 50% inhibition of TNFα production as compared to the LPS stimulated control wells.

All the examples were tested in the assay described above and found to have an $IC_{50}$ (TNFα screen) of less than 300 nM. And for most of the tested compounds, they were found to have an $IC_{50}$ (TNFα screen) of even less than 100 nM.

For illustrating purpose, the following table indicates the exact $IC_{50}$ (TNFα screen) of some representative examples of the present invention :

| Example N° | $IC_{50}$ (nM) | Example N° | $IC_{50}$ (nM) |
|---|---|---|---|
| 6 | 23.5 | 8 | 22 |
| 14 | 13 | 16 | 0.28 |
| 17 | 8.5 | 20 | 113 |
| 22 | 156 | 23 | 7.8 |
| 25 | 8.5 | 26 | 5.4 |
| 27 | 39.5 | 28 | 217 |
| 30 | 2.6 | 41 | 4.9 |
| 44 | 91 | 47 | 0.28 |
| 48 | 1.66 | 51 | 2.09 |
| 54 | 2.8 | 56 | 1.9 |
| 57 | 13 | 58 | 3.5 |
| 66 | 18.3 | 69 | 49 |
| 72 | 1.1 | 76 | 49 |
| 79 | 25.5 | 80 | 7.4 |
| 81 | 30 | 85 | 28 |
| 88 | 114 | 91 | 37 |
| 92 | 185 | 93 | 5 |
| 95 | 3.2 | 97 | 30 |
| 100 | 56 | 106 | 3.6 |
| 110 | 14 | 116 | 25 |
| 123 | 21 | 129 | 30 |
| 135 | 74 | 137 | 16 |
| 152 | 0.2 | 12 | 1 |
| 155 | 0.09 | 156 | 0.14 |
| 157 | 2 | 159 | 4.6 |

| | | | |
|---|---|---|---|
| 172 | 4.3 | 173 | 2.1 |
| 174 | 0.014 | 178 | 0.15 |
| 183 | 0.07 | 186 | 0.2 |
| 187 | 0.006 | 190 | 0.06 |
| 193 | 9 | 194 | 0.07 |
| 195 | 0.4 | 197 | 1.8 |
| 199 | 0.7 | 200 | 0.05 |
| 201 | 0.3 | 203 | 7 |
| 204 | 0.3 | 205 | 0.55 |
| 208 | 0.09 | 210 | 13 |
| 213 | 0.2 | 217 | 0.3 |

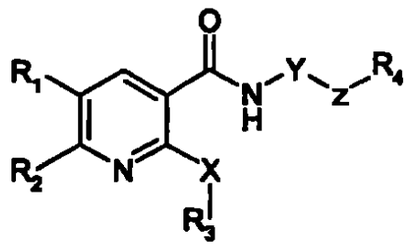
References.

1. Thompson JW, Teraski WL, Epstein PM, Strada SJ., "Assay of nucleotidephosphodiesterase and resolution of multiple molecular forms of the isoenzyme", *Advances in cyclic nucleotides research*, edited by Brooker G, Greengard P, Robinson GA. Raven Press, New York 1979, 10, p. 69-92.

2. Yoshimura T, Kurita C, Nagao T, Usami E, Nakao T, Watanabe S, Kobayashi J, Yamazaki F, Tanaka H, Nagai H., "Effects of cAMP-phosphodiesterase isozyme inhibitor on cytokine production by lipopolysaccharide-stimulated human peripheral blood mononuclear cells", *Gen. Pharmacol.*, 1997, 29(4), p. 63

## CLAIMS

1. A compound of the formula (1) :

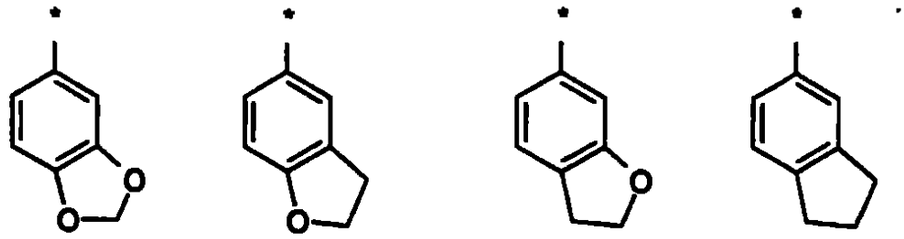


in which :

- ❖ $R_1$ and $R_2$ are each a member independently selected from the group consisting of hydrogen atom, halo, cyano, $(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$alkoxy,
- ❖ X is -O-, -S- or -NH-,
- ❖ $R_3$ is a member selected from the groups consisting of :

(a) phenyl, naphthyl, heteroaryl and $(C_3\text{-}C_8)$cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of halo, cyano, trifluoromethyl, trifluoroethyl, trifluoromethoxy, trifluoroethyloxy, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$thioalkyl, $-C(=O)NH_2$, $-C(=O)NH((C_1\text{-}C_4)\text{alkyl})$, hydroxy, $-O\text{-}C(=O)(C_1\text{-}C_4)$alkyl, $-C(=O)\text{-}O\text{-}(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_8)$cycloalkyl and $(C_3\text{-}C_8)$cycloalkyloxy, or

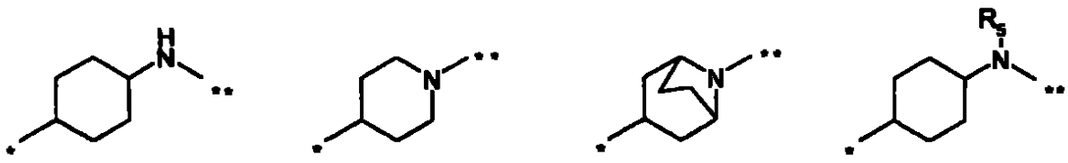
(b) the bicyclic groups conforming to one of the following structures (1.1) to (1.4) :



(1.1) (1.2) (1.3) (1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1) through (1.4) to the remaining portion of formula (1),

- ❖ Y is a member selected from the group consisting of partial formulas (1.5) through (1.8) :

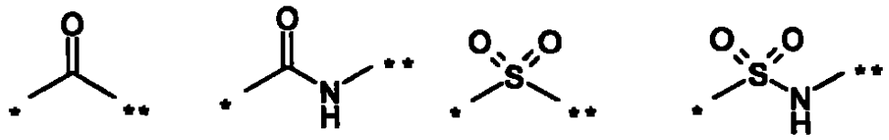


(1.5) (1.6) (1.7) (1.8)

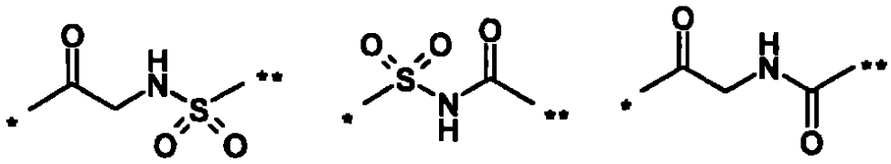
where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a member selected from the groups consisting of $(C_1\text{-}C_4)$alkyl and phenyl$(C_1\text{-}C_4)$alkyl, where said phenyl group is optionally substituted with 1 to 3 substituents each independently selected from the group consisting of halo, cyano, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, hydroxy, hydroxy$(C_1\text{-}C_4)$alkyl, carboxylic acid (-COOH), -C(=O)-O-$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$haloalkyl and –$C(=O)NH_2$,

- Z is a member selected from the group consisting of partial formulas (1.9) through (1.15) :



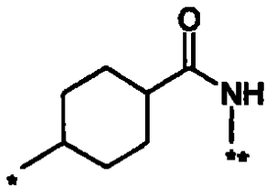
(1.9) (1.10) (1.11) (1.12)



(1.13) (1.14) (1.15)

where the symbol "*" indicates the point of attachment of each partial formula (1.9) through (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.15) to the remaining portions $R_4$ of formula (1),

- or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

- and $R_4$ is a member selected from the groups consisting of :-

(a) phenyl, naphthyl heteroaryl and $(C_3-C_8)$cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (-COOH), $-C(=O)-O-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkyl-COOH, $-(C_1-C_4)$alkyl-$C(=O)-O-(C_1-C_4)$alkyl, halo, cyano, $-C(=O)NH_2$, $-(C_1-C_4)$alkyl, $-(C_1-C_4)$alkoxy, $-(C_1-C_4)$haloalkyl, hydroxy and hydroxy$(C_1-C_4)$alkyl, or

(b) $(C_1-C_8)$alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, $-C(=O)-O-(C_1-C_4)$alkyl, phenyl, naphthyl, heteroaryl or $(C_3-C_8)$cycloalkyl group, where said phenyl, naphthyl, heteroaryl and $(C_3-C_8)$cycloalkyl groups are each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (-COOH), $C(=O)O(C_1-C_4)$alkyl, halo, cyano, $-C(=O)NH_2$, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy, $(C_1-C_4)$haloalkyl, hydroxy and hydroxy$(C_1-C_4)$alkyl,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

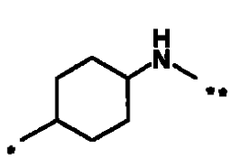
with the proviso that :

1) when :

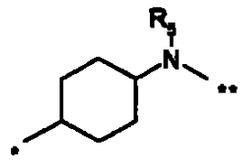
- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,

❖ $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy,

❖ Y is a partial formula (1.5) or (1.8) :



(1.5)



(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1),

and wherein $R_5$ is a member selected from the groups consisting of ($C_1$-$C_4$)alkyl and phenyl($C_1$-$C_4$)alkyl, where said phenyl group is optionally substituted by halo, ($C_1$-$C_3$)alkyl, ($C_1$-$C_3$)alkoxy or hydroxy, and

❖ Z is a radical –C(=O)-

then $R_4$ cannot be :

a) a ($C_3$-$C_8$)cycloalkyl optionally substituted by ($C_1$-$C_3$)alkyl,

b) a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy, or

c) a ($C_1$-$C_8$)alkyl optionally substituted with a hydroxy, or with a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

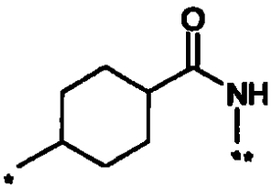
2) and when :

❖ $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,

❖ $R_2$ is a hydrogen atom,

❖ X is -O-,

- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy, and
- Y-Z represents a partial formula (1.16) :



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions –$R_4$ of formula (1),

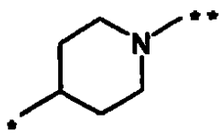
then $R_4$ cannot be :

a) a ($C_3$-$C_8$)cycloalkyl or

b) a ($C_1$-$C_6$)alkyl optionally substituted by a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 or 2 substituent(s) each independently selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy, and
- Y is a partial formula (1.6) :



(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and

- Z is a radical –C(=O)-,

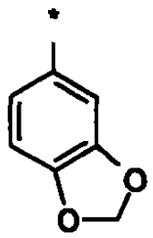
then $R_4$ cannot be a $(C_1\text{-}C_6)$alkyl optionally substituted by a hydroxy, or by a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S.

2. A compound according to claim 1 wherein :

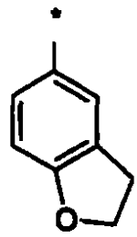
- $R_1$ and $R_2$ are each a member independently selected from the group consisting of hydrogen atom, halo, cyano, $(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$alkoxy,
- X is -O-,
- $R_3$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 to 3 substituents each independently selected from the group consisting of halo, cyano, trifluoromethyl, trifluoromethoxy, $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$thioalkyl, $-C(=O)NH_2$, $-C(=O)NH((C_1\text{-}C_4)alkyl)$, hydroxy, $-O-C(=O)(C_1\text{-}C_4)$alkyl, $-C(=O)-O-(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_8)$cycloalkyl and $(C_3\text{-}C_8)$cycloalkyloxy, or

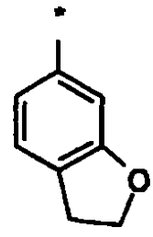
(b) the bicyclic groups conforming to one of the following structures (1.1) to (1.4) :



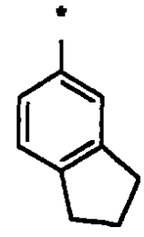
(1.1)



(1.2)



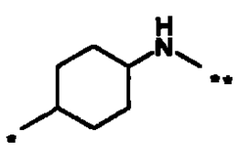
(1.3)



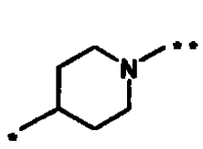
(1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1) through (1.4) to the remaining portion of formula (1),

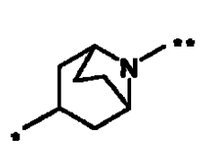
❖ Y is a member selected from the group consisting of partial formulas (1.5) through (1.8) :



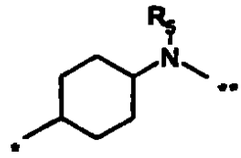
(1.5)



(1.6)



(1.7)

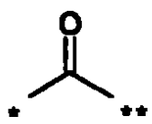


(1.8)

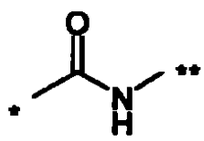
where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a member selected from the groups consisting of ($C_1$-$C_4$)alkyl and phenyl($C_1$-$C_4$)alkyl, where said phenyl group is optionally substituted with 1 to 3 substituents each independently selected from the group consisting of halo, cyano, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, hydroxy, hydroxy($C_1$-$C_4$)alkyl, carboxylic acid, -C(=O)-O-($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)haloalkyl and –C(=O)$NH_2$,

❖ Z is a member selected from the group consisting of partial formulas (1.9) through (1.11) and (1.15) :



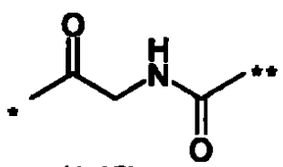
(1.9)



(1.10)



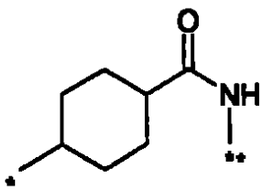
(1.11)



(1.15)

where the symbol "*" indicates the points of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions $R_4$ of formula (1),

❖ or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

- and $R_4$ is a member selected from the groups consisting of :

(a) phenyl, naphthyl, heteroaryl and $(C_3-C_8)$cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (-COOH), $-C(=O)-O-(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl-COOH, $(C_1-C_4)$alkyl-$C(=O)-O-(C_1-C_4)$alkyl, halo, cyano, $-C(=O)NH_2$, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy, $(C_1-C_4)$haloalkyl, hydroxy and hydroxy$(C_1-C_4)$alkyl, or

(b) $(C_1-C_8)$alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, $-C(=O)-O-(C_1-C_4)$alkyl, phenyl, naphthyl, heteroaryl or $(C_3-C_8)$cycloalkyl group, where said phenyl, naphthyl, heteroaryl and $(C_3-C_8)$cycloalkyl groups are each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid, $C(=O)O(C_1-C_4)$alkyl, halo, cyano, $-C(=O)NH_2$, $(C_1-C_4)$alkyl or $(C_1-C_4)$alkoxy, $(C_1-C_4)$haloalkyl, hydroxy and hydroxy$(C_1-C_4)$alkyl,

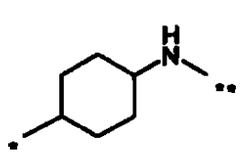
or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

with the proviso that :

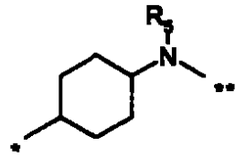
1) when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,

- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy,
- Y is a partial formula (1.5) or (1.8) :



(1.5)



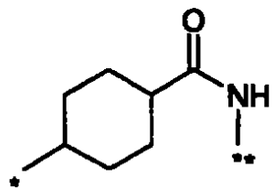
(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1),
and wherein $R_5$ is a member selected from the groups consisting of ($C_1$-$C_4$)alkyl and phenyl($C_1$-$C_4$)alkyl, where said phenyl group is optionally substituted by halo, ($C_1$-$C_3$)alkyl, ($C_1$-$C_3$)alkoxy or hydroxy, and
- Z is a radical –C(=O)-

then $R_4$ cannot be :
a) a ($C_3$-$C_8$)cycloalkyl optionally substituted by ($C_1$-$C_3$)alkyl,
b) a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy, or
c) a ($C_1$-$C_6$)alkyl optionally substituted with a hydroxy, or with a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

2) and when :
- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,

- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy, and
- Y-Z represents a partial formula (1.16) :



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

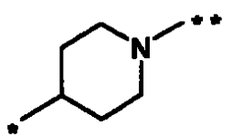
then $R_4$ cannot be :

a) a ($C_3$-$C_8$)cycloalkyl or

b) a ($C_1$-$C_6$)alkyl optionally substituted by a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom, halo and methyl,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 or 2 substituent(s) each independently selected from the group consisting of halo, ($C_1$-$C_3$)alkyl and ($C_1$-$C_3$)alkoxy, and
- Y is a partial formula (1.6) :



(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and

- Z is a radical –C(=O)-,

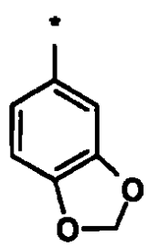
then $R_4$ cannot be a ($C_1$-$C_6$)alkyl optionally substituted by a hydroxy, or by a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S.

3. A compound according to claim 1 wherein:

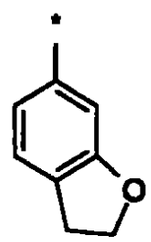
- $R_1$ and $R_2$ are each a member independently selected from the group consisting of hydrogen atom and halo,
- X is -O-,
- $R_3$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 or 2 substituents each independently selected from the group consisting of halo, ($C_1$-$C_4$)alkyl, ($C_1$-$C_4$)alkoxy, trifluoromethyl, trifluoromethoxy, ($C_3$-$C_8$)cycloalkyl, ($C_3$-$C_8$)cycloalkyloxy and ($C_1$-$C_4$)thioalkyl, or

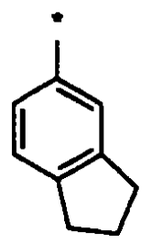
(b) the bicyclic groups conforming to one of the following structures (1.1), (1.3) or (1.4) :



(1.1)



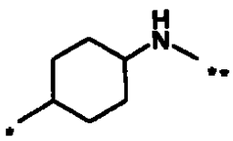
(1.3)



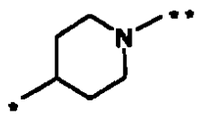
(1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1), (1.3) or (1.4) to the remaining portion of formula (1),

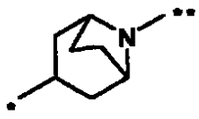
- Y is a member selected from the group consisting of partial formulas (1.5) through (1.8) :



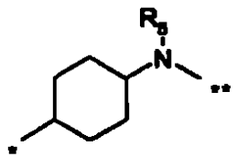
(1.5)



(1.6)



(1.7)

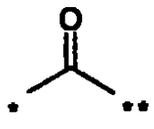


(1.8)

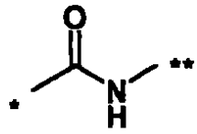
where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a phenyl($C_1$-$C_4$)alkyl where said phenyl is optionally substituted with 1 to 3 substituents each independently selected from the group consisting of hydroxy, carboxylic acid, C(=O)O($C_1$-$C_4$)alkyl and hydroxy($C_1$-$C_4$)alkyl,

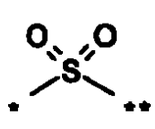
- Z is a member selected from the group consisting of partial formulas (1.9) through (1.11) and (1.15) :



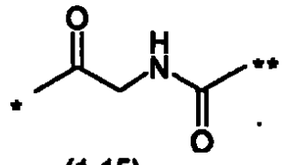
(1.9)



(1.10)



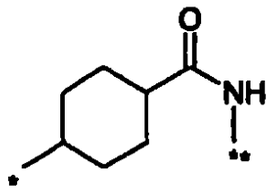
(1.11)



(1.15)

where the symbol "*" indicates the points of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions $R_4$ of formula (1),

- or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

❖ and $R_4$ is a member selected from the groups consisting of :

(a) phenyl, naphthyl, heteroaryl and $(C_3-C_8)$cycloalkyl, each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (-COOH), $-C(=O)-O-(C_1-C_4)$alkyl, $(C_1-C_4)$alkyl-COOH, $(C_1-C_4)$alkyl-$C(=O)-O-(C_1-C_4)$alkyl, halo, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy, hydroxy$(C_1-C_4)$alkyl and hydroxy, or

(b) $(C_1-C_6)$alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, $-C(=O)-O-(C_1-C_4)$alkyl, phenyl, naphthyl, heteroaryl or $(C_3-C_8)$cycloalkyl group, where said phenyl, naphthyl, heteroaryl and $(C_3-C_8)$cycloalkyl groups are each optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid (–COOH), $C(=O)O(C_1-C_4)$alkyl, halo, $(C_1-C_4)$alkyl, $(C_1-C_4)$alkoxy, hydroxy$(C_1-C_4)$alkyl and hydroxy,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

with the proviso that :

1) when :

❖ $R_1$ is selected from the group consisting of hydrogen atom and halo,

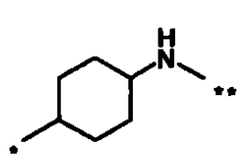
❖ $R_2$ is a hydrogen atom,

❖ X is -O-,

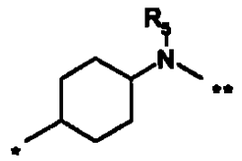
140
141

❖ $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo and ($C_1$-$C_3$)alkyl,

❖ Y is a partial formula (1.5) or (1.8) :



(1.5)



(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1),

and wherein $R_5$ is a phenyl($C_1$-$C_4$)alkyl, where said phenyl group is optionally substituted by hydroxy, and

❖ Z is a radical –C(=O)-

then $R_4$ cannot be :

a) a ($C_3$-$C_8$)cycloalkyl optionally substituted by ($C_1$-$C_3$)alkyl,

b) a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy, or

c) a ($C_1$-$C_6$)alkyl optionally substituted with a hydroxy, or with a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, ($C_1$-$C_3$)alkyl or ($C_1$-$C_3$)alkoxy,

2) and when :

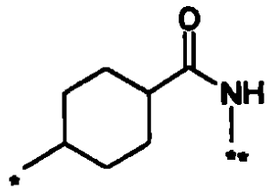
❖ $R_1$ is selected from the group consisting of hydrogen atom and halo,

❖ $R_2$ is a hydrogen atom,

❖ X is -O-,

❖ $R_3$ is a phenyl substituted by a ($C_1$-$C_4$)thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of halo and ($C_1$-$C_3$)alkyl, and

- Y-Z represents a partial formula (1.16) :



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

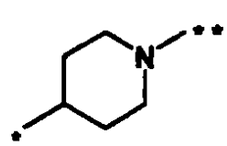
then $R_4$ cannot be :

a) a $(C_3-C_8)$cycloalkyl or

b) a $(C_1-C_8)$alkyl optionally substituted by a phenyl or a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S, which phenyl and heterocyclic ring are each optionally substituted by hydroxy, halo, $(C_1-C_3)$alkyl or $(C_1-C_3)$alkoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom and halo,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a $(C_1-C_4)$thioalkyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent(s) selected from the group consisting of halo and $(C_1-C_3)$alkyl,
- Y is a partial formula (1.6) :



(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of

attachment of each partial formula to the remaining portions Z of formula (1), and

❖ Z is a radical –C(=O)-,

then $R_4$ cannot be a ($C_1$-$C_6$)alkyl optionally substituted by a hydroxy, or by a 5- or 6-membered heterocyclic ring incorporating 1 to 3 heteroatom(s) independently selected from N, O and S.

4. A compound according to claim 1 wherein :

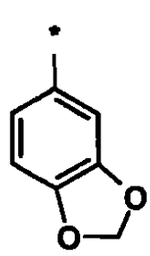
❖ $R_1$ is a hydrogen atom or fluoro and $R_2$ is a hydrogen atom,

❖ X is -O-,

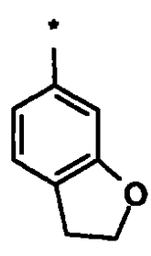
❖ $R_3$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, chloro, bromo, methyl, ethyl, methoxy, trifluoromethyl, trifluoromethoxy, cyclopropyl, cyclobutyloxy, and methylthio, or

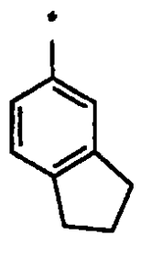
(b) the bicyclic groups conforming to one of the following structures (1.1), (1.3) or (1.4) :



(1.1)



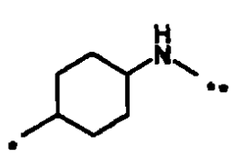
(1.3)



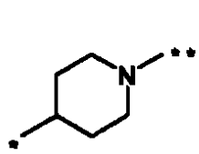
(1.4)

where the symbol "*" indicates the point of attachment of each partial formula (1.1), (1.3) or (1.4) to the remaining portion of formula (1),

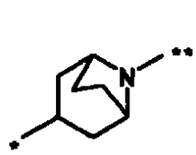
❖ Y is a member selected from the group consisting of partial formulas (1.5) through (1.8) :



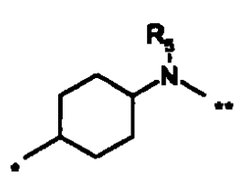
(1.5)



(1.6)



(1.7)

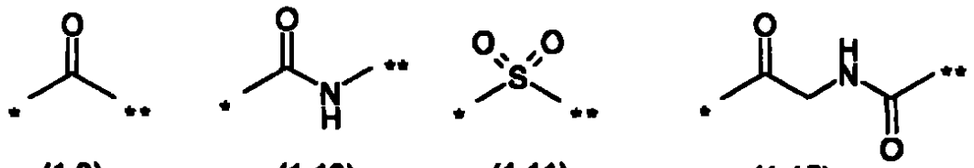


(1.8)

where the symbol "*" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula (1.5) through (1.8) to the remaining portions Z of formula (1),

and wherein $R_5$ is a benzyl group substituted by a hydroxy substitutent on th ring,

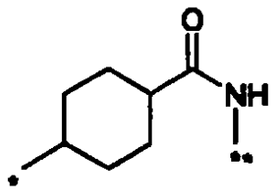
- Z is a member selected from the group consisting of partial formulas (1.9) through (1.11) and (1.15) :



(1.9) (1.10) (1.11) (1.15)

where the symbol "*" indicates the points of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions Y of formula (1) and "**" indicates the point of attachment of each partial formula (1.9) through (1.11) and (1.15) to the remaining portions $R_4$ of formula (1),

- or alternatively Y-Z together represents a group of formula (1.16):



(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

- and $R_4$ is a member selected from the groups consisting of :

(a) phenyl optionally substituted with 1 to 3 substituents each independently selected from the group consisting of carboxylic acid, -C(=O)-O-methyl, fluoro, chloro, methyl, *iso*-propyl, methoxy and hydroxy, or

(b) naphthyl optionally substituted by a hydroxy,

(c) pyridyl ptionally substituted by a hydroxy or a –C(=O)Omethyl group,

(d) a ($C_3$-$C_8$)cycloalkyl optionally substituted with a substituent selected from the group consisting of hydroxy, -C(=O)-O-($C_1$-$C_4$)alkyl and ($C_1$-$C_4$)alkyl-C(=O)-O-($C_1$-$C_4$)alkyl,

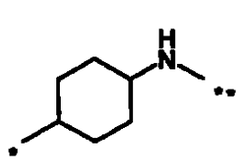
(e) ($C_1$-$C_8$)alkyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of hydroxy, carboxylic acid, –C(=O)Omethyl, –C(=O)Oethyl, ($C_3$-$C_8$)cycloalkyl and phenyl, where said phenyl is optionally substituted with 1 or 2 substituents each independently selected from the group consisting of fluoro, chloro, methyl, methoxy and hydroxy,

or, if appropriate, their pharmaceutically acceptable salts and/or isomers, tautomers, solvates, polymorphs, isotopic variations and metabolites thereof,

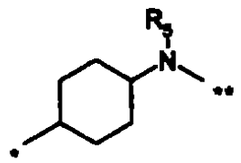
with the proviso that :

1) when :

- $R_1$ is selected from the group consisting of hydrogen atom and fluoro,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by a –S-methyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of fluoro, chloro, methyl and ethyl,
- Y is a partial formula (1.5) or (1.8) :



(1.5)



(1.8)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and wherein $R_5$ is a benzyl optionally substituted by hydroxy, and

- Z is a radical –C(=O)-

then $R_4$ cannot be :

a) an unsubstituted ($C_3$-$C_8$)cycloalkyl,

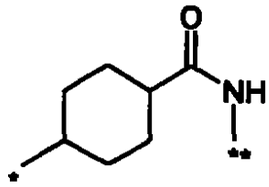
b) a phenyl optionally substituted by hydroxy, fluoro, chloro, methyl, *iso*-propyl or methoxy or $(C_1$-$C_3)$alkoxy,

c) a pyridyl optionally substituted by a hydroxy, or

d) a $(C_1$-$C_6)$alkyl optionally substituted with a hydroxy, or with a phenyl optionally substituted by hydroxy, fluoro, chloro, methyl or methoxy,

2) and when :

- $R_1$ is selected from the group consisting of hydrogen atom and fluoro,
- $R_2$ is a hydrogen atom,
- X is -O-,
- $R_3$ is a phenyl substituted by –S-methyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent selected from the group consisting of fluoro, chloro, methyl and ethyl, and
- Y-Z represents a partial formula (1.16) :




(1.16)

where the symbol "*" indicates the point of attachment of the partial formula (1.16) to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of the partial formula (1.16) to the remaining portions $-R_4$ of formula (1),

then $R_4$ cannot be :

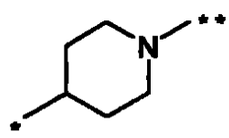
a) a $(C_3$-$C_8)$cycloalkyl or

b) a $(C_1$-$C_6)$alkyl optionally substituted by a phenyl optionally substituted by hydroxy, fluoro, chloro, methyl and methoxy,

3) and when :

- $R_1$ is selected from the group consisting of hydrogen atom and fluoro,
- $R_2$ is a hydrogen atom,
- X is -O-,

- $R_3$ is a phenyl substituted by –S-methyl in the –3 or –4 position of said phenyl and is also optionally substituted by 1 substituent(s) selected from the group consisting of fluoro, chloro, methyl and ethyl,
- Y is a partial formula (1.6) :



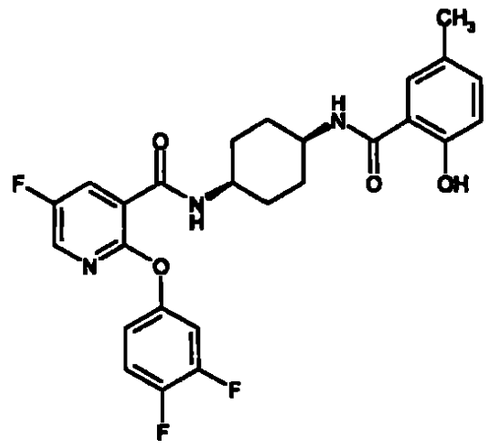
(1.6)

where the symbol "*" indicates the point of attachment of each partial formula to the remaining portions –NH- of formula (1) and "**" indicates the point of attachment of each partial formula to the remaining portions Z of formula (1), and

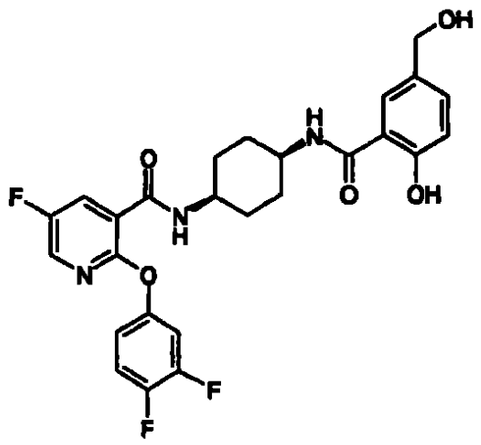
- Z is a radical –C(=O)-,

then $R_4$ cannot be a ($C_1$-$C_6$)alkyl optionally substituted by a hydroxy.

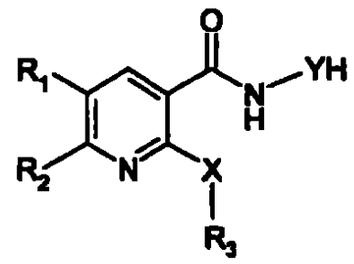
5. A compound according to claim 1 of formula :



6. A compound according to claim 1 of formula :



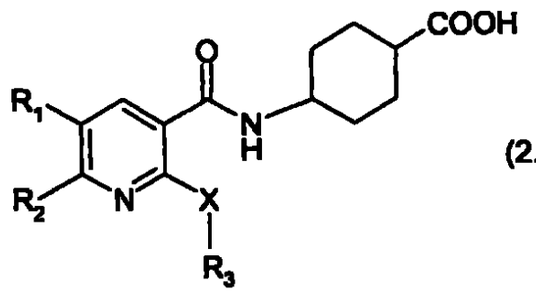
7. A process for the preparation of a compound of the formula (1) as described in claim 1 wherein Z represent a group of partial formula (1.9) to (1.15), or a pharmaceutically acceptable salt or derived form thereof, characterized in that it comprises the step of reacting a compound of formula :



(2.1)

wherein $R_1$, $R_2$, X, $R_3$ and Y are as defined in claim 1,
with the corresponding $R_4$-sulfonyl chloride derivative where Z represents a group of partial formula (1.11), (1.12) or (1.14),
or with the corresponding $R_4$-carboxylic acid derivative where Z represents a group of partial formula (1.9), (1.13) or (1.15),
or with carbonyldiimidazole where Z represents a group of partial formula (1.10).

8. A process for the preparation of a compound of the formula (1) as described in claim 1 wherein Y-Z represents together a group of partial formula (1.16) or a pharmaceutically acceptable salt or derived form thereof, characterized in that it comprises the step of reacting a compound of formula :



(2.2)

wherein $R_1$, $R_2$, X, and $R_3$ are as defined in claim 1,
with an amine bearing a $R_4$ substituent.

9. A pharmaceutical composition including a compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt or derived form thereof, together with customary pharmaceutically innocuous excipients and/or additives.

10. A compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use as a medicament.

11. A compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use in the treatment of diseases, disorders, and conditions in which the PDE4 isozymes are involved.

12. A compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use in the treatment of inflammatory, respiratory and allergic diseases, disorders, and conditions and in the treatment of wounds.

13. A compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt, derived form or composition thereof, for use in the treatment of diseases, disorders, and conditions selected from the group consisting of :

- asthma of whatever type, etiology, or pathogenesis, in particular 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, allergen induced asthma, cold air induced asthma, occupational asthma, infective asthma caused by bacterial, fungal, protozoal, or viral infection, non-allergic asthma, incipient asthma and 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, in particular an obstructive or inflammatory airways disease that is a member selected from the group consisting of 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, in particular 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, in particular 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, in particular 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, in particular 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, in particular 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, in particular 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, allergic dermatitis, contact dermatitis, or allergic or atopic eczema,

- urticaria of whatever type, etiology, or pathogenesis, in particular 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 autos mal dominant form or in the acquired form, contact urticaria, giant urticaria and papular urticaria,

- conjunctivitis of whatever type, etiology, or pathogenesis, in particular 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, in particular 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, in particular 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, in particular 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, endocrin opthamopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, primary biliary cirrhosis, juvenile diabetes or diabetes mellitus type I, keratoconjunctivitis sicca, epidemic keratoconjunctivitis, diffuse interstitial pulmonary fibrosis or interstitial lung fibrosis, idiopathic pulmonary fibrosis, cystic fibrosis, glomerulonephritis with and without nephrotic syndrome, acute glomerulonephritis, idiopathic nephrotic syndrome, minimal change nephropathy, inflammatory/hyperproliferative skin diseases, 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, in particular inflammatory bowel disease that is a member selected from the group consisting of collagenous colitis, colitis polyposa, transmural colitis, ulcerative colitis and Crohn's disease (CD),
- septic shock of whatever type, etiology, or pathogenesis, in particular 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 of whatever type, etiology or pathogenesis including primary pulmonary hypertension / essential hypertension, pulmonary hypertension secondary to congestive heart failure, pulmonary hypertension secondary to chronic obstructive pulmonary

disease, pulmonary venous hypertension, pulmonary arterial hypertension and hypoxia-induced pulmonary hypertension,

- bone loss diseases, primary osteoporosis and secondary osteoporosis,
- central nervous system disorders of whatever type, etiology, or pathogenesis, in particular a central nervous system disorder that is a member selected from the group consisting of depression, Alzheimers disease, Parkinson's disease, learning and memory impairment, tardive dyskinesia, drug dependence, arteriosclerotic dementia and dementias that accompany Huntington's chorea, Wilson's disease, paralysis agitans, and thalamic atrophies,
- infection, especially infection by viruses wherein such viruses increase the production of TNF-α in their host, or wherein such viruses are sensitive to upregulation of TNF-α in their host so that their replication or other vital activities are adversely impacted, including a virus which is a member selected from the group consisting of HIV-1, HIV-2, and HIV-3, cytomegalovirus (CMV), influenza, adenoviruses and Herpes viruses including *Herpes zoster* and *Herpes simplex*,
- yeast and fungus infections wherein said yeast and fungi are sensitive to upregulation by TNF-α or elicit TNF-α production in their host, *e.g.*, fungal meningitis, particularly when administered in conjunction with other drugs of choice for the treatment of systemic yeast and fungus infections, including but are not limited to, polymixins, *e.g.* Polymycin B, imidazoles, *e.g.* clotrimazole, econazole, miconazole, and ketoconazole, triazoles, *e.g.* fluconazole and itranazole as well as amphotericins, *e.g.* Amphotericin B and liposomal Amphotericin B,
- ischemia-reperfusion injury, ischemic heart disease, autoimmune diabetes, retinal autoimmunity, chronic lymphocytic leukemia, HIV infections, lupus erythematosus, kidney and ureter disease, urogenital and gastrointestinal disorders and prostate diseases,

- reduction of scar formation in the human or animal body, such as scar formation in the healing of acute wounds, and

- psoriasis, other dermatological and cosmetic uses, including antiphlogistic, skin-softening, skin elasticity and moisture-increasing activities.

14. The use of a compound of the formula (1) as defined in claim 1 or of a pharmaceutically acceptable salt, derived form or composition thereof, for the manufacture of a drug having a PDE4 inhibitory activity.

15. The use of a compound of the formula (1) as defined in claim 1 or of a pharmaceutically acceptable salt, derived form or composition thereof, for the manufacture of a drug useful in the treatment of inflammatory, respiratory and allergic diseases, disorders and conditions and in the treatment of wounds.

16. The use of a compound of the formula (1) as defined in claim 1 or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a drug for the treatment of diseases, disorders, and conditions selected from the group described in claim 13.

17. A method of treatment of a mammal, including a human being, with a PDE4 inhibitor including treating said mammal with an effective amount of a compound of the formula (1) as defined in claim 1 or with a pharmaceutically acceptable salt, derived form or composition thereof.

18. A method according to claim 17 where the disease, disorder or condition to treat is selected from the group described in claim 13.

# INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 03/00439

148
149

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/455 A61P29/00 A61P11/00 C07D405/12 C07D213/82
C07D401/12 C07D451/04

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, 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. |
|---|---|---|
| X | WO 98 45268 A (CHAMBERS ROBERT JAMES ;KLEINMAN EDWARD FOX (US); CHENG JOHN BIN (U) 15 October 1998 (1998-10-15) cited in the application claims 1,19 | 1-18 |

☐ Further documents are listed in the continuation of box C.

☒ 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 |
|---|---|
| 7 April 2003 | 17/04/2003 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Johnson, C |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inte.....onal application No.
PCT/IB 03/00439

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-4(part), 9-15(part),17(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

International Application No. PCT/IB 03 00439

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4(part), 9-15(part),17(part)

Claims 1-4 encompass metabolites of the compounds of formula (1). No further information is given as to the structure of these metabolites, hence these claims cover all possible metabolic products, regardless of whether they have been identified or isolated. It is considered an undue and impossible burden for the skilled person to determine the scope of the claims insofar as the metabolites are concerned, as he would have to administer all compounds of formula (1) to all biological systems and thereafter isolate and identify all metabolites. Thus these claims do not fulfil the requirements of Article 6 PCT. On p. 36-37 of the description, a few exemplary metabolites are defined, namely N-oxide, glucuronide and sulfonate derivatives. However, in view of the large number of possible substituents in various positions, it is not clear which positions and substituents would in fact metabolically form glucuronide or sulfonate derivatives. Thus the scope of the claims in which the metabolites are glucuronide or sulfonated derivatives is not clear. In contrast, the metabolites which are N-oxides of the compounds of formula (1) are considered to be limited and clearly defined. Thus the metabolites have only been searched insofar as they are N-oxides of the compounds of formula (1).

Claims 9-15 and 17 refer to compositions containing a compound of formula (1) as defined in claim 1 or a derived form thereof. Derived forms have only been searched insofar as they are covered by the definition in claim 1 (excluding metabolites except N-oxides, vide supra).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

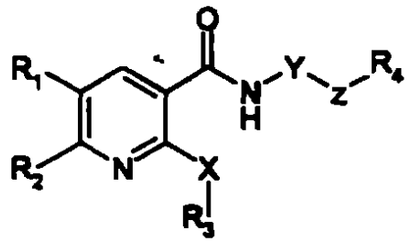
# INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 03/00439

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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| | | AU | 6227398 A | 30-10-1998 |
| | | BG | 103725 A | 31-07-2000 |
| | | BR | 9810733 A | 12-09-2000 |
| | | CN | 1254335 T | 24-05-2000 |
| | | EP | 0971894 A1 | 19-01-2000 |
| | | HR | 980181 A1 | 28-02-1999 |
| | | HU | 0001243 A2 | 28-09-2000 |
| | | WO | 9845268 A1 | 15-10-1998 |
| | | JP | 2000510481 T | 15-08-2000 |
| | | NO | 994791 A | 01-12-1999 |
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| | | TR | 9902432 T2 | 21-01-2000 |
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**DERIVADOS DE NICOTINAMIDA ÚTILES COMO INHIBIDORES DE PDE4**

Esta invención se refiere a derivados de nicotinamida de fórmula general:



en la cual $R_1$, $R_2$, $R_3$, $R_4$, X, Y, y Z tienen los significados indicados más adelante,

y a procedimientos para la preparación de tales derivados, intermedios utilizados en su preparación, composiciones que los contienen y usos de los mismos.

Las fosfodiesterasas de nucleótidos 3',5'-cíclicos (PDE) comprenden una amplia clase de enzimas dividida en al menos once familias diferentes que son estructuralmente, bioquímicamente y farmacológicamente distintas unas de otras. Las enzimas dentro de cada familia se refieren comúnmente como isoenzimas, o isozimas. Un total de más de quince productos genéticos se incluye dentro de esta clase, y se obtiene una diversidad adicional como resultado del corte y empalme diferencial y del procesado post-traduccional de esos productos génicos. La presente invención se refiere en primer lugar a los cuatro productos génicos de la cuarta familia de PDE; esto es, PDE4A, PDE4B, PDE4C, y PDE4D. Estas enzimas son colectivamente consideradas como isoformas o subtipos de la familia de isozimas PDE4.

Las PDE4 se caracterizan por una degradación hidrolítica de elevada afinidad, selectiva, del nucleótido cíclico segundo mensajero, el monofosfato 3',5'-cíclico de

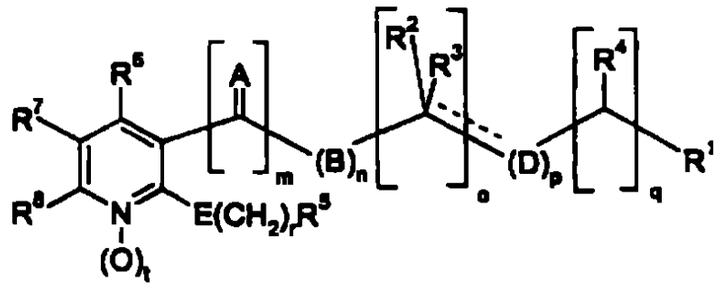
adenosina (cAMP), y por una sensibilidad a la inhibición por rolipram. En los últimos años se ha descubierto un cierto número de inhibidores selectivos de PDE4, y los efectos farmacológicos beneficiosos resultantes de esa inhibición han sido mostrados en una diversidad de modelos de enfermedades (véase, por ejemplo, Torphy et al., Environ. Health Perspect., 1994, 102 Suppl. 10, p. 79-84; Duplantier et al., J. Med. Chem., 1996, 39, p. 120-125; Schneider et al., Pharmacol. Biochem. Behav., 1995, 50, p. 211-217; Banner y Page, Br. J. Pharmacol., 1995, 114, p. 93-98; Barnette et al., J. Pharmacol. Exp. Ther., 1995, 273, p. 674-679; Wright et al., Can. J. Physiol. Pharmacol., 1997, 75, p. 1001-1008; Manabe et al., Eur. J. Pharmacol., 1997, 332, p. 97-107 y Ukita et al., J. Med. Chem., 1999, 42, p. 1088-1099). Consecuentemente, continúa existiendo un considerable interés en la técnica con vistas al descubrimiento de más inhibidores selectivos de PDE4.

Ya se han obtenido resultados exitosos en la técnica con el descubrimiento y desarrollo de los inhibidores selectivos de PDE4. *In vivo*, los inhibidores de PDE4 reducen la afluencia de eosinófilos a los pulmones de animales expuestos al alergeno al tiempo que se reduce la broncoconstricción y la elevada respuesta bronquial que tiene lugar después de la exposición al alergeno. Los inhibidores de PDE4 también suprimen la actividad de células inmunes (incluyendo linfocitos T $CD4^+$, monocitos, células cebadas, 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 de la musculatura lisa de las vías respiratorias, e inducen broncodilatación. Los inhibidores de PDE4 también suprimen la actividad de un cierto número de células inflamatorias asociadas con la patofi-

siología de COPD, incluyendo monocitos/macrófagos, linfocitos-T CD4$^+$, eosinófilos y neutrófilos. Los inhibidores de PDE4 también reducen la mitogénesis de la musculatura lisa vascular e interfieren potencialmente con la capacidad de las células epiteliales de las vías respiratorias para generar mediadores proinflamatorios. A través de la liberación de proteasas neutras y de hidrolasas ácidas procedentes de sus gránulos, y de la generación de especies oxígeno reactivas, los neutrófilos contribuyen a la destrucción de los tejidos asociada con la inflamación crónica, y están adicionalmente implicados en la patología de dolencias tales como el enfisema. Por lo tanto, los inhibidores de PDE4 son particularmente útiles para el tratamiento de un gran número de enfermedades, trastornos o dolencias inflamatorias, respiratorias y alérgicas y para heridas y algunos de ellos están en desarrollo clínico principalmente para el tratamiento del asma, COPD, bronquitis y enfisema.

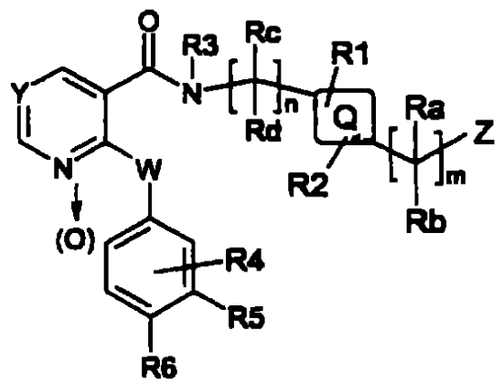
Los efectos de los inhibidores de PDE4 sobre diversas respuestas de células inflamatorias pueden utilizarse como base para perfilar y seleccionar inhibidores para estudios adicionales. Estos efectos incluyen la elevación de cAMP y la inhibición de la producción superóxido, desgranulación, quimiotaxia y liberación de factor de necrosis tumoral alfa (TNFα) en eosinófilos, neutrófilos y monocitos.

Algunos derivados de nicotinamida que tienen una actividad inhibitoria de PDE4 ya han sido sintetizados. Por ejemplo, la solicitud de patente N° WO 98/45268 describe derivados de nicotinamida que tienen actividad como inhibidores selectivos de la isozima PDE4D. Estos inhibidores de PDE4D selectivos están representados por la siguiente fórmula:



en que r puede ser igual a 0, $(A)_m$ puede ser oxígeno y $(B)_n$ puede ser NH, o puede ser igual a 0 ó 1, $R^2$ y $R^3$ pueden tomarse junto con el carbono al cual están unidos para formar u anillo cicloalquilo($C_3$-$C_8$), $(D)_p$ puede estar ausente o puede ser -NH- o -Nalquil($C_1$-$C_6$)-, q puede ser igual a 0 ó 1, $R^1$ puede estar ausente o puede representar un carboxi, R puede elegirse entre numerosos sustituyentes entre los cuales están un grupo alquilo($C_1$-$C_6$), cicloalquilo($C_3$-$C_8$), arilo($C_6$-$C_{10}$) o heterocíclico($C_1$-$C_7$) (in)saturado, en que cada uno de dichos cicloalquilo, arilo o heterociclo puede estar opcionalmente sustituido con uno a tres sustituyentes.

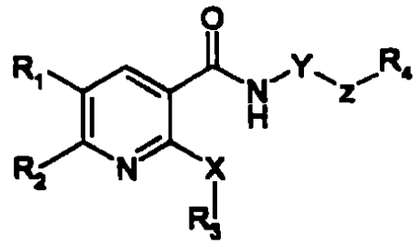
La solicitud de patente N° WO 01/57036 también describe derivados de nicotinamida que son inhibidores de PDE4 útiles en el tratamiento de diversas enfermedades y dolencias alérgicas y respiratorias inflamatorias, de fórmula:



en la que en particular: n es 1 ó 2, m es 0 a 2, Y es $=C(R^E)-$ o $-[N\rightarrow(O)]-$, W es -O-, $S(O)_t-$ o $-N(R_3)-$, Q representa varios anillos entre los cuales los restos cicloalquilo($C_3$-$C_7$) monocíclicos, Z es $-OR_{12}$, $-C(=O)R_{12}$ o CN y $R_{12}$ se elige entre alquilo, alquenilo, cicloalquilo, fenilo, bencilo y restos heterocíclicos monocíclicos.

Sin embargo, todavía existe una enorme necesidad de inhibidores de PDE4 mejorados que muestren un índice terapéutico mejorado con menos efectos secundarios tales como por ejemplo émesis.

Así, la presente invención se refiere a nuevos derivados de nicotinamida de fórmula general (1):



(1)

en la cual

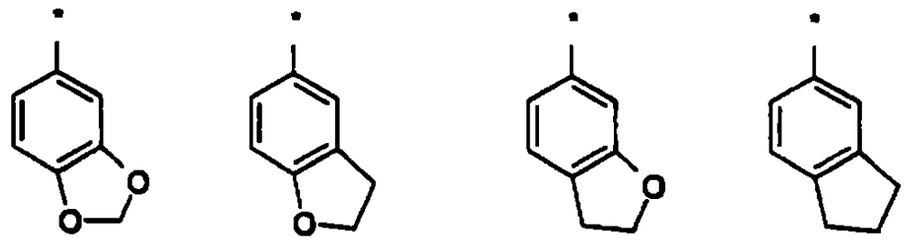
- $R_1$ y $R_2$ son cada uno un miembro independientemente seleccionado entre el grupo formado por átomo de hidrógeno, halo, ciano, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$),

❖ X es -O-, -S- o -NH-,

❖ $R_1$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes cada uno seleccionado independientemente entre el grupo formado por halo, ciano, trifluorometilo, trifluoroetilo, trifluorometoxi, trifluoroetoxi, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), tioalquilo($C_1$-$C_4$), -C(=O)$NH_2$, -C(=O)NH-(alquilo($C_1$-$C_4$)), hidroxi, -O-C(=O)alquilo($C_1$-$C_4$), -C(=O)-O-alquilo($C_1$-$C_4$) e hidroxialquilo($C_1$-$C_4$), cicloalquilo($C_3$-$C_8$) y cicloalquiloxi($C_3$-$C_8$), o

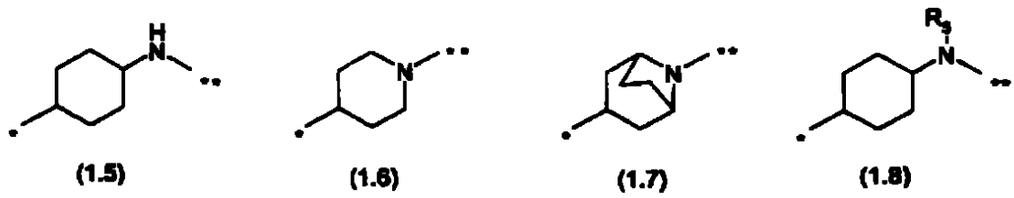
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1) a (1.4):



(1.1) (1.2) (1.3) (1.4)

en la que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1) a (1.4) a la porción restante de fórmula (1),

❖ Y es un miembro seleccionado entre el grupo formado por las fórmulas parciales (1.5) a (1.8):

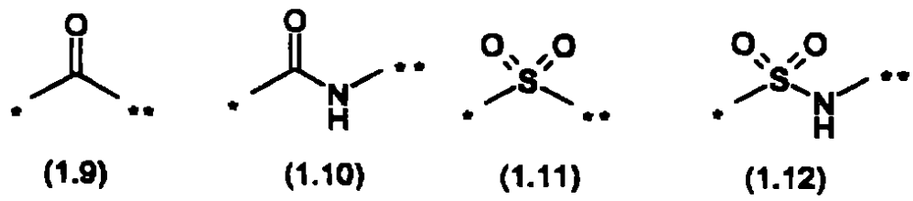


(1.5) (1.6) (1.7) (1.8)

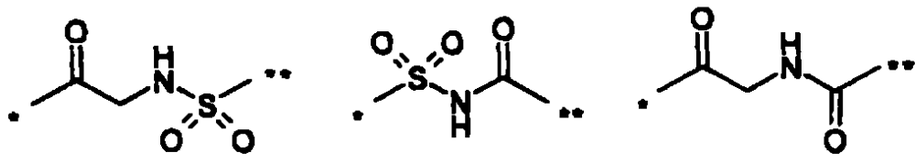
en la que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones -NH- restantes de fórmula (1) y "***" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones Z restantes de fórmula (1),

y en que $R_4$ es un miembro seleccionado entre los grupos formados por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido independientemente con 1 a 3 sustituyentes cada uno seleccionado entre el grupo formado por halo, ciano, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxi, hidroxialquilo($C_1$-$C_4$), ácido carboxílico (-COOH), -C(=O)-O-alquilo($C_1$-$C_4$), haloalquilo($C_1$-$C_4$) y $-C(O)NH_2$,

❖ Z es un miembro seleccionado entre el grupo formado por las fórmulas parciales (1.9) a (1.15):



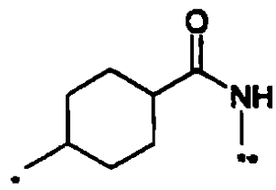
(1.9) (1.10) (1.11) (1.12)



(1.13) (1.14) (1.15)

en la que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.9) a (1.15) a las porciones Y restantes de fórmula (1) y "***" indica el punto de unión de cada fórmula parcial (1.9) a (1.15) a las porciones $R_4$ restantes de fórmula (1),

❖ o alternativamente Y-Z juntos representa un grupo de fórmula (1.16):



(1.16)

en la que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones -$R_1$ restantes de fórmula (1),

❖ y $R_1$ es un miembro seleccionado entre el grupo formado por:

(a) fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes cada uno seleccionado independientemente entre el grupo formado por ácido carboxílico (-COOH), -C(=O)-O-alquilo-($C_1$-$C_4$), alquil($C_1$-$C_4$)-COOH, alquil($C_1$-$C_4$)-C(O)-O-alquilo-($C_1$-$C_4$), halo, ciano, -C(=O)$NH_2$, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), haloalquilo($C_1$-$C_4$), hidroxi e hidroxialquilo($C_1$-$C_4$), o

(b) alquilo($C_1$-$C_4$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grupo formado por un grupo hidroxi, ácido carboxílico, -C(=O)-Oalquilo($C_1$-$C_4$), fenilo, naftilo, heteroarilo o cicloalquilo($C_3$-$C_8$), en que dichos grupos fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$) están opcionalmente sustituidos con 1 a 3 sustituyentes cada uno seleccionado independientemente entre el grupo formado por ácido carboxílico (-COOH), C(=O)Oalquilo($C_1$-$C_4$), halo, ciano, -C(=O)$NH_2$, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), haloalquilo($C_1$-$C_4$), hidroxi e hidroxialquilo($C_1$-$C_4$),

o, si es apropiado, sus sales y/o tautómeros isómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos farmacéuticamente aceptables del mismo,

con la condición que:

1) cuando:

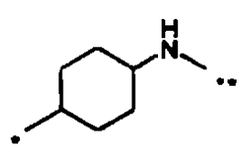
❖ $R_1$ se selecciona entre el grupo formado por átomo de hidrógeno, halo y metilo

❖ $R_2$ es un átomo de hidrógeno,

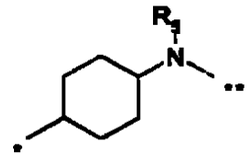
❖ X es -O-,

❖ $R_4$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_3$) y alcoxi($C_1$-$C_4$),

❖ Y es una fórmula parcial (1.5) o (1.8)



(1.5)



(1.8)

en la que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de fórmula (1), y en que $R_5$ es un miembro seleccionado entre los grupos formados por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$) o hidroxi, y

❖ Z es un radical -C(=O)-

entonces $R_4$ no puede ser:

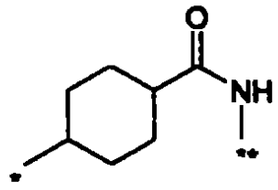
a) un cicloalquilo($C_3$-$C_8$) opcionalmente sustituido con alquilo($C_1$-$C_3$),

b) un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico están cada uno opcionalmente sustituidos con hidroxi, halo, alquilo($C_1$-$C_3$) o alcoxi($C_1$-$C_3$), o

c) un alquilo($C_1$-$C_7$) opcionalmente sustituido con un hidroxi, o con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

2) y cuando:

- ❖ $R_1$ se selecciona entre el grupo formado por un átomo de hidrógeno, halo y metilo,
- ❖ $R_2$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_4$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$), y
- ❖ Y-Z representa una fórmula parcial (1.16):




**(1.16)**

en la que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones -$R_4$ restantes de fórmula (1),

entonces $R_4$ no puede ser:

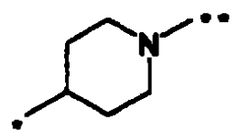
a) un cicloalquilo($C_3$-$C_8$) o

b) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independiente-

mente entre N, O y S, cuyo fenilo y anillo heterocíclico están cada uno opcionalmente sustituidos con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

3) y cuando:

- ❖ $R_1$ se selecciona entre el grupo formado por átomo de hidrógeno, halo y metilo,
- ❖ $R_2$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_4$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 ó 2 sustituyente(s) cada uno independientemente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$), y
- ❖ Y es una fórmula parcial (1.6):



(1.6)

en la que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de fórmula (1),

y

- ❖ Z es un radical -C(O)-,

entonces $R_4$ no puede ser un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S.

Se ha encontrado que estos derivados de nicotinamida son inhibidores de isoenzimas PDE4, particularmente útiles para el tratamiento de enfermedades y dolencias inflamatorias, respiratorias y alérgicas, mostrando una ex-

celente utilidad terapéutica e índice terapéutico.

En la aquí anterior fórmula general (1), halo significa un átomo de halógeno seleccionado entre el grupo formado por flúor, cloro, bromo y yodo en particular flúor o cloro.

Los radicales alquilo($C_1$-$C_4$) o alquilo($C_1$-$C_6$) significan un grupo de cadena lineal o ramificada que contiene respectivamente 1 a 4 y 1 a 6 átomos de carbono. Esto también se aplica si llevan otros sustituyentes o se encuentran como sustituyentes de otros radicales, por ejemplo en radicales alcoxi($C_1$-$C_4$), radicales tioalquilo($C_1$-$C_4$), radicales haloalquilo($C_1$-$C_4$), radicales hidroxialquilo($C_1$-$C_4$), radicales C(=O)O-alquilo($C_1$-$C_4$) etc. Ejemplos de radicales alquilo($C_1$-$C_4$) y alquilo($C_1$-$C_6$) adecuados son metilo, etilo, n-propilo, iso-propilo, n-butilo, iso-butilo, sec-butilo, terc-butilo, pentilo y hexilo. Ejemplos de radicales alcoxi($C_1$-$C_4$) adecuados son metoxi, etoxi, n-propiloxi, iso-propiloxi, n-butiloxi, iso-butiloxi, sec-butiloxi y terc-butiloxi. Ejemplos de radicales tioalquilo($C_1$-$C_4$) adecuados son tiometilo, tioetilo, tio-n-propilo, tio-iso-propilo, tio-n-butilo, tio-iso-butilo, tio-sec-butilo y tio-terc-butilo. Los radicales haloalquilo($C_1$-$C_4$) son radicales alquilo sustituidos con halo. Pueden contener 1, 2, 3, 4, 5, 6 ó 7 átomos de halógeno, si no se establece otra cosa. Dicho halo preferiblemente es un flúor, un cloro, un bromo o un yodo, en particular flúor o cloro. Por ejemplo en un radical alquilo sustituido con flúor, un grupo metilo puede estar presente como un grupo trifluorometilo. Lo mismo se aplica a radicales hidroxialquilo($C_1$-$C_4$) excepto que son radicales alquilo sustituidos por un grupo hidroxi (-OH). De acuerdo con una realización preferida de dicha invención, tales radicales contienen un sustituyente hidroxi. Ejemplos de radicales hidroxialquilo($C_1$-$C_4$) adecuados son hidroximetilo, 1-hidroxietilo ó 2-hidroxietilo.

Los radicales cicloalquilo($C_1$-$C_8$) representan anillos monocíclicos saturados de 3 miembros a 8 miembros. Ejemplos de radicales cicloalquilo($C_1$-$C_8$) adecuados son en particular ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo. Este radical puede estar opcionalmente sustituido como se indica en la definición de $R_1$. Ejemplos de radicales cicloalquilo($C_1$-$C_8$) sustituidos son por ejemplo 2-metilciclohexilo, 3-metilciclohexilo, 4-metilciclohexilo, 5-metilciclohexilo, 6-metilciclohexilo, 2-hidroxiciclohexilo, 3-hidroxiciclohexilo, 4-hidroxiciclohexilo, 5-hidroxiciclohexilo, 6-hidroxiciclohexilo, 2-fluorociclohexilo, 3-fluorociclohexilo, 4-fluorociclohexilo, 5-fluorociclohexilo, 6-fluorociclohexilo, 2-metil-3-hidroxiciclohexilo, 2-metil-4-hidroxiciclohexilo, 2-hidroxi-4-metilciclohexilo, etc.

En la fórmula general (1) anterior, heteroarilo es un radical de un sistema aromático monocíclico o policíclico que tiene 5 a 14 miembros de anillo, que contiene 1, 2, 3, 4 ó 5 heteroátomo(s) dependiendo en número y calidad del número total de miembros de anillo. Ejemplos de heteroátomos son nitrógeno (N), oxígeno (O) y azufre (S). Si contiene varios heteroátomos, pueden ser iguales o diferentes. Los radicales heteroarilo también pueden ser sin sustituir, monosustituidos o polisustituidos, como se indica en la definición de $R_1$ y $R_4$ anteriores para fórmula general (1) de acuerdo con la presente invención. Preferiblemente heteroarilo es un radical aromático monocíclico o bicíclico que contiene 1, 2, 3 ó 4, en particular 1, 2 ó 3, heteroátomos idénticos o diferentes seleccionados entre el grupo formado por N, O y S. Heteroarilo particularmente preferido, es un radical aromático monocíclico o bicíclico que tiene 5 a 10 miembros de anillo, en particular un radical aromático monocíclico de 5 miembros a 6 miembros que contiene (i) de 1 a 4 heteroátomo(s) nitrógeno o (ii) 1 ó 2 heteroátomo(s) nitrógeno y 1 heteroáto-

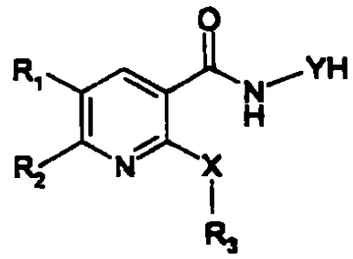
mo oxígeno ó 1 heteroátomo azufre o (iii) 1 ó 2 heteroátomo(s) oxígeno o azufre. Ejemplos de radicales heteroarilo adecuados son los radicales derivados de pirrol, furano, furazano, tiofeno, imidazol, pirazol, oxazol, isoxazol, tiazol, isotiazol, tetrazol, triazina, piridina, pirazina, pirimidina, piridazina, indolizina, indol, isoindol, indazol, purina, naftiridina, ftalazina, quinolina, isoquinolina, quinoxalina, quinazolina, cinolina, y derivados benzo fusionados de estos heteroarilos, tales como por ejemplo benzofurano, benzotiofeno, benzoxazol, y benzotiazol. Particularmente preferidos son los radicales heteroarilo seleccionados entre pirrolilo, pirazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, tetrazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, furanilo, tienilo, piridinilo, piridazinilo, pirimidinilo, y pirazinilo. El nitrógeno de los radicales heteroarilo también puede estar presente como N-óxidos o como sales cuaternarias.

En la fórmula general (1) de acuerdo con la presente invención, cuando un radical es mono- o poli-sustituido, dicho(s) sustituyente(s) puede estar localizado en cualquier posición(es) deseada. También, cuando un radical está polisustituido, dichos sustituyentes pueden ser iguales o diferentes, a menos que se establezca otra cosa.

Los derivados de nicotinamida de fórmula (1) pueden prepararse usando procedimientos convencionales tales como por los siguientes métodos ilustrativos en los cuales $R_1$, $R_2$, $R_3$, $R_4$, X, Y, y Z son como se ha definido previamente para los derivados de nicotinamida de fórmula (1) a menos que se establezca otra cosa.

Cuando Z en la fórmula general (1) representa un grupo de fórmula parcial (1.9) a (1.15), los derivados de nicotinamida de fórmula (1) pueden prepararse partiendo

de un compuesto de fórmula (2.1):



(2.1)

en la que $R_1$, $R_2$, X, $R_3$ e Y son como se ha descrito previamente para los derivados de nicotinamida de fórmula (1).

Cuando Z representa un grupo de fórmula parcial (1.11), (1.12) o (1.14), los compuestos de fórmula (2.1) se hacen reaccionar con el correspondiente derivado cloruro de $R_1$-sulfonilo ($R_1SO_2Cl$ o $R_1NHSO_2Cl$ o $R_4C(O)NHSO_2Cl$) en un disolvente adecuado (por ejemplo diclorometano) y en presencia de una base orgánica (por ejemplo trietilamina) a una temperatura que varía de 0°C a temperatura ambiente (aproximadamente 20°C).

Cuando Z representa un grupo de fórmula parcial (1.9), (1.13) o (1.15), los compuestos de fórmula (2.1) se hacen reaccionar con el correspondiente derivado de ácido $R_1$-carboxílico ($R_4COOH$ o $R_4SO_2NH-CH_2-COOH$ o $R_4C(O)NH-CH2COOH$) usando un agente activante en presencia de un disolvente adecuado (por ejemplo dimetilformamida) y una base orgánica (por ejemplo N-metilmorfolina) a temperatura ambiente. La activación del ácido puede conseguirse usando por ejemplo:

a) 1-hidroxibenzotriazol e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida, o

b) carbonildiimidazol, o

c) cloruro de oxalilo y dimetilformamida (con diclorometano como disolvente).

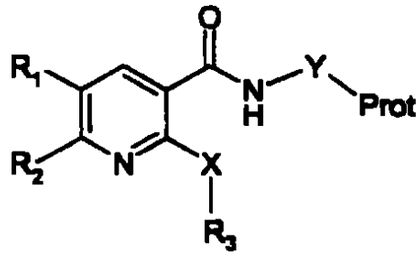
d) hexafluorofosfato de o-(7-azabenzotriazol-1-il)-

N,N,N',N'-tetrametiluronio (reactivo HATU)

Cuando Z representa un grupo de fórmula parcial (1.10), los compuestos de fórmula (2.1) pueden hacerse reaccionar con carbonildiimidazol en un disolvente adecuado (tal como diclorometano) o con un equivalente de fosgeno (tal como trifosgeno) y el intermedio obtenido se hace reaccionar con una amina que lleva el sustituyente $R_4$.

Debe enfatizarse que cuando $R_1$ y $R_4$ en los derivados de nicotinamida de fórmula (1) representan anillos fenilo sustituidos con alcoxi, estas estructuras pueden convertirse en el análogo hidroxi utilizando ciertas condiciones de desprotección bien conocidas para el experto en la técnica. Similarmente, cuando $R_4$ contiene una funcionalidad éster, estas estructuras pueden convertirse fácilmente en el ácido carboxílico por simple saponificación utilizando hidróxidos de metal alcalino bien conocidos por el experto en la técnica.

Los compuestos de fórmula general (2.1) pueden prepararse por separación del grupo protector "Prot" de los compuestos de fórmula general (3.1):

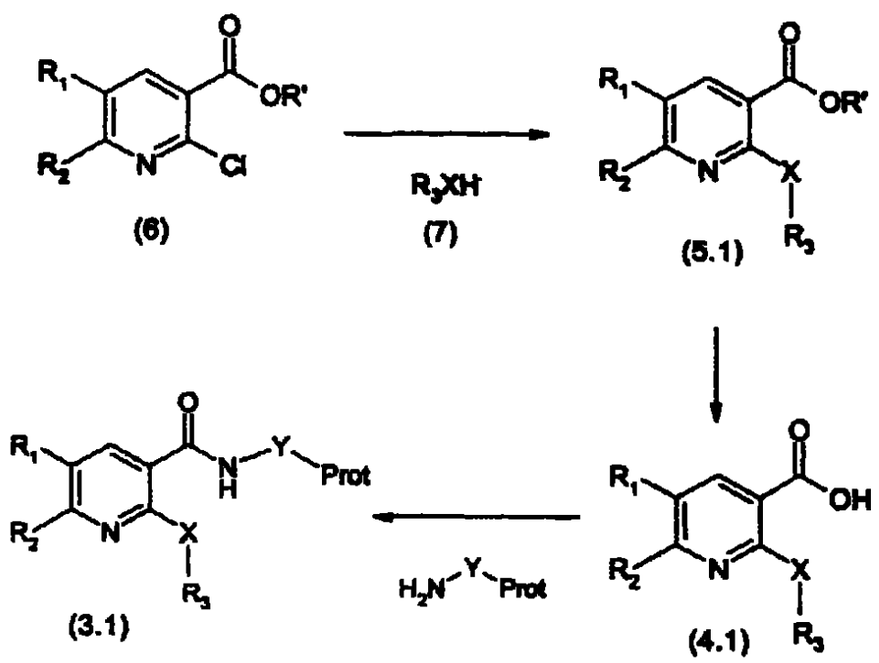



(3.1)

en la que $R_1$, $R_2$, X, $R_3$ e Y son como se describió anteriormente para los derivados de nicotinamida de fórmula (1) y Prot es un grupo protector adecuado, que incluye pero no está limitado a bencilo o a carbamato (por ejemplo, butoxicarbonilo),

por métodos bien conocidos para los expertos en la técnica.

Los compuestos de fórmula (3.1) pueden prepararse de acuerdo con dos rutas sintéticas. La primera ruta sintética se muestra en el esquema 1:



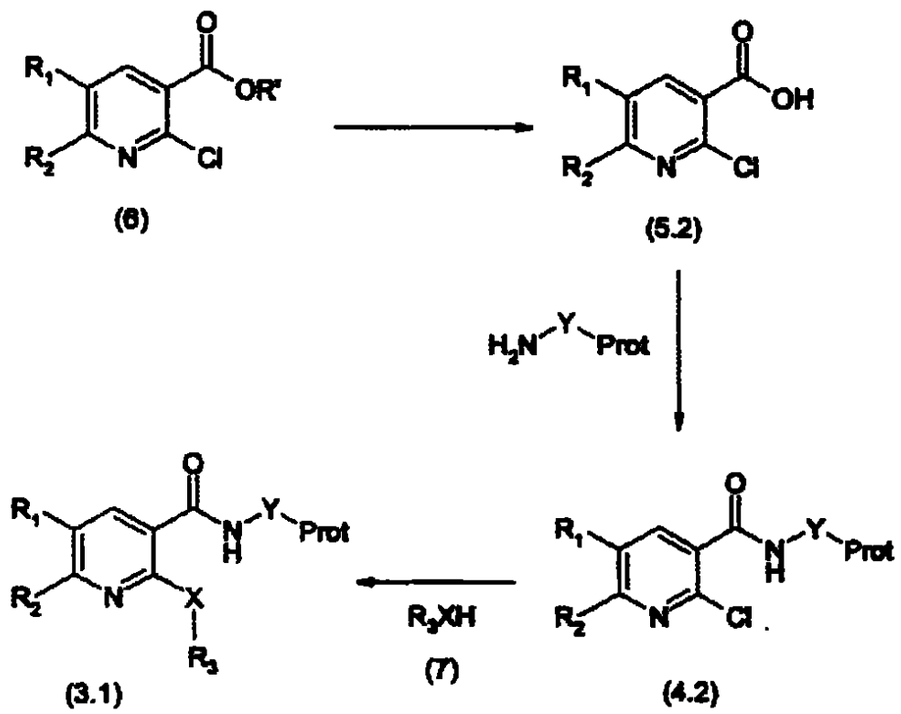

Esquema 1

en que R., $R_2$, X, $R_1$, e Y Prot son como se ha descrito previamente y R' representa un radical alquilo($C_1$-$C_4$).

En un procedimiento típico el éster nicotinato de la fórmula (6) puede hacerse reaccionar con el alcohol, tiol o amina de fórmula $R_3XH$ (7) apropiado en el disolvente apropiado (por ejemplo dimetilformamida o dioxano) conteniendo una base, tal como carbonato de cesio, a temperaturas comprendidas entre la temperatura ambiente y 100°C para dar un compuesto de fórmula (5.1). Éste puede saponificarse con un hidróxido alcalino para dar un ácido de fórmula (4.1) que después se convierte en un compuesto de

fórmula (3) por reacción con una diamina monoprotegida de fórmula $NH_2$-Y-Prot, utilizando un agente activante tal como los descritos en uno de los métodos de activación indicados anteriormente (esto es, a) 1-hidroxibenzotriazol e hidrocloruro de 1-(3-dimetilaminopropil-3-etilcarbodiimida o b) carbonildiimidazol o c) cloruro de oxalilo y dimetilformamida, con diclorometano como disolvente).

De acuerdo con otra alternativa, los compuestos de fórmula (3.1) pueden prepararse como se muestra en el esquema 2:




Esquema 2

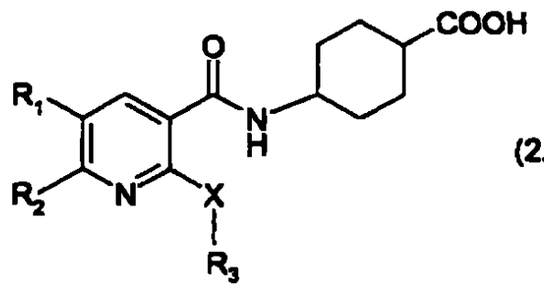
en que $R_1$, $R_2$, X, $R_3$, Y, R' y Prot son como se ha descrito previamente.

En un procedimiento típico el éster nicotinato de fórmula (6) puede hidrolizarse utilizando un hidróxido de

metal alcalino en un ácido nicotínico de la fórmula (5.2), que se hace reaccionar con una diamina monoprotegida de la fórmula $NH_2$-Y-Prot, utilizando uno de los métodos de activación indicados anteriormente. La cloropiridina de fórmula (4.2) obtenida en la etapa precedente puede, después, hacerse reaccionar con el alcohol, tiol o amina de fórmula R.XH (7) apropiado en el disolvente apropiado (por ejemplo, dimetilformamida o dioxano) conteniendo una base, tal como carbonato de cesio, a temperaturas comprendidas entre la temperatura ambiente (aproximadamente 20°C) y 100°C.

Los compuestos de fórmula (6) y (7), así como la diamina monoprotegida de fórmula $NH_2$-Y-Prot, son o bien comerciales o pueden prepararse por procedimientos convencionales bien conocidos por los expertos en la técnica.

Cuando Y-Z en la fórmula general (1) representa junto al grupo de fórmula parcial (1.16), los derivados de nicotinamida de la fórmula (1) pueden prepararse a partir de un compuesto de fórmula (2.2):

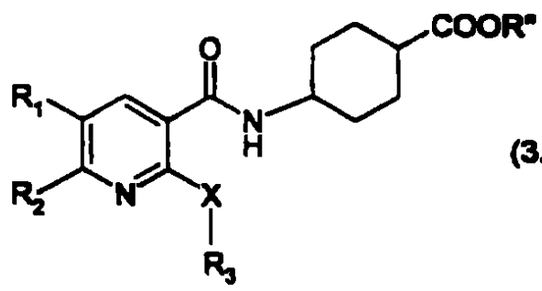



(2.2)

en la que $R_1$, $R_2$, X y $R_3$ son como se describieron previamente para los derivados de nicotinamida de fórmula (1), por reacción de una amina que lleva un sustituyente $R_4$ y utilizando uno de los métodos de activación indicados anteriormente.

Los compuestos de fórmula (2.2) pueden prepararse a

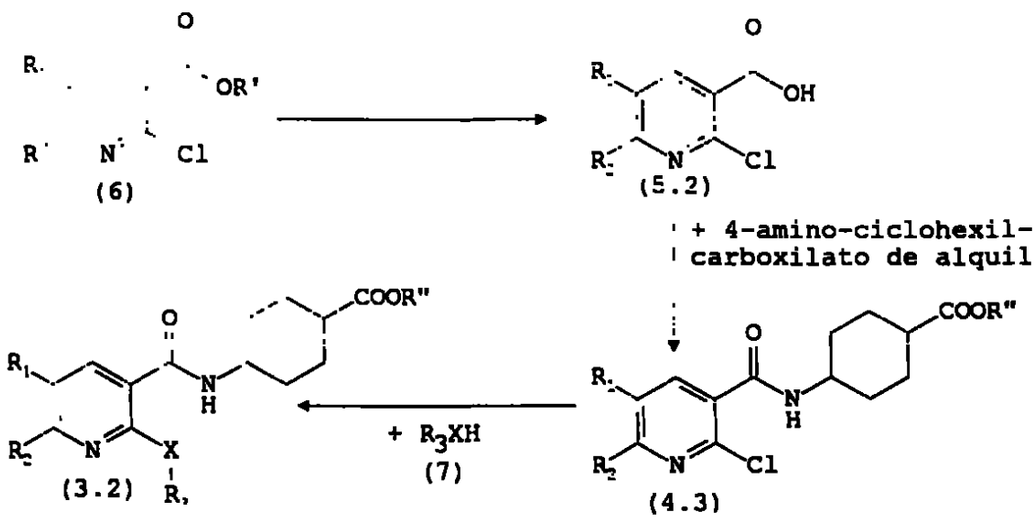
partir del correspondiente éster de fórmula (3.2):




(3.2)

en la que R., R., X, y R, son como se ha descrito previamente para los derivados de nicotinamida de fórmula (1), y R" representa un radical alquilo($C_1$-$C_4$) o un radical bencilo. Si R" representa un radical alquilo($C_1$-$C_4$), los compuestos de fórmula (2.2) se obtienen vía saponificación conforme a los procedimientos estándar, los otros compuestos de fórmula (2.2) se obtienen vía hidrogenación conforme a procedimientos estándar bien conocidos por los expertos en la técnica.

Los compuestos de fórmula (3.2) pueden prepararse de acuerdo con dos rutas sintéticas. La primera ruta sintética se muestra en el esquema 3:

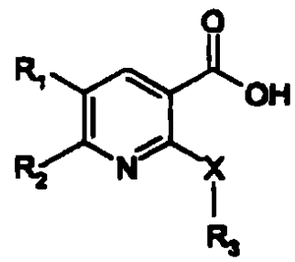


Esquema 3

en que $R_1$, $R_2$, X, $R_3$, R' y R" son como se ha descrito previamente.

En un procedimiento típico, el ácido nicotínico de fórmula (5.2), que se obtiene a partir de un compuesto de fórmula (6) como se ha descrito previamente, puede hacerse reaccionar con un 4-aminociclohexilcarboxilato de alquilo utilizando uno de los métodos de activación indicados anteriormente. La cloropiridina de fórmula (4.3) se hace reaccionar después con el alcohol, tiol o amina de fórmula $R_3XH$ (7) apropiado en el disolvente apropiado (por ejemplo, dimetilformamida o dioxano) conteniendo una base, tal como carbonato de cesio, a temperaturas comprendidas entre la temperatura ambiente (aproximadamente 20°C) y 100°C.

De acuerdo con otra alternativa, los compuestos de fórmula (3.2) pueden también prepararse directamente a partir de compuestos de fórmula (4.1) como se ha descrito previamente:

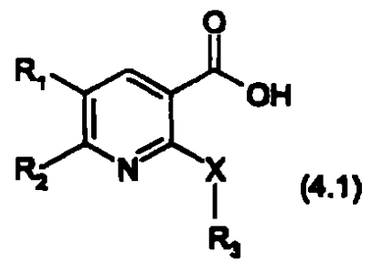



(4.1)

mediante reacción con un 4-aminociclohexilcarboxilato de alquilo utilizando uno de los métodos de activación indicados anteriormente. Dicho compuesto de fórmula (1.4) puede prepararse como ya se ha descrito aquí anteriormente.

De acuerdo con una alternativa final, los derivados de nicotinamida de fórmula (I) también pueden prepararse

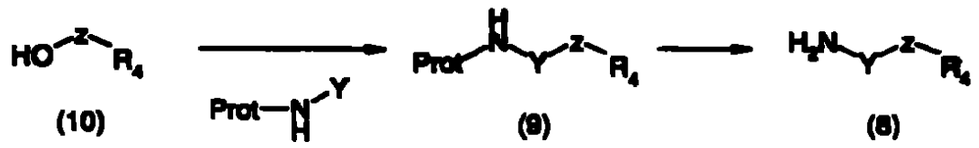
por reacción del ácido de fórmula (4.1) como se describió anteriormente:




(4.1)

con un derivado de amina de fórmula (8): $NH_2$-Y-Z-$R_4$, utilizando uno de los métodos de activación indicados anteriormente. Dicho compuesto de fórmula (4.1) puede prepararse como ya se describió aquí anteriormente.

El derivado de amina de fórmula (8) puede prepararse de acuerdo con el siguiente esquema 4:




Esquema 4

En que R, Z e Y son como se describieron anteriormente para los derivados de nicotinamida de fórmula (1) y Prot es un grupo protector adecuado, que incluye pero no está limitado a bencilo o a carbamato (por ejemplo, butoxicarbonilo).

En un procedimiento típico, la amina protegida Prot-NH-Y puede hacerse reaccionar con el ácido de fórmula (10), utilizando uno de los métodos de activación indicados anteriormente. La desprotección del compuesto resultante de fórmula (9) por métodos bien conocidos para los expertos en la técnica, proporciona la amina de fórmula (8).

Los compuestos de fórmula (10) así como la amina monoprotegida de fórmula Y-Prot-NH-Y, son o bien comerciales o bien pueden prepararse por procedimientos convencionales bien conocidos por el experto en la técnica.

Todas las reacciones anteriores y las preparaciones de los nuevos productos de partida utilizados en los métodos precedentes son convencionales y los reactivos y condiciones de reacción apropiados para su realización o preparación así como los procedimientos para el aislamiento de los productos deseados serán bien conocidos para los expertos en la técnica con referencia a la bibliografía previa y a los ejemplos y preparaciones de aquí.

Para alguna de las etapas de los procedimientos de preparación de los derivados de nicotinamida de fórmula (1) descritos anteriormente, puede ser necesario proteger las funciones potencialmente reactivas que no se desee que reaccionen. En tal caso, puede utilizarse cualquier radical protector compatible. En particular, pueden utilizarse métodos tales como los descritos por T.W. GREENE (Protective Groups in Organic Synthesis, A. Wiley-Interscience Publication, 1981) o por McOMIE (Protective Groups in Organic Chemistry, Plenum Press, 1973).

También, los derivados de nicotinamida de fórmula (1) así como los intermedios para la preparación de los mismos pueden purificarse de acuerdo con diversos métodos bien conocidos, tales como por ejemplo cristalización o cromatografía.

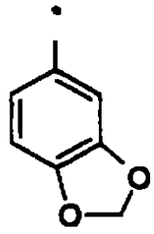
De acuerdo con el primer aspecto, son particularmente preferidos los derivados de nicotinamida de fórmula (1) en la cual:

- $R_1$ y $R_2$ son cada uno un miembro independientemente seleccionado del grupo formado por un átomo de hidrógeno, halo, ciano, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$),
- X es -O-,
- $R_3$ es un miembro seleccionado entre los grupos formados

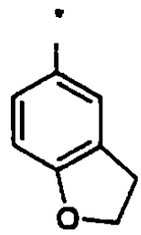
por:

(a) fenilo opcionalmente sustituido con 1 a 3 sustituyentes cada uno seleccionado independientemente del grupo formado por halo, ciano, trifluorometilo, trifluorometoxi, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$), tioalquilo($C_1$-$C_4$), -C(=O)$NH_2$, -C(=O)NH(alquilo($C_1$-$C_4$)), hidroxi, -O-C(=O)-alquilo($C_1$-$C_4$), -C(O)-O-alquilo($C_1$-$C_4$) e hidroxi alquilo($C_1$-$C_4$), cicloalquilo($C_3$-$C_8$) y cicloalquiloxi($C_3$-$C_8$), o

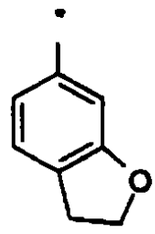
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1) a (1.4):



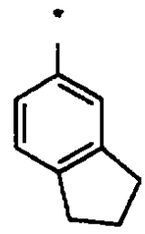
(1.1)



(1.2)



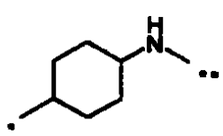
(1.3)



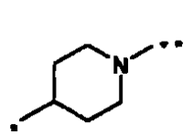
(1.4)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1) a (1.4) a la porción restante de fórmula (1),

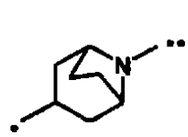
❖ Y es un miembro seleccionado del grupo formado por las fórmulas parciales (1.5) a (1.8):



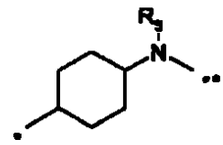
(1.5)



(1.6)



(1.7)



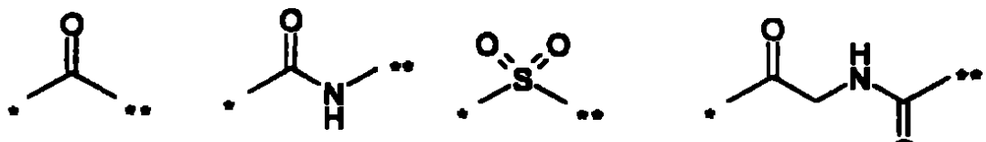
(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones -NH- restantes de fórmula (1) y "***" indica el punto de unión de

cada fórmula parcial (1.5) a (1.8) a las porciones Z restantes de fórmula (1),

y en que $R_4$ es un miembro seleccionado entre los grupos formados por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionado independientemente cada uno del grupo formado por halo, ciano, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxi, hidroxialquilo($C_1$-$C_4$), ácido carboxílico, -C(O)-O-alquilo($C_1$-$C_4$), haloalquilo($C_1$-$C_4$) y -C(=O)$NH_2$,

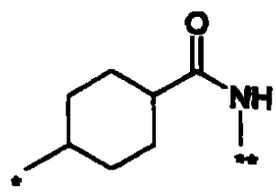
❖ Z es un miembro seleccionado del grupo formado por las fórmulas parciales (1.9) a (1.11) y (1.15):



(1.9) (1.10) (1.11) (1.15)

en que el símbolo "*" indica los puntos de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones Y restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones $R_4$ restantes de fórmula (1),

❖ o alternativamente Y-Z juntos representan un grupo de fórmula (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de

fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones -$R_4$ restantes de fórmula (1),

❖ y $R_1$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente cada uno del grupo formado por ácido carboxílico (-COOH), -C(=O)-O-alquilo($C_1$-$C_4$), alquil($C_1$-$C_4$)-COOH, alquil($C_1$-$C_4$)-C(=O)-O-alquilo($C_1$-$C_4$), halo, ciano, -$C(=O)NH_2$, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), haloalquilo($C_1$-$C_4$), hidroxi e hidroxialquilo($C_1$-$C_4$), o

(b) alquilo($C_1$-$C_4$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grupo formado por un grupo hidroxi, ácido carboxílico, -C(=O)-O-alquilo($C_1$-$C_4$), fenilo, naftilo, heteroarilo o cicloalquilo($C_3$-$C_{11}$), en que dichos grupos fenilo, naftilo heteroarilo y cicloalquilo($C_3$-$C_8$) está cada uno opcionalmente sustituido con 1 a 3 sustituyentes cada uno independientemente seleccionado del grupo formado por ácido carboxílico, C(C=O)Oalquilo($C_1$-$C_4$), halo, ciano, -$C(=O)NH_2$, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$), haloalquilo($C_1$-$C_4$), hidroxi e hidroxialquilo($C_1$-$C_4$),

o, si es apropiado, sus sales y/o isómeros, tautómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos farmacéuticamente aceptables del mismo,

con la condición de que:

1) cuando:

❖ $R_3$ se selecciona del grupo formado por un átomo de hidrógeno, halo y metilo

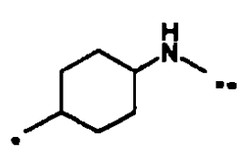
❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

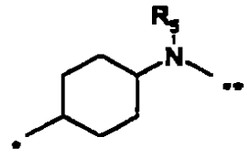
❖ $R_1$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y también está opcionalmente sustituido con 1 sustituyente seleccionado del

grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$),

❖ Y es una fórmula parcial (1.5) o (1.8):



(1.5)



(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de fórmula (1), y en que $R_3$ es un miembro seleccionado entre el grupo formado por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$) o hidroxi, y

❖ Z es un radical -C(=O)-

entonces $R_1$ no puede ser:

a) un cicloalquilo($C_4$-$C_6$) opcionalmente sustituido con alquilo($C_1$-$C_4$),

b) un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, estando dicho fenilo y anillo heterocíclico cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$), o

c) un alquilo($C_1$-$C_4$) opcionalmente sustituido con un hidroxi, o con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S, estando el fenilo y el anillo heterocíclico cada uno opcionalmente sustituidos por hidroxi, halo, alquilo($C_1$-$C_3$) o alcoxi($C_1$-$C_3$),

2) y cuando:

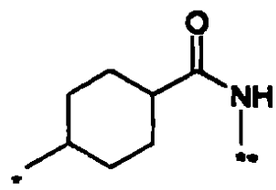
❖ $R_1$ se selecciona entre el grupo formado por un átomo de hidrógeno, halo y metilo,

❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_1$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$), y

❖ Y-Z representa una fórmula parcial (1.16):




**(1.16)**

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones $R_4$ restantes de la fórmula (1),

entonces $R_4$ no puede ser:

a) un cicloalquilo($C_3$-$C_6$) o

b) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S, estando el fenilo y el anillo heterocíclico cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

3) y cuando:

❖ $R_1$ se selecciona entre el grupo formado por un átomo de hidrógeno, halo y metilo,

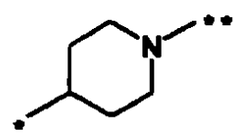
❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_3$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 ó 2 sustituyente(s) cada uno

independientemente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$), y

❖ Y es una fórmula parcial (1.6):



(1.6)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de la fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de la fórmula (1), y

❖ Z es un radical -C(=O)-,

entonces $R_1$ no puede ser un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o por un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S.

Más particularmente preferidos son los derivados de nicotinamida de fórmula (1) en la cual:

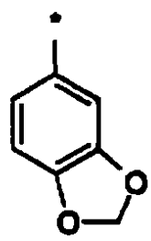
❖ $R_1$ y $R_2$ son cada uno un miembro independientemente seleccionado del grupo formado por un átomo de hidrógeno y halo,

❖ X es -O-,

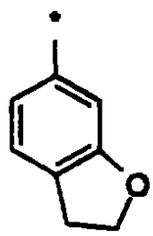
❖ $R_3$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo opcionalmente sustituido con 1 ó 2 sustituyentes seleccionado cada uno independientemente del grupo formado por halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), trifluorometilo, trifluorometoxi, cicloalquilo($C_3$-$C_8$), cicloalquiloxi($C_1$-$C_8$) y tioalquilo($C_1$-$C_4$), o

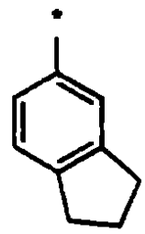
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1), (1,3) o (1.4):



(1.1)



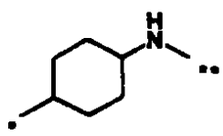
(1.3)



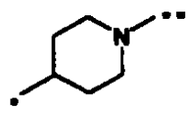
(1.4)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1), (1,3) o (1.4) a la porción restante de fórmula (1),

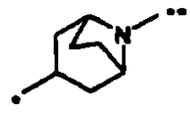
❖ Y es un miembro seleccionado del grupo formado por las fórmulas parciales (1.5) a (1.8):



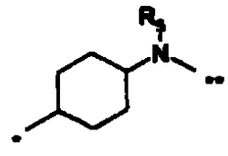
(1.5)



(1.6)



(1.7)

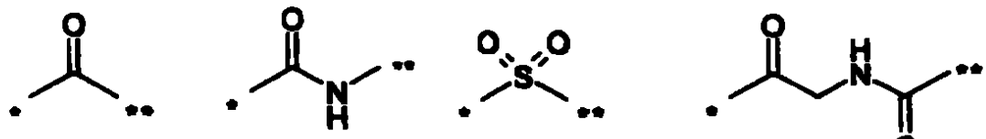


(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones Z restantes de fórmula (1),

y en que $R_4$ es un grupo alquil($C_1$-$C_4$)-fenilo en que dicho fenilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionado cada uno independientemente del grupo formado por hidroxi, ácido carboxílico, C(=O)Oalquilo($C_1$-$C_4$) e hidroxialquilo($C_1$-$C_4$),

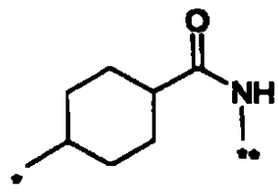
❖ Z es un miembro seleccionado entre el grupo formado por las fórmulas parciales (1.9) a (1.11) y (1.15):



(1.9) (1.10) (1.11) (1.15)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones restantes Y de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones restantes $R_4$ de fórmula (1),

❖ o alternativamente Y-Z juntos representan un grupo de fórmula (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones $-R_1$ de fórmula (1),

❖ y $R_1$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionado independientemente cada uno del grupo formado por un ácido carboxílico (-COOH), -C(O)-O-alquilo($C_1$-$C_4$), alquil($C_1$-$C_4$)-COOH, alquil($C_1$-$C_4$)-C(=O)-O-alquilo($C_1$-$C_4$), halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxialquilo($C_1$-$C_4$) e hidroxi, o

(b) alquilo($C_1$-$C_4$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grup formado por un grupo hidroxi, ácido carboxílico, -

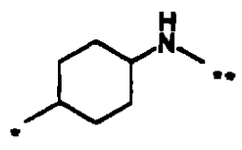
C(=O)-O-alquilo($C_1$-$C_7$), fenilo, naftilo, heteroarilo o cicloalquilo($C_3$-$C_8$), en que dichos grupos fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$) está cada uno opcionalmente sustituidos con 1 a 3 sustituyentes seleccionado cada uno independientemente del grupo formado por ácido carboxílico (-COOH), C(=O)Oalquilo($C_1$-$C_4$), halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxialquilo($C_1$-$C_4$) e hidroxi,

o, si es apropiado, sus sales farmacéuticamente aceptables y/o isómeros, tautómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos del mismo,

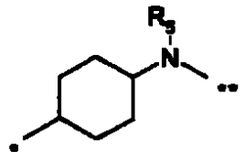
con la condición que:

1) cuando:

- ❖ $R_1$ está seleccionado del grupo formado por un átomo de hidrógeno y halo,
- ❖ $R_2$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_3$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo y alquilo($C_1$-$C_4$),
- ❖ Y es una fórmula parcial (1.5) o (1.8):



(1.5)



(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de fórmula (1), y en que $R_5$ es un alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con hidroxi, y

- ❖ Z es un radical -C(=O)-

entonces $R_4$ no puede ser:

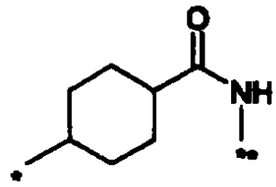
a) un cicloalquilo($C_3$-$C_8$) opcionalmente sustituido con alquilo($C_1$-$C_4$),

b) un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$), o

c) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

2) y cuando:

- ❖ $R_3$ se selecciona del grupo formado por un átomo de hidrógeno y halo,
- ❖ $R_4$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_5$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado del grupo formado por halo y alquilo($C_1$-$C_4$), y
- ❖ Y-Z representa una fórmula parcial (1.16):




**(1.16)**

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones restantes -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones restantes -$R_4$ de fórmula (1),

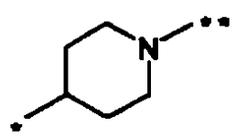
entonces $R_4$ no puede ser:

a) un cicloalquilo($C_3$-$C_8$) o

b) un alquilo($C_1$-$C_7$) opcionalmente sustituido con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

3) y cuando:

- ❖ $R_1$ está seleccionado del grupo formado por un átomo de hidrógeno y halo,
- ❖ $R_2$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_4$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente(s) seleccionado entre el grupo formado por halo y alquilo($C_1$-$C_4$),
- ❖ Y es una fórmula parcial (1.6):




**(1.6)**

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones restantes Z de fórmula (1), y

- ❖ Z es un radical -C(=O)-,

entonces $R_4$ no puede ser un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) independientemente seleccionados entre N, O y S.

Aún más particularmente preferidos son los derivados de nicotinamida de la fórmula (1) en la cual:

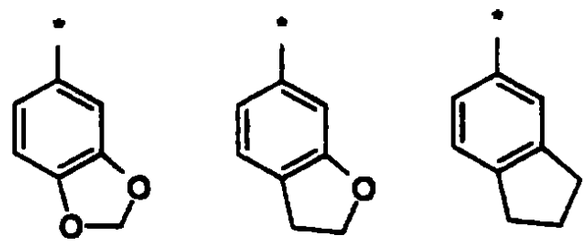
❖ $R_1$ es un átomo de hidrógeno o flúor y $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_3$ es un miembro seleccionado de los grupos formados por:

(a) fenilo opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados independientemente del grupo formado por flúor, cloro, bromo, metilo, etilo, metoxi, trifluorometilo, trifluorometoxi, ciclopropilo, ciclobutiloxi, y metiltio, o

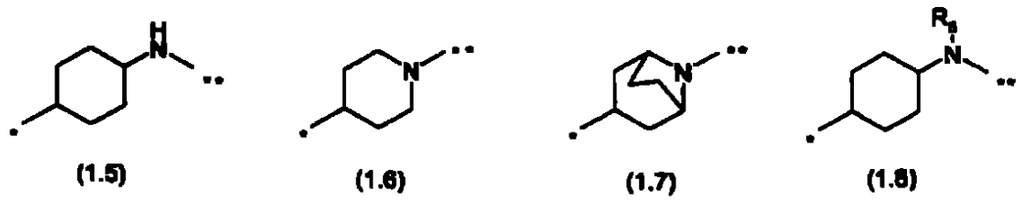
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1), (1,3) o (1.4):



(1.1) (1.3) (1.4)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1), (1.3) o (1.4) a la porción restante de fórmula (1),

❖ Y es un miembro seleccionado del grupo formado por las fórmulas parciales (1.5) a (1.8):



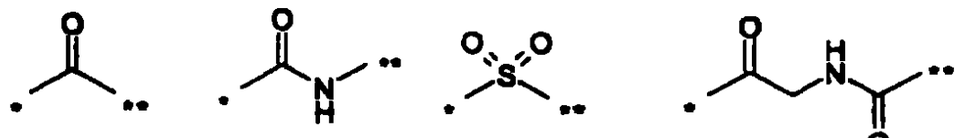
(1.5) (1.6) (1.7) (1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de ca-

da fórmula parcial (1.5) a (1.8) a las restantes porciones Z de fórmula (1),

y en que $R_4$ es un grupo bencilo sustituido con un sustituyente hidroxi sobre el anillo

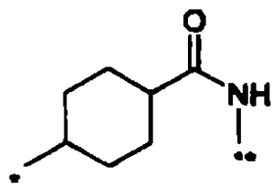
❖ Z es un miembro seleccionado del grupo formado por las fórmulas parciales (1.9) a (1.11) y (1.15):



(1.9) (1.10) (1.11) (1.15)

en que el símbolo "*" indica los puntos de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las restante porciones Y de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las restantes porciones $R_4$ de fórmula (1),

❖ o alternativamente Y-Z juntos representa un grupo de fórmula (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones $-R_4$ de fórmula (1),

❖ y $R_4$ es un miembro seleccionado de los grupos formados por:

(a) fenilo opcionalmente sustituido con 1 a 3 sustitu-

yentes seleccionado independientemente cada uno del grupo formado por un ácido carboxílico, -C(=O)-O-metilo, flúor, cloro, metilo, iso-propilo, metoxi e hidroxi, o

(b) naftilo opcionalmente sustituido con un hidroxi,

(c) piridilo opcionalmente sustituido con un hidroxi o un grupo -C(=O)Ometilo,

(d) un cicloalquilo($C_3$-$C_8$) opcionalmente sustituido con un sustituyente seleccionado del grupo formado por hidroxi, -C(=O)-O-alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-C(=O)-O-alquilo($C_1$-$C_4$),

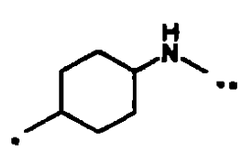
(e) alquilo($C_1$-$C_6$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grupo formado por un hidroxi, ácido carboxílico, -C(=O)Ometilo, -C(=O)Oetilo, cicloalquilo($C_3$-$C_8$) y fenilo, en que dicho fenilo está opcionalmente sustituido con 1 ó 2 sustituyentes seleccionado cada uno independientemente del grupo formado por flúor, cloro, metilo, metoxi e hidroxi,

o, si es apropiado, sus sales y/o isómeros, tautómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos farmacéuticamente aceptables de los mismos,

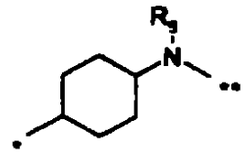
con la condición de que:

1) cuando:

- $R_1$ está seleccionado del grupo formado por un átomo de hidrógeno y flúor,
- $R_2$ es un átomo de hidrógeno,
- X es -O-,
- $R_3$ es un fenilo sustituido con un -S-metilo en posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado del grupo formado por flúor, cloro, metilo y etilo,
- Y es una fórmula parcial (1.5) o (1.8):



(1.5)



(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las restantes porciones Z de fórmula (1), y en que $R_4$ es un bencilo opcionalmente sustituido con hidroxi, y

- Z es un radical -C(=O)-

entonces $R_1$ no puede ser:

a) un cicloalquilo($C_3$-$C_6$) sin sustituir,

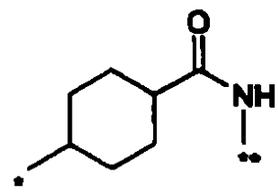
b) un fenilo opcionalmente sustituido con hidroxi, flúor, cloro, metilo, iso-propilo o metoxi o alcoxi($C_1$-$C_4$),

c) un piridilo opcionalmente sustituido con un hidroxi, o

d) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un fenilo opcionalmente sustituido con hidroxi, flúor, cloro, metilo o metoxi,

2) y cuando:

- $R_1$ está seleccionado del grupo formado por un átomo de hidrógeno y flúor,
- $R_2$ es un átomo de hidrógeno,
- X es -O-,
- $R_3$ es un fenilo sustituido con -S-metilo en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado del grupo formado por flúor, cloro, metilo y etilo, y
- Y-Z representa una fórmula parcial (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -$R_4$ de la fórmula (1),

entonces $R_4$ no puede ser:

a) un cicloalquilo($C_4$-$C_9$) o

b) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un fenilo opcionalmente sustituido con hidroxi, flúor, cloro, metilo y metoxi,

3) y cuando:

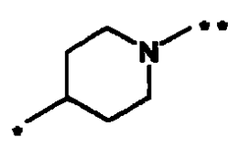
❖ $R_1$ está seleccionado del grupo formado por un átomo de hidrógeno y flúor,

❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_3$ es un fenilo sustituido con -S-metilo en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente(s) seleccionado del grupo formado por flúor, cloro, metilo y etilo,

❖ Y es una fórmula parcial (1.6):



(1.6)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las restantes porciones -NH- de fórmula (I) y "**" indica el punto de unión de cada fórmula par-

cial a las restantes porciones de Z de fórmula (1), y

❖ Z es un radical -C(=O)-,

entonces $R_1$ no puede ser alquilo($C_1$-$C_4$) opcionalmente sustituido con un hidroxi.

Ejemplos particularmente preferidos de los compuestos derivados de nicotinamida de fórmula (1) son como se describe en la sección de Ejemplos aquí más adelante.

Los derivados de nicotinamida de fórmula (1) también pueden ser opcionalmente transformados en sales farmacéuticamente aceptables. En particular, estas sales farmacéuticamente aceptables de los derivados de nicotinamida de la fórmula (1) incluyen las sales de adición de ácido y las sales de base de los mismos.

Las sales de adición de ácido adecuadas están formadas a partir de ácidos minerales u orgánicos no tóxicos que forman sales no tóxicas. Ejemplos adecuados de estas sales de adición de ácido son hidrocloruro, hidrobromuro, hidroyoduro, sulfato, bisulfato, nitrato, fosfato, hidrogenofosfato, acetato, maleato, fumarato, lactato, tartrato, citrato, gluconato, succinato, sacarato, benzoato, metanosulfonato, etanosulfonato, bencenosulfonato, p-toluenosulfonato y sales pamoato.

Las sales de base adecuadas están formadas a partir de bases, que formen sales no tóxicas, tales como sales de metales alcalinos, sales de metales alcalinotérreos o sales de adición con amoníaco y aminas orgánicas fisiológicamente tolerables. Ejemplos adecuados de estas sales de base son las sales de sodio, potasio, aluminio, calcio, magnesio, cinc o amonio así como las sales de adición con trietilamina, etanolamina, dietanolamina, trimetilamina, metilamina, propilamina, diisopropilamina, N,N-dimetiletanolamina, bencilamina, diciclohexilamina, N-bencil-β-fenetilamina, N,N'-dibenciletilendiamina, difenilendiamina, quinina, colina, arginina, lisina, leucina, dibencilamina, tris(2-hidroxietil)amina, o α,α,α-tris-

(hidroximetil)metilamina.

Para compuestos que contienen, ambos, grupos ácidos y grupos básicos, pueden también presentarse en forma de sales internas o betaínas, que también están incluidas en la presente invención. Para una recopilación de las sales adecuadas véase Berge et al, J. Pharm. Sci., 66, 1-19, 1977.

Las sales pueden obtenerse generalmente a partir de los derivados de nicotinamida de fórmula (1) de acuerdo con los procedimientos acostumbrados conocidos por los expertos en la técnica, por ejemplo mediante la combinación con un dispersante o disolvente de base o ácido inorgánico u orgánico, o alternativamente a partir de otras sales mediante intercambio aniónico o intercambio catiónico. La sal puede precipitar a partir de la solución y recogerse por filtración o puede recuperarse por evaporación del disolvente.

Los derivados de nicotinamida de la fórmula (1) también pueden estar presentes en formas estereoisómeras. Si los derivados de nicotinamida de fórmula (1) contienen uno o más centros de asimetría, éstos pueden tener independientemente uno de otro la configuración (S) o la configuración (R). La invención incluye la totalidad de posibles estereisómeros de los derivados de nicotinamida de la fórmula (1), por ejemplo enantiómeros y diastereómeros, y mezclas de dos o más formas estereoisómeras, por ejemplo, mezclas de enantiómeros y/o diastereómeros, en todas las relaciones. Así, la invención se refiere a enantiómeros en forma enantioméricamente pura, como ambos antípodas levorrotatorio y dextrorrotatorio, en forma de racematos y en forma de mezclas de dos enantiómeros en todas las relaciones. La invención se refiere igualmente a los diastereómeros en forma diastereómeramente pura y en forma de mezclas en todas las relaciones. En presencia de isomería cis/trans, la invención se refiere tanto a la

forma cis como la forma trans, como a las mezclas de estas formas en todas las relaciones. Si se desea, pueden prepararse estereoisómeros individuales, mediante el empleo de sustancias de partida estereoquímicamente homogéneas en la síntesis, mediante síntesis estereoselectiva o mediante separación de una mezcla de acuerdo con los métodos acostumbrados, por ejemplo, mediante cromatografía, cristalización o mediante cromatografía en fases quirales. Si es apropiado, la derivatización puede llevarse a cabo antes de la separación de los estereoisómeros. Una mezcla de estereisómeros puede separarse en la fase de los derivados de nicotinamida de fórmula (1) o en la fase de una sustancia de partida o de un intermedio en el transcurso de la síntesis.

Los compuestos de fórmula (1) de acuerdo con la invención pueden por otra parte contener átomos de hidrógeno móviles, esto es, estar presentes en diversas formas tautómeras. La presente invención también se refiere a todos los tautómeros de los compuestos de fórmula (1).

La presente invención incluye adicionalmente otros tipos de derivados de los derivados de nicotinamida de fórmula (1), por ejemplo, solvatos tales como hidratos y polimorfos, esto es, las diversas estructuras cristalinas diferentes de los derivados de nicotinamida de acuerdo con la presente invención.

La presente invención también incluye todas las variaciones isotópicas adecuadas de los derivados de nicotinamida de formula (1) o una sal farmacéuticamente aceptable de las mismas. Una variación isotópica de los derivados de nicotinamida de la fórmula (1) o una sal farmacéuticamente aceptable de los mismos se define como una en la cual al menos un átomo está remplazado por un átomo que tiene el mismo número atómico pero una masa atómica diferente de la masa atómica habitualmente encontrada en la naturaleza. Ejemplos de los isótopos que pueden incor-

porarse en los derivados de nicotinamida de la fórmula (1) y de las sales farmacéuticamente aceptables de los mismos incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, azufre, flúor y cloro tales como $^{2}H$, $^{3}H$, $^{11}C$, $^{13}C$, $^{14}N$, $^{17}O$, $^{18}O$, $^{35}S$, $^{18}F$ y $^{36}Cl$, respectivamente. Algunas variaciones isotópicas de los derivados de nicotinamida de la fórmula (1) y las sales farmacéuticamente aceptables de los mismos, por ejemplo, aquellas en las cuales se incorpora un isótopo radioactivo tal como $^{3}H$ ó $^{14}C$, son útiles en estudios de distribución en los tejidos de fármacos y/o sustratos. Los isótopos tritio, esto es, $^{3}H$, y carbono-14, esto es, $^{14}C$, son particularmente preferidos por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos tal como deuterio, esto es, $^{2}H$, puede proporcionar ciertas ventajas terapéuticas resultantes de mayor estabilidad metabólica, por ejemplo, vida media *in vivo* aumentada o requerimientos de dosificación reducidos y de aquí pueden ser preferidos en algunas circunstancias. Las variaciones isotópicas de los derivados de nicotinamida de fórmula (1) y de las sales farmacéuticamente aceptables de los mismos de esta invención pueden prepararse generalmente por procedimientos convencionales tales como mediante los métodos ilustrativos o mediante las preparaciones descritas en las secciones de Ejemplos y Preparaciones aquí más adelante utilizando las variaciones isotópicas adecuadas de los reactivos adecuados.

Si es apropiado, la presente invención también se refiere a los metabolitos activos de los derivados de nicotinamida de fórmula (1), esto es, los derivados que se forman durante el metabolismo celular y que son activos sobre el organismo. Por ejemplo, dichos metabolitos pueden ser derivados glucurónidos, derivados de N-óxido o derivados sulfonato de los compuestos de fórmula (1).

De acuerdo con un aspecto adicional, la presente in-

vención se refiere a mezclas de derivados de nicotinamida de fórmula (1), así como a mezclas con o de sus sales, solvatos, polimorfos, formas isómeras, metabolitos y/o formas isotópicas farmacéuticamente aceptables.

De acuerdo con la presente invención, la totalidad de las formas mencionadas aquí anteriormente de los derivados de nicotinamida de fórmula (1) excepto las sales farmacéuticamente aceptables (esto es, dichos solvatos, polimorfos, formas isómeras, metabolitos y formas isotópicas), se definen como "formas derivadas" de los derivados de nicotinamida de fórmula (1) en lo que sigue.

Los derivados de nicotinamida de fórmula (1), sus sales y/o formas derivadas farmacéuticamente aceptables son compuestos farmacéuticos activos valiosos, que son adecuados para la terapia y la profilaxis de numerosos trastornos en los que están implicados las enzimas PDE4, en particular los trastornos inflamatorios, trastornos alérgicos, enfermedades respiratorias y heridas. Los derivados de nicotinamida de fórmula (1) y sus sales y formas derivadas farmacéuticamente aceptables como se mencionaron anteriormente pueden administrarse de acuerdo con la invención a animales, preferiblemente mamíferos, y en particular a humanos, como fármacos para terapia o profilaxis. Pueden administrarse per se, en mezclas de unos con otros o en forma de preparaciones farmacéuticas que permitan la administración enteral (gástrica) o parenteral (no gástrica) y que como constituyente activo contienen una dosis eficaz de al menos un derivado de nicotinamida de la fórmula (1), sus sales y/o formas derivadas farmacéuticamente aceptables, además de los excipientes y/o aditivos farmacéuticamente inocuos acostumbrados.

Así, la presente invención se refiere también a composiciones farmacéuticas que contienen una dosis eficaz de al menos un derivado de nicotinamida de fórmula (1) y/o sus sales y/o formas derivadas farmacéuticamente

y/o sus sales y/o formas derivadas farmacéuticamente aceptables, además de los excipientes y/o aditivos farmacéuticamente inocuos acostumbrados. Dichas composiciones se preparan de acuerdo con métodos bien conocidos compatibles con la práctica farmacéutica estándar. Dicha composición contiene generalmente de 0,5% a 60% en peso del compuesto activo y de 40% a 99,5% en peso de excipientes y/o aditivos. De acuerdo con la presente invención, dichos excipientes y/o aditivos son agentes bien conocidos para los artesanos con vistas a proporcionar propiedades favorables en la composición farmacéutica final. Los excipientes y/o aditivos típicos incluyen, pero no significa que estén limitados a, agentes acidulantes y alcalinizantes, propelentes de aerosoles, agentes antimicrobianos (incluyendo agentes antibacterianos, agentes antifúngicos y agentes antiprotozoarios)), antioxidantes, agentes tamponantes, agentes quelantes, agentes dermatológicamente activos, agentes dispersantes, agentes suspensores, emolientes, agentes emulsionantes, mejoradores de la penetración, conservantes, agentes secuestrantes, disolventes, estabilizantes, agentes espesantes, azúcares, tensioactivos y agentes saborizantes. Adicionalmente, dichas composiciones se preparan en una forma compatible para la vía de administración pretendida, la cual se utiliza para cualquier paciente dado, así como para la enfermedad, trastorno o dolencia para cual esté siendo tratado cualquier paciente dado. Las vías adecuadas de administración que pueden ser consideradas son las vías de administración enteral y parenteral, tal como por ejemplo las vías tópica, oral, intranasal, pulmonar, rectal, intravenosa, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intraesternal, intracraneal, intramuscular, subcutánea u ocular.

Cuando se pretende una administración por vía oral, los derivados de nicotinamida de fórmula (1), sus sales

farmacéuticamente aceptables y/o sus formas derivadas, pueden administrarse en forma de comprimidos, cápsulas, multipartículas, geles, filmes, óvulos, elixires, soluciones o suspensiones, que pueden contener agentes saborizantes o colorantes, para aplicaciones de liberación inmediata, retardada, modificada, sostenida, pulsada o controlada. Los derivados de nicotinamida de fórmula (1), sus sales farmacéuticamente aceptables y/o sus formas derivadas, también pueden administrarse como formas de dosificación de rápida dispersión o rápida disolución o en forma de una dispersión de alta energía o como partículas recubiertas. Las formulaciones adecuadas de los derivados de nicotinamida de fórmula (1), sus sales farmacéuticamente aceptables y/o sus formas derivadas, pueden estar en forma recubierta o no recubierta, según se desee.

Dichas composiciones farmacéuticas sólidas, por ejemplo, los comprimidos, pueden contener excipientes tales como celulosa microcristalina, lactosa, citrato de sodio, carbonato de calcio, fosfato dibásico de calcio, glicina y almidón (preferiblemente almidón de maíz, patata o tapioca), disgregantes tales como almidón glicolato de sodio, croscarmelosa de sodio y algunos silicatos complejos, y aglutinantes de granulación tales como polivinilpirrolidona, hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC), sacarosa, gelatina y goma arábiga. Adicionalmente, pueden incluirse agentes lubricantes tales como estearato de magnesio, ácido esteárico, behenato de glicerilo y talco.

Como un ejemplo general, una formulación de comprimidos podría contener típicamente entre aproximadamente 0,01 mg y 500 mg de compuesto activo mientras los pesos del comprimido completo podrían oscilar entre 50 mg y 1000 mg. Los comprimidos pueden fabricarse mediante procedimientos clásicos, por ejemplo por prensado directo o un procedimiento de granulación en seco o en húmedo. Los

núcleos de los comprimidos pueden recubrirse con los sobrerrecubrimientos apropiados.

También pueden emplearse composiciones sólidas de un tipo similar como cargas en cápsulas de gelatina o HPMC. Los excipientes preferidos a este respecto incluyen lactosa, almidón, una celulosa, azúcar de leche o polietilén glicoles de alto peso molecular.

Para los elixires y/o suspensiones acuosas, los derivados de nicotinamida de fórmula (1), sus sales y/o sus formas derivadas farmacéuticamente aceptables, pueden combinarse con diversos agentes edulcorantes o saborizantes, materias colorantes o tintes, con agentes emulsionantes y/o de suspensión y con diluyentes tales como agua, etanol, propilén glicol y glicerina, y combinaciones de los mismos.

Los derivados de nicotinamida de fórmula (1), sus sales y/o sus formas derivadas farmacéuticamente aceptables, también pueden administrarse por inyección, por ejemplo, intravenosamente, intraarterialmente, intraperitonealmente, intratecalmente, intraventricularmente, intrauretralmente, intraesternalmente, intracranealmente, intramuscularmente o subcutáneamente, o pueden administrarse por infusión o técnicas de inyección sin aguja. Para tal administración, lo mejor es utilizarlas en forma de una solución acuosa estéril que puede contener otras sustancias, por ejemplo, suficientes sales o glucosa para hacer la solución isotónica con la sangre. Las soluciones acuosas estarían adecuadamente tamponadas (preferiblemente a un pH de 3 a 9), si fuera necesario. La preparación de dichas formulaciones bajo condiciones estériles se lleva a cabo fácilmente mediante técnicas farmacéuticas estándar bien conocidas por los expertos en la técnica.

Para, ambas, administración oral e inyección, a pacientes humanos, el nivel de dosificación diario de los derivados de nicotinamida de fórmula (1), sus sales y/o

sus formas derivadas farmacéuticamente aceptables, estará habitualmente entre 0,001 mg/kg y 100 mg/kg (en dosis únicas o divididas).

Los derivados de nicotinamida de fórmula (1), sus sales farmacéuticamente aceptables y/o sus formas derivadas, también pueden ser administradas intranasalmente o mediante inhalación y son convenientemente liberadas en forma de un inhalador de polvo seco o una presentación en spray de aerosol procedente de un contenedor presurizado, bomba, spray, atomizador o nebulizador, con o sin el uso de un propelente adecuado, por ejemplo, diclorodifluorometano, triclorofluorometano, un hidrofluoroalcano tal como 1,1,1,2-tetrafluoroetano (HFA 134A [marca comercial]) ó 1,1,1,2,3,3,3-heptafluoropropano (HFA 2277EA [marca comercial]), dióxido de carbono u otro gas adecuado. En el caso de un aerosol presurizado, la unidad de dosificación puede ser determinada proporcionando una válvula para liberar una cantidad medida. El contenedor presurizado, bomba, pulverizador, atomizador o nebulizador puede contener una solución o suspensión del compuesto activo, por ejemplo, utilizando una mezcla de etanol y del propelente como disolvente, el cual puede adicionalmente contener un lubricante, por ejemplo, trioleato de sorbitano. Las cápsulas y cartuchos (fabricados, por ejemplo, de gelatina) para uso en un inhalador o insuflador pueden formularse para contener una mezcla en polvo de un derivado de nicotinamida de la fórmula (1) y una base en polvo adecuada tal como lactosa o almidón.

Las formulaciones en polvo seco o aerosol se disponen preferiblemente de modo que cada dosis medida o "aspirada" contenga de 1 µg a 4000 µg de un derivado de nicotinamida de fórmula (1) para liberar al paciente. La dosis diaria global con un aerosol estará en el intervalo de 1 mg a 20 µg, la cual puede administrarse en una sola dosis o, más habitualmente, en dosis divididas a lo largo

del día.

Los derivados de nicotinamida de fórmula (1), sus sales y/o sus formas derivadas farmacéuticamente aceptables, también pueden administrarse tópicamente, o transdérmicamente, en forma de cremas, geles, suspensiones, lociones, ungüentos, polvos espolvoreables, pulverizaciones, espumas, cremas, apósitos con el fármaco incorporado, soluciones, esponjas, fibras, microemulsiones, películas, parches para la piel, ungüentos tales como petrolato o ungüentos a base de parafina blanda blanca o a través de un parche u otro dispositivo para la piel. Pueden utilizarse mejoradores de la penetración, y el compuesto puede utilizarse en combinación con ciclodextrinas. Además, el compuesto puede liberarse utilizando iontoforesis, electroporación, fonoforesis o sonoforesis. Podrían administrarse directamente sobre el sitio de la herida. Podrían incorporarse en una sutura recubierta. Por ejemplo, pueden incorporarse en una loción o crema constituida por una emulsión acuosa u oleosa de aceites minerales, monoestearato de sorbitano, polisorbato 60, ceras de ésteres de cetilo, alcohol cetearílico, 2-octildodecanol, alcohol bencílico, agua, polietilén glicoles y/o parafina líquida, o pueden incorporarse en un ungüento adecuado formado por uno o más de los siguientes: aceite mineral, petrolato líquido, petrolato blanco, propilén glicol, compuesto de polioxietileno polioxipropileno, cera y agua emulsionantes, o como hidrogel con celulosa o derivados de poliacrilato u otros modificadores de la viscosidad, o como un polvo seco o un pulverizador líquido o aerosol con butano/propano, HFA, CFC, $CO_2$, u otro propelente adecuado, incluyendo también opcionalmente un lubricante tal como trioleato de sorbitano, o como un apósito con el fármaco incorporado ya sea como un apósito de tul, con parafina blanda blanca o apósitos de gasa impregnados con polietilén glicoles o con

apósitos de hidrogel, hidrocoloide, alginato o filme.

Para la administración tópica a pacientes humanos con heridas agudas/quirúrgicas o escaras, el nivel de dosificación diario de los compuestos, en suspensión u otra formulación, podría estar entre 0,01 y 50 mg/ml, preferiblemente entre 0,3 y 30 mg/ml. La dosificación variará con el tamaño de la herida, dependiendo de si la herida está abierta o cerrada o parcialmente cerrada, y de si la piel está intacta o no.

Alternativamente, los derivados de nicotinamida de fórmula (1), sus sales farmacéuticamente aceptables y/o sus formas derivadas, pueden administrarse rectalmente, por ejemplo en forma de un supositorio de un gel, aunque pueden considerarse otras formas.

También pueden administrarse a través de la vía ocular, en particular para las cicatrices oculares. Para uso oftálmico, los compuestos pueden formularse como suspensiones micronizadas en salino estéril, de pH ajustado, isotónico, o, preferiblemente, como soluciones en salino estéril, de pH ajustado, isotónico, opcionalmente en combinación con un conservante tal como cloruro de benzalconio. Alternativamente, pueden formularse en un ungüento tal como petrolato.

Las diversas formulaciones farmacéuticas como se describen aquí anteriormente están también detalladas en "Pharmacie galénique" de A. Lehir (Ed. Mason, 1992, 2ª edición).

El médico en cualquier caso determinará la dosificación real que sea más adecuada para cualquier paciente individual y que variará con la edad, el peso, el estado de salud y el sexo del paciente así como con la gravedad de la enfermedad, trastorno o dolencia a tratar, la combinación opcional con otro(s) tratamiento(s), la respuesta del paciente particular y en general cualquier factor peculiar de la enfermedad, trastorno o dolencia referidos

y del paciente. Así, la dosis diaria entre los hombres puede contener habitualmente entre 50 mg y 5 g de compuesto activo para la administración de una sola o dos o más en un tiempo, según sea apropiado. Por supuesto, puede haber casos individuales en que se precisen márgenes de dosificación mayores o menores y tales están dentro del alcance de esta invención.

De acuerdo con la presente invención, los derivados de nicotinamida de fórmula (1), sus sales y/o sus formas derivadas farmacéuticamente aceptables pueden también utilizarse en combinación con una ciclodextrina. Las ciclodextrinas son conocidas por formar complejos de inclusión y no inclusión con moléculas de fármacos. La formación de un complejo de fármaco-ciclodextrina puede modificar la solubilidad, velocidad de disolución, biodisponibilidad y/o propiedades de estabilidad de una molécula de fármaco. Los complejos de fármaco-ciclodextrina son generalmente útiles para la mayoría de las formas de dosificación y vías de administración. Como una alternativa para la complejación directa con el fármaco, la ciclodextrina puede utilizarse como un aditivo auxiliar, por ejemplo, como un portador, diluyente o solubilizante. La $\alpha$-, $\beta$-, y $\gamma$-ciclodextrinas son las más comúnmente utilizadas y ejemplos adecuados se describen en WO-A-91/11172, WO-A-94/02518 y WO-A-98/55148.

De acuerdo con otra realización de la presente invención, los derivados de fórmula (1), sus sales y/o sus formas derivadas farmacéuticamente aceptables, también pueden utilizarse como una combinación con uno o más agentes terapéuticos adicionales para ser coadministrados a un paciente para obtener algún resultado final terapéutico particularmente deseado. El segundo y más agentes terapéuticos adicionales también pueden ser derivados de nicotinamida de la formula (1), sus sales y/o sus formas derivadas farmacéuticamente aceptables, o

uno o más inhibidores de PDE4 conocidos en la técnica. Más típicamente, el segundo y más agentes terapéuticos se seleccionarán entre una clase diferente de agentes terapéuticos.

Como se utiliza aquí, los términos "co-administración", "co-administrado" y "en combinación con", referidos a los derivados de nicotinamida de fórmula (1) y uno o más agentes terapéuticos distintos, se pretende que signifiquen, y se refieran a, e incluyan lo siguiente:

- administración simultánea de dicha combinación de derivado(s) de nicotinamida y agente(s) terapéutico(s) a un paciente necesitado de tratamiento, cuando tales componentes se formulan juntos en una sola forma de dosificación que libera dichos componentes, a sustancialmente el mismo tiempo, a dicho paciente,
- administración sustancialmente simultánea de dicha combinación de derivado(s) de nicotinamida y agente(s) terapéutico(s) a un paciente necesitado de tratamiento, cuando dichos componentes se formulan aparte uno de otro en formas de dosificación separadas, que se toman a sustancialmente el mismo tiempo por dicho paciente, después de lo cual dichos componentes se liberan a sustancialmente el mismo tiempo a dicho paciente,
- administración secuencial de dicha combinación de derivado(s) de nicotinamida y agente(s) terapéutico(s) a un paciente necesitado de tratamiento, cuando dichos componentes se formulan aparte uno de otro en formas de dosificación separadas que se toman en veces consecutivas por dicho paciente con un intervalo de tiempo significativo entre cada administración, después de lo cual dichos componentes se liberan a sustancialmente tiempos diferentes a dicho paciente; y
- administración secuencial de dicha combinación de derivado(s) de nicotinamida y agente(s) terapéutico(s) a un

paciente necesitado de tratamiento, cuando dichos componentes se formulan juntos en una forma de dosificación única que libera dichos componentes de una forma controlada después de lo cual se administran concurrentemente, consecutivamente, y/o solapadamente a la misma y/o en diferentes veces por dicho paciente.

Ejemplos adecuados de otros agentes terapéuticos que pueden utilizarse en combinación con los derivados de nicotinamida de fórmula (1), sus sales farmacéuticamente aceptables y/o sus formas derivadas incluyen, pero no están limitados a:

(a) inhibidores de 5-lipoxigenasa (5-LO) o antagonistas de la proteína activante de 5-lipoxigenasa (FLAP),

(b) antagonistas de leucotrieno (LTRA) incluyendo antagonistas de $LTB_4$, $LTC_4$, $LTD_4$, y $LTE_4$,

(c) antagonistas del receptor histamínico incluyendo los antagonistas $H_1$ y $H_2$,

(d) agentes simpatomiméticos vasoconstrictores agonistas de los receptores adrenérgicos $\alpha_1$ y $\alpha_2$ para uso descongestivo,

(e) antagonistas del receptor M3 muscarínico o agentes anticolinérgicos,

(f) agonistas del receptor adrenérgico $\beta_2$,

(g) Teofilina,

(h) cromoglicato de sodio,

(i) inhibidores selectivos de COX-1 (NSAIDs) e inhibidores selectivos de COX-2,

(j) Glucocorticoesteroides orales o inhalados,

(k) Anticuerpos monoclonales activos frente a entidades inflamatorias endógenas.

(l) Agentes de anti-factor de necrosis tumoral (anti-TNF-$\alpha$),

(m) Inhibidores de las moléculas de adhesión, incluyendo los antagonistas de VLA-4,

(n) Antagonistas del receptor-$B_1$ y -$B_2$ de cininina,

(o) Agentes inmunosupresores,

(p) Inhibidores de matriz de metaloproteasas (MMPs),

(q) Antagonistas de los receptores NK1, NK2 y NK3 de taquicinina,

(r) Inhibidores de elastasa,

(s) Agonistas del receptor A2a de adenosina,

(t) Inhibidores de uroquinasa,

(u) Compuestos que actuan sobre los receptores de dopamina, por ejemplo, agonistas D2 y

(v) Moduladores de ruta NFκβ, por ejemplo, inhibidores IKK .

De acuerdo con la presente invención, son preferidos la combinación de los derivados de nicotinamida de fórmula (1) con:

De acuerdo con la presente invención, se prefiere la combinación de los derivados de fórmula (1) con:

- antagonistas del receptor M3 muscarínico o agentes anticolinérgicos incluyendo en particular sales de ipratropio, a saber bromuro, sales de tiotropio, a saber bromuro, sales de oxitropio, a saber bromuro, perenzepina y telenzepina,

- agonistas del receptor adrenérgico $\beta_2$, incluyendo albutarol, salbutamol, formoterol y salmeterol

- glucocorticoesteroides, en particular glucocorticoesteroides inhalados con efectos secundarios sistémicos reducidos, incluyendo prednisona, prednisolona, flunisolida, acetónido de triamcinolona, dipropionato de beclometasona, budesonida, propionato de fluticasona y furoato de mometasona, o

- agonistas del receptor A2a de adenosina.

Se tendrá en consideración que todas las referencias efectuadas aquí a tratamiento incluyen tratamiento curativo, paliativo y profiláctico. La descripción que sigue se refiere a las aplicaciones terapéuticas a las cuales pueden aplicarse los derivados de nicotinamida de fórmula

(1).

Los derivados de nicotinamida de fórmula (1) inhiben la isozima PDE4 y por ello tienen una amplia gama de aplicaciones terapéuticas, como se describen adicionalmente más adelante, a causa del papel esencial, que la familia de isozimas PDE4 juega en la fisiología de todos los mamíferos. El papel enzimático realizado por las isozimas PDE4 es la hidrólisis intracelular del 3',5'-monofosfato de adenosina (cAMP) dentro de los leucocitos pro-inflamatorios. El cAMP, es a su vez, responsable para mediar los efectos de numerosas hormonas en el cuerpo, y como consecuencia, la inhibición de PDE4 juega un papel significativo en una diversidad de procesos biológicos. Hay una amplia bibliografía en la técnica que describe los efectos de los inhibidores de PDE sobre las diversas respuestas de las células inflamatorias, que además del aumento del cAMP, incluyen la inhibición de la producción de superóxido, la desgranulación, la quimotaxia y la liberación del factor de necrosis tumoral (TNF) en eosinófilos, neutrófilos y monocitos.

Por lo tanto, un aspecto adicional de la presente invención se refiere a los derivados de nicotinamida de fórmula (1), a sus sales y/o formas derivadas farmacéuticamente aceptables, para uso en el tratamiento de enfermedades, trastornos, y dolencias en los cuales están implicadas las isozimas PDE4. Más específicamente, la presente invención se refiere también a los derivados de nicotinamida de fórmula (1), a sus sales y/o formas derivadas farmacéuticamente aceptables, para uso en el tratamiento de enfermedades, trastornos y dolencias seleccionadas del grupo formado por:

- asma de cualquier tipo, etiología, o patogénesis, en particular asma que es un miembro seleccionado del grupo formado por asma atópica, asma no atópica, asma alérgica, asma bronquial atópica mediada por IgE, asma

bronquial, asma esencial, asma verdadera, asma intrínseca provocada por alteraciones patofisiológicas, asma extrínseca provocada por factores ambientales, asma esencial de causa inaparente o desconocida, asma no atópica, asma bronquítica, asma enfisematosa, asma inducida por el ejercicio, asma inducida por alergenos, asma inducida por aire frío, asma ocupacional, asma infecciosa provocada por infección bacteriana, fúngica, protozoaria o vírica, asma no alérgica, asma incipiente y síndrome del niño jadeante,

- broncoconstricción crónica o aguda, bronquitis crónica, obstrucción de las vías respiratorias pequeñas, y enfisema,
- enfermedades obstructivas o inflamatorias de las vías respiratorias de cualquier tipo, etiología o patogénesis, en particular una enfermedad obstructiva o inflamatoria de las vías respiratorias que es un miembro seleccionado del grupo formado por neumonía eosinófila crónica, enfermedad pulmonar obstructiva crónica (COPD), COPD que incluye bronquitis crónica, enfisema pulmonar o disnea asociadas con la misma, CODP que está caracterizada por la obstrucción progresiva irreversible de las vías respiratorias, el síndrome de insuficiencia respiratoria del adulto (ARDS) y exacerbación de la hiperreactividad de las vías respiratorias consecuente a la terapia con otros fármacos,
- neumoconiosis de cualquier tipo, etiología o patogénesis, en particular neumoconiosis que es un miembro seleccionado del grupo formado por aluminosis o enfermedades de trabajadores de la bauxita, antracosis o asma de los mineros, asbestosis o asma de los ajustadores de vapor, calicosis o enfermedad de los obreros del pedernal, ptilosis provocada por la inhalación del polvo procedente de las plumas de avestruz, siderosis provocada por la inhalación de partículas de hierro, silico-

sis o enfermedad de los molineros, bisinosis o asma del polvo del algodón y neumoconiosis del talco;

- bronquitis de cualquier tipo, etiología o patogénesis, en particular bronquitis que es un miembro seleccionado del grupo formado por bronquitis aguda, bronquitis laringotraqueal aguda, bronquitis araquídica, bronquitis catarral, bronquitis seudomembranosa, bronquitis seca, bronquitis asmática infecciosa, bronquitis productiva, bronquitis estafilococica o bronquitis estreptococica y bronquitis vesicular,
- bronquiectasia de cualquier tipo, etiología o patogénesis, en particular bronquiectasia que es un miembro seleccionado del grupo formado por bronquiectasia cilíndrica, bronquiectasia saculiforme, bronquiectasia fusiforme, bronquiectasia capilar, bronquiectasia quística, bronquiectasia seca y bronquiectasia folicular,
- rinitis alérgica estacional o rinitis alérgica perenne o sinusitis de cualquier tipo, etiología o patogénesis, en particular sinusitis que es un miembro seleccionado del grupo formado por sinusitis purulenta o no purulenta, sinusitis aguda o crónica y sinusitis etmoidal, frontal, maxilar o esfenoidal,
- artritis reumatoide de cualquier tipo, etiología o patogénesis, en particular artritis reumatoide que es un miembro seleccionado del grupo formado 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, en particular un trastorno relacionado con eosinófilos que es un miembro seleccionado del grupo formado por eosinofilia, eosinofilia de infiltración pulmonar, síndrome de Loffler, neu-

monía eosinofílica crónica, eosinofilia pulmonar tropical, aspergilosis bronconeumónica, aspergiloma, granulomas conteniendo eosinófilos, vasculitis granulomatosa alérgica o síndrome de Churg-Strauss, poliarteritis nodosa (PAN) y vasculitis necrotizante sistémica.

- dermatitis atópica, dermatitis alérgica, dermatitis de contacto, o eczema atópico o alérgico,
- urticaria de cualquier tipo, etiología o patogénesis, en particular urticaria que es un miembro seleccionado del grupo formado por urticaria mediada por el sistema inmune, urticaria mediada por el complemento, urticaria inducida por material urticariogénico, urticaria inducida por agentes físicos, urticaria inducida por estrés, urticaria idiopática, urticaria aguda, urticaria crónica, angioedema, urticaria colinérgica, urticaria por frío en la forma dominante autosómica o en la forma adquirida, urticaria de contacto, urticaria gigante y urticaria papular,
- conjuntivitis de cualquier tipo, etiología o patogénesis, en particular conjuntivitis, que es un miembro seleccionado del grupo formado por conjuntivitis actínica, conjuntivitis catarral aguda, conjuntivitis contagiosa aguda, conjuntivitis alérgica, conjuntivitis atópica, conjuntivitis catarral crónica, conjuntivitis purulenta y conjuntivitis primaveral,
- uveítis de cualquier tipo, etiología o patogénesis, en particular uveítes que es un miembro seleccionado del grupo formado por inflamación de toda o parte de la uvea, uveítis anterior, iritis, ciclitis, iridociclitis, uveítis granulomatosa, uveítis no granulomatosa, uveítis facoantigénica, uveítis posterior, coroiditis; y corioretinitis,
- psoriasis;
- esclerosis múltiple de cualquier tipo, etiología o patogénesis, en particular esclerosis múltiple que es un

miembro seleccionado del grupo formado por esclerosis múltiple progresiva primaria y esclerosis múltiple que remite con recidivas,

- enfermedades autoinmunes/inflamatorias de cualquier tipo, etiología o patogénesis, en particular una enfermedad auntoinmune/inflamatoria que es un miembro seleccionado del grupo formado por trastornos hematológicos autoinmunes, anemia hemolítica, anemia aplásica, anemia pura de glóbulos rojos, púrpura trombocitopénica idiopática, lupus eritematoso sistémico, policondritis, escleroderma, granulomatosis de Wegner, dermatomiositis, hepatitis activa crónica, miastenia gravis, síndrome de Stevens-Johnson, síndrome de malabsorción intestinal idiopático, enfermedades inflamatorias del intestino autoinmunes, colitis ulcerativas, oftalmopatía endocrina, enfermedad de Grave, sarcoidosis, alveolitis, neumonitis de hipersensibilidad crónica, cirrosis biliar primaria, diabetes juvenil o diabetes melitus tipo I, queratoconjuntivitis sicca, queratoconjuntivitis epidémica, fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial, fibrosis pulmonar idiopática, fibrosis quística, glomerulonefritis con y sin síndrome nefrótico, glomerulonefritis aguda, síndrome nefrótico idiopático, nefropatía de cambio mínimo, enfermedades inflamatorias/hiperproliferativas de la piel, pénfigo familiar benigno, pénfigo eritematoso, pénfigo foliáceo y pénfigo vulgar,
- prevención del rechazo de injertos alogénicos posteriores al transplante de órganos,
- enfermedad inflamatoria del intestino (IBD) de cualquier tipo, etiología o patogénesis, en particular enfermedad inflamatoria del intestino que es un miembro seleccionado del grupo formado por colitis colágena, colitis poliposa, colitis transmural, colitis ulcerativa y enfermedad de Crohn (CD),

- choque séptico de cualquier tipo, etiología o patogénesis, en particular choque séptico que es un miembro seleccionado del grupo formado por insuficiencia renal, insuficiencia renal aguda, caquexia, caquexia malárica, caquexia hipofisial, caquexia urémica, caquexia cardíaca, caquexia suprarrenal o enfermedad de Adison, caquexia cancerosa y caquexia como consecuencia de infección por el virus de inmunodeficiencia humana (HIV),
- daño hepático,
- hipertensión pulmonar de cualquier tipo, etiología o patogénesis incluyendo hipertensión pulmonar primaria/hipertensión esencial, hipertensión pulmonar secundaria a la insuficiencia cardíaca congestiva, hipertensión pulmonar secundaria a la enfermedad pulmonar obstructiva crónica, hipertensión venosa pulmonar, hipertensión arterial 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, en particular un trastorno del sistema nervioso central que es un miembro seleccionado del grupo formado por depresión, enfermedad de Alzheimer, enfermedad de Parkinson, empeoramiento de la memoria y el aprendizaje, disquinesia tardía, dependencia de fármacos, demencia arterioesclerótica y demencias que acompañan la corea de Huntington, enfermedad de Wilson, parálisis agitans, y atrofías talámicas,
- infección, especialmente infección por virus en que dichos virus aumentan la producción de TNF-α en su hospedador, o en que dichos virus son sensibles a la regulación en ascenso del TNF-α en su huésped de modo que su replicación u otras actividades vitales estén adversamente impactadas, incluyendo un virus que es un miembro

seleccionado del grupo formado por HIV-1, HIV-2, y HIV-3, citomegalovirus (CMV), influenza, adenovirus y virus Herpes incluyendo Herpes zoster y Herpes simplex,

- infecciones por levaduras y hongos en que dichas levaduras y hongos son sensibles a la sobrerregulación por TNF-α o incitan la producción de TNF-α en su huésped, por ejemplo, meningitis fúngica, particularmente cuando se administra conjuntamente con otros fármacos de elección para el tratamiento de las infecciones sistémicas por levaduras y hongos, incluyendo pero no limitadas a, polimixinas, por ejemplo, Polimicina B, imidazoles, por ejemplo, clotrimazol, econazol, miconazol y ketoconazol, triazoles, por ejemplo, fluconazol e itranazol así como anfotericinas, por ejemplo, Anfotericina B y Anfotericina B liposomal,
- daño por reperfusión-isquemia, cardiopatía isquémica, diabetes autoinmune, autoinmunidad retinal, leucemia linfocítica crónica, infecciones HIV, lupus eritematoso, enfermedad del uréter y riñón, trastornos gastrointestinales y urogenitales y enfermedades de próstata,
- reducción de la formación de cicatrices en el cuerpo de animales y humanos, tales como la formación de cicatrices en la curación de heridas agudas, y
- psoriasis, otros usos dermatológicos y cosméticos, incluyendo antiflogísticos, suavizantes de la piel, y productos con actividades que aumenten la elasticidad y humedad de la piel.

Aún, un aspecto adicional de la presente invención se refiere también al uso de los derivados de nicotinamida de fórmula (1), sus sales y/o formas derivadas farmacéuticamente aceptables, para la fabricación de un fármaco que tiene una actividad inhibidora de PDE4. En particular, la presente invención se refiere al uso de los derivados de nicotinamida de fórmula (1), sus sales y/o formas derivadas farmacéuticamente aceptables, para la

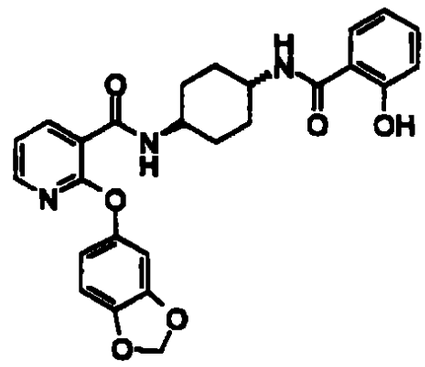
fabricación de un fármaco para el tratamiento de enfermedades, trastornos y dolencias inflamatorias, respiratorias, alérgicas y con formación de cicatrices, y más precisamente para el tratamiento de enfermedades, trastornos y dolencias que se han enumerado anteriormente.

Como consecuencia, la presente invención proporciona un método particularmente interesante de tratamiento de un mamífero, incluyendo un ser humano, con un inhibidor de PDE4 incluyendo el tratamiento de dicho mamífero con una cantidad efectiva de un derivado de nicotinamida de fórmula (1), sus sales y/o formas derivadas farmacéuticamente aceptables. Más precisamente, la presente invención proporciona un método particularmente interesante de tratamiento de un mamífero, incluyendo un ser humano, para el tratamiento de una enfermedad, trastorno o dolencia inflamatoria, respiratoria, alérgica y que forma cicatrices, que incluye el tratamiento de dicho mamífero con una cantidad efectiva de un derivado de nicotinamida de fórmula (1), sus sales y/o formas derivadas farmacéuticamente aceptables.

Los siguientes ejemplos ilustran la preparación de los derivados de nicotinamida de la fórmula (1):

**EJEMPLOS**

**Ejemplo 1 : anti-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(2-hidroxi-benzoil-amina)-ciclohexil]-nicotinamida**



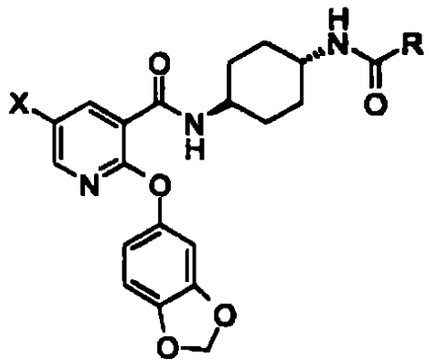
Se agitaron ácido 2-hidroxibenzoico (101 mg, 0,767 mmol), 1-hidroxibenzotriazol hidrato (155 mg, 1,15 mmol) e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (220 mg, 1,15 mmol) en N,N-dimetilformamida (5 ml) en una atmósfera de nitrógeno a temperatura ambiente durante 1,5 horas. Entonces se adicionaron hidrocloruro de anti-N-(4-amino-ciclohexil)-2-(benzo[1,3]dioxol-5-iloxi)-nicotinamida (0,3 g, 0,767 mmol) (véase Preparación 2) y N-metil morfolina (0,167 ml, 0,767 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante otras 18 horas. Se repartió la mezcla entre diclorometano (10 ml) y ácido cítrico al 10% (10 ml). Se separó la capa orgánica y se pasó a través de una membrana hidrófoba. Se separó el disolvente a vacío, y el residuo se trituró con metanol (5 ml) para dar anti-2-(benzo[1,3]dioxol-5-iloxi)-N-[4-(2-hidroxi-benzoilamino)-ciclohexil]-nicotinamida (160,7 mg) como un sólido blanco.

$^1$H NMR (400MHz, $CDCl_3$): $\delta$ = 12,30 (1H, s), 8,57-8,61 (1H, d), 8,01-8,05 (1H, d), 7,74-7,79 (1H, d), 7,33-7,40 (1H, d), 7,12-7,17 (1H, m), 6,93-6,99 (1H, d), 6,78-6,84 (2H, m), 6,69-6,70 (1H, d), 6,59-6,63 (1H, d), 6,19-6,23 (1H, d), 6,02 (2H, s), 3,96-4,09 (2H, m), 2,14-2,26 (4H, m), 1,39-1,50 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 476

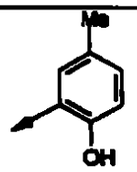
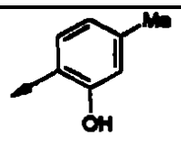
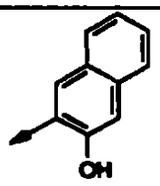
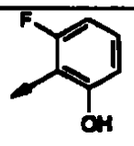
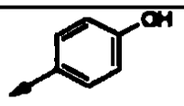
**Ejemplos 2-10**

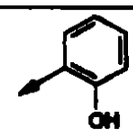
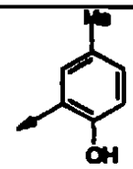
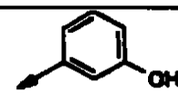
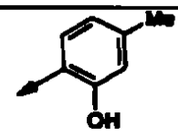
Se prepararon los compuestos de los ejemplos tabulados siguientes (Tabla 1) de fórmula general:



por un método similar al del Ejemplo 1 empleando el ácido carboxílico y la amina apropiados como productos de partida.

**TABLA 1**

| Ejemplo N° | Amina de partida Prep. N° | X | R |
|---|---|---|---|
| 2 | 2 | H |  |
| 3 | 2 | H |  |
| 4 | 2 | H |  |
| 5 | 39 | F |  |
| 6 | 39 | F |  |

| | | | |
|---|---|---|---|
| 7· | 39 | F |  |
| 8· | 39 | F |  |
| 9· | 39 | F |  |
| 10· | 39 | F |  |

Se purificaron estos ejemplos por cromatografía instantánea en columna sobre gel de sílice eluyendo con una mezcla disolvente de diclorometano : pentano (1 : 1, en volumen) cambiando a diclorometano : metanol (50 : 1, en volumen) antes de trituración con éter dietílico.

**Ejemplo 2:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12,08 (1H, s), 8,57-8,61 (1H, d), 8,20-8,24 (1H, d), 7,74-7,79 (1H, d), 7,10-7,20 (3H, m), 6,81-6,89 (2H, m), 6,69 (1H, s), 6,59-6,63 (1H, d), 6,13-6,18 (1H, d), 6,02 (2H, s), 3,96-4,09 (2H, m), 2,31 (3H, s); 2,09-2,29 (4H, m), 1,39-1,53 (4H, m) ppm.

LRMS (electropulverización): m/z [M+H]· 490

**Ejemplo 3:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12,23 (1H, s), 8,73-8,78 (1H, d), 8,18-8,22 (1H, d), 7,67-7,76 (1H, d), 7,14-7,20 (1H, d), 7,05-7,12 (1H, m), 6,79-6,82 (1H, d), 6,77 (1H, s), 6,64 (1H, s), 6,56-6,62 (2H, m), 6,00-6,04 (1H, d), 5,99 (2H, s), 3,90-4,05 (2H, m), 2,30 (3H, s); 2,05-2,22 (4H, m), 1,36-1,49 (4H, m) ppm.

LRMS (electropulverización): m/z [M+H]· 490

8,79%.

**Ejemplo 4:**

H NMR (400MHz, $CDCl_3$): δ = 11,68 (1H, s), 8,53-8,58 (1H, d), 8,17-8,19 (1H, d), 7,93 (1H, s), 7,70-7,78 (2H, m), 7,62-7,66 (1H, d), 7,38-7,44 (1H, t), 7,23-7,28 (2H, m), 7,03-7,08 (1H, m), 6,79-6,83 (1H, d), 6,64 (1H, s), 6,52-6,60 (2H, m), 6,00 (2H, s), 3,97-4,05 (2H, m), 2,17-2,23 (4H, t ancho), 1,39-1,58 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 526

**Ejemplo 5:**

H NMR (400MHz, $CDCl_3$): δ = 13,24 (1H, s), 8,34-8,38 (1H, m), 8,05-8,07 (1H, d), 7,73-7,99 (1H, d), 7,25-7,32 (1H, m, parcialmente enmascarada por el disolvente), 6,88-6,96 (1H, m), 6,83-6,87 (1H, d), 6,76-6,81 (1H, d), 6,66 (1H, s), 6,53-6,63 (2H, m), 6,03 (2H, s), 3,95-4,15 (2H, m), 2,12-2,26 (4H, m), 1,39-1,54 (4H, m) ppm.

LCMS (electropulverización): m/z $[M-H]^-$ 510

**Ejemplo 6:**

H NMR (400MHz, $CDCl_3$): δ = 8,28-8,35 (1H, m), 8,03-4,08 (1H, d), 7,73-7,84 (1H, d), 7,57-7,71 (2H, d), 6,76-6,91 (3H, m), 6,67 (1H, s), 6,57-6,62 (1H, d), 6,16 (1H, s), 6,02 (2H, s), 5,83-5,92 (1H, d), 3,90-4,08 (2H, m), 2,08-2,23 (4H, m), 1,35-1,50 (4H, m) ppm.

LCMS (electropulverización): m/z $[M-H]^-$ 492

**Ejemplo 7:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,30-8,36 (1H, m), 8,04-8,08 (1H, d), 7,73-7,82 (1H, d), 7,29-7,41 (2H, m), 6,93-6,98 (1H, d), 6,79-6,87 (2H, m), 6,66 (1H, s), 6,57-6,63 (1H, d), 6,11-6,20 (1H, d), 6,03 (2H, s), 3,93-4,10 (2H, m), 2,10-2,29 (4H, m), 1,39-1,57 (4H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 492

**Ejemplo 8:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,27-8,36 (1H, m), 8,01-8,07 (1H, m), 7,73-7,82 (1H, m), 7,15-7,22 (1H, m), 6,78-6,90 (2H, m), 6,63-6,67 (1H, m), 6,54-6,62 (1H, m), 6,05-6,15 (1H, m), 6,02 (2H, s), 3,88-4,09 (2H, m), 2,29 (3H, s), 2,09-2,26 (4H, m), 1,37-1,49 (4H, m) ppm.

LRMS (electropulverización): m/z [M-H]⁻ 506

**Ejemplo 9:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,03-8,09 (1H, d), 7,93-7,99 (1H, m), 7,17-7,27 (3H, m), 6,87-6,93 (1H, m), 6,77-6,84 (1H, d), 6,70-6,73 (1H, d), 6,57-6,62 (1H, d), 5,97 (2H, s), 3,80-3,98 (2H, m), 1,96-2,18 (4H, m), 1,41-1,63 (4H, m) ppm.

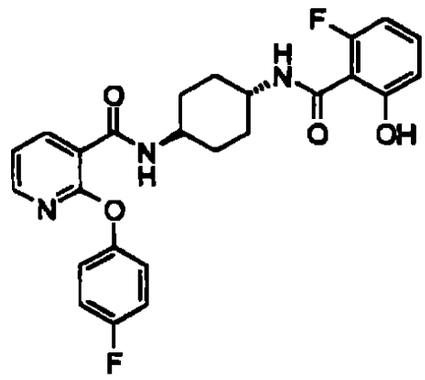
LRMS (electropulverización): m/z [M-H]⁻ 492

**Ejemplo 10:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12,26 (1H, s), 8,30-8,36 (1H, m), 8,04-8,07 (1H, d), 7,74-7,82 (1H, d), 7,17-7,22 (1H, d), 6,83-6,86 (1H, d), 6,77 (1H, s), 6,55-6,67 (3H, m), 6,03-6,12 (1H, d), 6,02 (2H, s), 3,92-4,08 (2H, m), 2,33 (3H, s), 2,12-2,25 (4H, m), 1,36-1,51 (4H, m) ppm.

LRMS (electropulverización) m/z [M-H]⁻ 506

**Ejemplo 11: anti-N-[4-(2-fluoro-6-hidroxi-benzoilamino)-ciclohexil]-2-(4-fluoro-fenoxi)-nicotinamida**

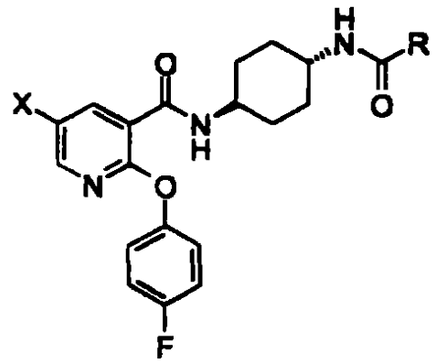


Se agitaron ácido 2-fluoro-6-hidroxilbenzoico (128 mg, 0,82 mmol), 1-hidroxibenzotriazol (166 mg, 1,23 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (204 mg, 1,07 mmol), hidrocloruro de anti-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)nicotinamida (300 mg, 0,82 mmol) (véase Preparación 4) y N-metil morfolina (0,18 ml, 1,64 mmol) en N,N-dimetilformamida (5 ml) en una atmósfera de nitrógeno a temperatura ambiente

durante 18 horas. Se repartió la mezcla entre diclorometano (6 ml) y ácido acético al 10 % (6 ml) y se separó la capa orgánica. La capa orgánica se secó sobre sulfato de magnesio anhidro y se concentró a vacío. Se trituró el residuo con éter dietílico (5 ml) para dar anti-N-[4-(2-fluoro-6-hidroxi-benzoilamino)-ciclohexil]-2-(4-fluoro-fenoxi)-nicotinamida (110 mg) como un sólido blanco.
$^1$H NMR (400MHz, DMSO-d$^6$): δ = 10,95 (1H, s ancho), 8,23-8,28 (1H, d), 8,19-8,22 (1H, d), 8,04-8,18 (1H, m), 7,98-8,03 (1H, d), 7,15-7,28 (5H, m), 6,60-6,75 (2H, m), 3,70-3,80 (2H, m), 1,80-2,00 (4H, m), 1,31-1,49 (4H, m) ppm.
LRMS (termopulverización): m/z [M+H]$^+$ 488

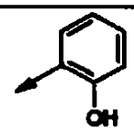
**Ejemplos 12-40**

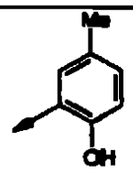
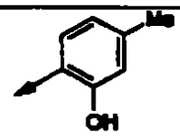
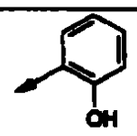
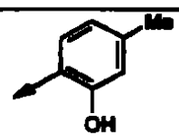
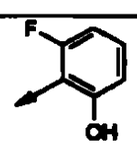
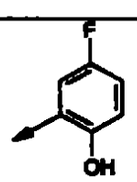
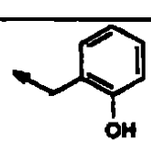
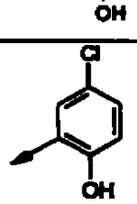
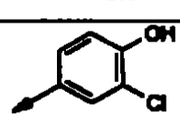
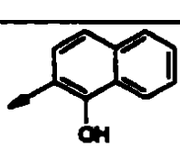
Se prepararon los compuestos de los siguientes ejemplos tabulados (Tabla 2) de fórmula general:

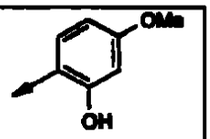
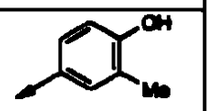
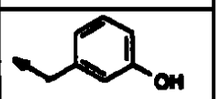
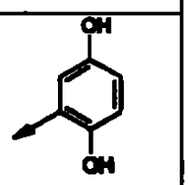
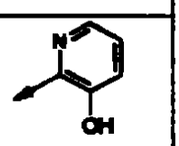
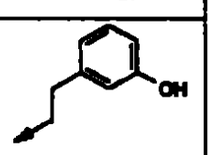
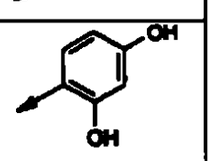
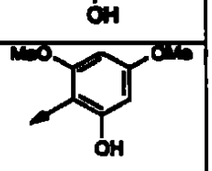
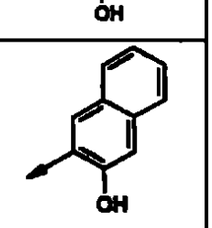
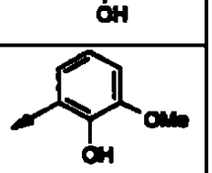
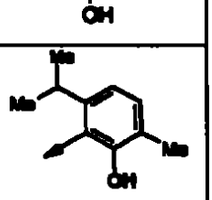


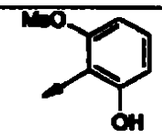
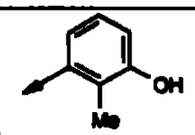
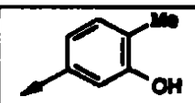
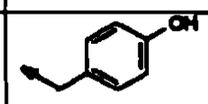
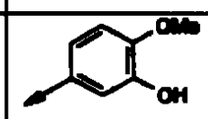
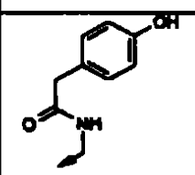
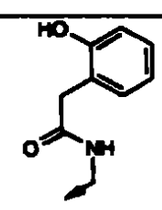

por un método similar al del Ejemplo 11 empleando el ácido carboxílico y la amina apropiados como productos de partida.

**TABLA 2**

| Ejemplo N° | Amina de partida Prep. N° | X | R |
|---|---|---|---|
| 12 | 4 | H |  |

| | | | |
|---|---|---|---|
| 13 | 4 | H |  |
| 14 | 4 | H |  |
| 15[1] | 7 | F |  |
| 16[1] | 7 | F |  |
| 17[1] | 7 | F |  |
| 18[1] | 7 | F |  |
| 19[1,4] | 7 | F |  |
| 20[1] | 7 | F |  |
| 21[1] | 7 | F |  |
| 22[1] | 7 | F |  |

| | | | |
|---|---|---|---|
| 23 | 7 | F |  |
| 24 | 7 | F |  |
| 25 | 7 | F |  |
| 26 | 7 | F |  |
| 27 | 7 | F |  |
| 28 | 7 | F |  |
| 29 | 7 | F |  |
| 30 | 7 | F |  |
| 31 | 7 | F |  |
| 32 | 7 | F |  |
| 33 | 7 | F |  |

| | | | |
|---|---|---|---|
| 34[1] | 7 | F |  |
| 35[1] | 7 | F |  |
| 36[1] | 7 | F |  |
| 37[1] | 7 | F |  |
| 38[1] | 7 | F |  |
| 39[1] | 9 | F |  |
| 40 | 9 | F |  |

[1] Se repartieron estos ejemplos entre acetato de etilo y agua, y se lavó la fase orgánica con una disolución acuosa saturada de cloruro de sodio.

[2] Estos ejemplos se purificaron por cromatografía instantánea en columna sobre gel de sílice eluyendo con un gradiente de disolventes de diclorometano metanol (100 : 0 cambiando hasta 95 : 5, en volumen) para dar el compuesto final.

**Ejemplo 12:**

$^1$H NMR (400MHz, $CDCl_3$): $\delta$ = 12,29 (1H, s), 8,56-8,60 (1H, d), 8,18-8,21 (1H, d), 7,66-7,72 (1H, d), 7,36-7,40 (2H, m), 7,12-7,18 (4H, d), 6,96-6,99 (1H, d), 6,78-6,83 (1H,

d), 6,17-6,22 (1H, d), 3,96-4,12 (2H, m), 2,12-2,29 (4H, m), 1,40-1,53 (4H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 450

**Ejemplo 13:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 12,05 (1H, s), 8,58-8,62 (1H, d), 8,18-8,22 (1H, d), 7,68-7,75 (1H, d), 7,09-7,20 (6H, m), 6,83-6,88 (1H, d), 6,15-6,19 (1H, d), 3,94-4,11 (2H, m), 2,29 (3H, s), 2,13-2,24 (4H, m), 1,40-1,55 (4H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 464

**Ejemplo 14:**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 12,26 (1H, s), 8,58-8,62 (1H, d), 8,18-8,22 (1H, m), 7,68-7,73 (1H, d), 7,20-7,24 (1H, d), 7,10-7,19 (4H, m), 6,78 (1H, s), 6,61-6,67 (2H, d), 6,04-6,10 (2H, d), 3,92-4,10 (2H, m), 2,32 (3H, s), 2,15-2,23 (4H, m), 1,40-1,55 (4H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 464

Encontrado C, 67,14; H, 5,62; N, 8,82. $C_{24}H_{25}FN_4O_4$ requiere C, 67,37; H, 5,65; N, 9,07%.

**Ejemplo 15:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12,55 (1H, 5), 8,43-8,49 (1H, d), 8,24-8,30 (1H, d), 8,08-8,14 (1H, d), 7,84-7,90 (1H, d), 7,22-7,35 (1H, t), 7,08-7,20 (4H, m), 6,74-6,83 (2H, d), 3,60-3,80 (2H, m), 1,76-1,90 (4H, m), 1,20-1,50 (4H, m) ppm.

LRMS (electropulverización): m/z [M-H]$^-$ 466

**Ejemplo 16:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12,28 (1H, s), 8,50-8,57 (1H, m), 8,02-8,06 (1H, d), 7,70-7,78 (1H, d), 7,10-7,20 (4H, m), 6,68 (1H, s), 6,62-6,67 (1H, d), 6,12-6,21 (1H, d), 3,85-3,95 (2H, m), 2,33 (3H, s), 2,00-2,28 (4H, m), 1,40-1,50 (4H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 482

**Ejemplo 17:**

$^1$H NMR (300MHz, $CDCl_3$): δ = 13,25 (1H, s), 8,33-8,40 (1H,

m), 8,03-8,07 (1H, d), 7,70-7,79 (1H, d), 7,25-7,35 (1H, m, parcialmente enmascarada por el disolvente), 7,12-7,20 (4H, m), 6,85-7,00 (1H, dd), 6,75-6,83 (1H, d), 6,50-6,63 (1H, dd), 3,87-4,12 (2H, m), 2,13-2,26 (4H, m), 1,41-1,52 (4H, m) ppm.

LRMS (termopulverización) m/z $[M+NH_4]^+$ 503

**Ejemplo 18:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 8,55-8,63 (1H, d), 8,32-8,38 (1H, d), 8,19-8,23 (1H, d), 7,92-7,99 (1H, m), 7,70-7,80 (1H, d), 7,17-7,28 (5H, m), 6,88-6,96 (1H, m), 3,69-3,85 (2H, m), 1,83-2,00 (4H, m), 1,33-1,53 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+NH_4]^+$ 503

**Ejemplo 19:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9,69 (1H, s), 8,23-8,34 (1H, d), 8,18 (1H, s), 7,90-7,98 (2H, m), 7,15-7,28 (5H, m), 6,98-7,07 (1H, t), 6,66-6,80 (2H, m), 3,61-3,78 (1H, m), 3,40-3,60 (1H, m), 3,35 (2H, s, enmascarada por el disolvente), 1,75-1,95 (4H, m), 1,22-1,46 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 482

**Ejemplo 20:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 8,63-8,69 (1H, d), 8,32-8,37 (1H, d), 8,17-8,21 (1H, d), 7,92-7,99 (2H, m), 7,37-7,42 (1H, m), 7,16-7,27 (4H, m), 6,86-6,93 (1H, d), 3,70-3,86 (2H, m), 1,85-2,01 (4H, m), 1,30-1,52 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 502, 504

**Ejemplo 21**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 10,72 (1H, s) 8,29-8,36 (1H, m), 8,17-8,22 (1H, m), 8,05-8,15 (1H, m), 7,92-7,98 (1H, m), 7,85 (1H, s), 7,63-7,68 (1H, d), 7,15-7,26 (4H, m), 6,92-6,99 (1H, d), 3,63-3,82 (2H, m), 1,76-1,98 (4H, m), 1,28-1,48 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 502, 504

**Ejemplo 22:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 14,67 (1H, s), 8,63-8,76 (1H, m), 8,34-8,43 (1H, d), 8,16-8,32 (2H, m), 7,83-8,03

(3H, m), 7,59-7,69 (1H, t), 7,32-7,40 (1H, d), 7,17-7,31 (4H, m), 6,88-6,96 (1H, m), 3,69-3,85 (2H, m), 1,83-2,00 (4H, m), 1,33-1,53 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 518

**Ejemplo 23:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 13,08 (1H, s) 8,28-8,36 (2H, t), 8,18-8,22 (1H, d), 7,91-7,97 (1H, m), 7,77-7,82 (1H, d), 7,15-7,31 (4H, m), 6,40-6,44 (1H, d), 6,38 (1H, s), 3,65-3,88 (2H, m), 1,78-2,04 (4H, m), 1,30-1,60 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 498

**Ejemplo 24:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9,76 (1H, s), 8,29-8,35 (1H, d), 8,18-8,21 (1H, d), 7,90-7,96 (1H, m), 7,83-7,89 (1H, d), 7,58 (1H, s), 7,45-7,52 (1H, d), 7,16-7,23 (4H, m), 6,72-6,78 (1H, d), 3,63-3,83 (2H, m), 2,11 (3H, s), 1,80-1,98 (4H m), 1,30-1,52 (4H, m) ppm.

LRMS (termopulverización) m/z $[M+H]^+$ 482

**Ejemplo 25:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9,24 (1H, s), 8,25-8,32 (1H, d), 8,20 (1H, s), 7,84-7,99 (2H, t), 7,17-7,27 (4H, m), 6,99-7,10 (1H, t), 6,54-6,68 (3H, m), 3,60-3,77 (2H, m), 3,35 (2H, s, enmascarada por el disolvente), 1,74-1,95 (4H, m), 1,12-1,42 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 482

**Ejemplo 26:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 11,68 (1H, s), 8,96 (1H, s), 8,45-8,50 (1H, d), 8,32-8,37 (1H, d), 8,18-8,22 (1H, d), 7,92-7,99 (1H, m), 7,16-7,32 (5H, m), 6,81-6,87 (1H, m), 6,68-6,74 (1H, d), 3,67-4,06 (2H, m), 1,78-1,98 (4H, m), 1,35-1,56 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 484

**Ejemplo 27:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12,59 (1H, s), 8,89-8,97 (1H, d), 8,32-8,38 (1H, d), 8,19-8,22 (1H, d), 8,13-8,17

(1H, m), 7,93-8,01 (1H, m), 7,93-8,01 (1H, m), 7,48-7,53 (1H, m), 7,38-7,42 (1H, d), 7,16-7,36 (4H, m), 3,67-3,90 (2H, m), 1,79-2,02 (4H, m), 1,48-1,77 (2H, m), 1,32-1,47 (2H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 469

Encontrado C, 60,94; H, 4,79; N, 11,83. $C_{24}H_{22}F_2N_4O_4$. 0,1 moles $CH_2Cl_2$ requiere C, 60,69; H,4,69; N, 11,75%.

**Ejemplo 28:**

H NMR (300MHz, DMSO-$d^6$): δ 9,19 (1H, s), 8,23-8,31 (1H, d), 8,18-8,21 (1H, m), 7,91-7,96 (1H, d), 7,65-70 (1H, d), 7,16-7,25 (4H, m), 6,98-7,09 (1H, m), 6,51-6,62 (3H, m), 3,56-3,77 (2H, m), 2,61-2,47 (2H, m), 2,23-2,33 (2H, m), 1,72-1,93 (4H, m), 1,18-1,40 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 496

**Ejemplo 29:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12,96 (1H, s), 10,04 (1H, s), 8,18-8,42 (3H, m), 7,90-8,10 (1H, m), 7,63-7,76 (1H, d), 7,07-7,45 (4H, m), 6,13-6,40 (2H, m), 3,60-3,90 (2H, m), 1,72-2,15 (4H, m), 1,28-1,60 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 484

Encontrado C, 60,11; H, 4,99; N, 7,95. $C_{25}H_{21}F_2N_1O_5$. 0,25 moles $CH_2Cl_2$ requiere C, 60,09; H, 4,64; N, 8,33%.

**Ejemplo 30:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 14,27 (1H, s), 8,33-8,38 (1H, d), 8,19-8,23 (1H, d), 7,92-8,01 (1H, m), 7,17-7,37 (5H, m), 6,12 (1H, s), 6,08 (1H, s), 3,60-4,00 (8H, parcialmente enmascarada por el disolvente), 1,82-2,03 (4H, d), 1,24-1,60 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 528

**Ejemplo 31:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12,08 (1H, s ancho), 8,80-8,86 (1H, d), 8,51 (1H, s), 8,35-8,42 (1H, d), 8,20-8,24 (1H, d), 7,92-7,99 (1H, m), 7,84-7,89 (1H, d), 7,72-7,78 (1H, d), 7,44-7,52 (1H, t), 7,28-7,36 (1H, t), 7,19-7,24 (5H, m), 3,72-3,93 (2H, m), 1,93-2,06 (4H, d), 1,36-1,62

(4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 518

**Ejemplo 32:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 12,77 (1H, s), 8,50-8,58 (1H, d), 8,33-8,38 (1H, d), 8,18-8,23 (1H, d), 7,92-8,02 (1H, m), 7,42-7,48 (1H, d), 7,16-7,38 (4H, m), 7,07-7,14 (1H, d), 6,73-6,83 (1H, t), 3,70-3,92 (5H, m), 1,80-2,08 (4H, m), 1,23-1,58 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 498

**Ejemplo 33:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 8,26-8,38 (1H, d), 8,19-8,22 (1H, m), 7,92-8,08 (2H, m), 7,16-7,36 (4H, m), 6,96-7,05 (1H, d), 6,68-6,75 (1H, d), 3,62-3,83 (2H, m), 2,80-2,95 (1H, m), 2,16 (3H, s), 1,78-2,02 (4H, m), 1,23-1,48 (4H, m), 1,08-1,16 (6H, d) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 522

**Ejemplo 34:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 13,43 (1H, s), 8,32-8,39 (2H, m), 8,22-8,25 (1H, d), 7,92-8,02 (1H, m), 7,18-7,37 (5H, m), 6,54-6,60 (1H, d), 6,47-6,53 (1H, d), 3,89 (3H, s), 3,73-3,88 (2H, m), 1,89-2,04 (4H, d), 1,37-1,43 (4H, m) ppm.

LCMS (electropulverización): m/z $[M-H]^-$ 496

**Ejemplo 35:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9,41 (1H, s), 8,32-8,38 (1H, d), 8,08-8,10 (1H, d), 7,96-8,04 (2H, m), 7,20-7,30 (4H, m), 6,96-7,02 (1H, t), 6,78-6,83 (1H, d), 6,64-6,70 (1H, d), 3,61-3,78 (2H, s ancho), 2,08 (3H, s), 1,80-1,98 (4H, m), 1,30-1,44 (4H, m) ppm.

LCMS (termopulverización): m/z $[M+H]^+$ 482, $[M+NH_4]^+$ 499.

**Ejemplo 36:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9,42 (1H, s), 8,32-828 (1H, d), 8,18-8,20 (1H, d), 8,00-8,05 (1H, d), 7,93-8,00 (1H, m), 7,15-7,26 (6H, m), 7,08-7,13 (1H, d), 3,66-3,80 (2H, s ancho), 2,14 (3H, s), 1,80-1,97 (4H, m), 1,27-1,50 (4H,

m) ppm.

LCMS (termopulverización): m/z $[M+H]^+$ 482, $[M+NH_4]^+$ 499.

**Ejemplo 37:**

$^1H$ NMR (300MHz, DMSO-$d^6$): δ = 9,18 (1H, s), 8,28-8,33 (1H, d), 8,18-8,20 (1H, d), 7,93-7,99 (1H, m), 7,83-7,89 (1H, d), 7,17-7,28 (4H, m), 6,98-7,05 (2H, d), 6,63-6,67 (2H, d), 3,60-3,80 (2H, s ancho), 3,30 (2H, s, enmascarada por el disolvente), 1,73-1,92 (4H, m), 1,19-1,40 (4H, m) ppm.

LCMS (termopulverización): m/z $[M+H]^+$ 482, $[M+NH_4]^+$ 499.

**Ejemplo 38:**

$^1H$ NMR (300MHz, DMSO-d6): δ = 9,08-9,13 (1H, s ancho), 8,32-8,37 (1H, d), 8,09-8,11 (1H, m), 7,94-8,00 (2H, m), 7,19-7,32 (6H, m), 6,91-6,96 (1H, d), 3,64-3,84 (5H, s + s ancho), 1,80-1,98 (4H, m), 1,30-1,50 (4H, m) ppm.

LCMS (termopulverización): m/z $[M+H]^+$ 498.

**Ejemplo 39:**

$^1H$ NMR (300MHz, DMSO-$d^6$): δ = 9,18-9,28 (1H, s ancho), 8,28-8,34 (1H, d), 8,19-8,21 (1H, d), 8,02-8,08 (1H, t), 7,95-7,99 (1H, m), 7,67-7,71 (1H, d), 7,18-7,29 (4H, m), 7,00-7,08 (2H, d), 6,65-6,70 (2H, d), 3,60-3,79 (3H, s ancho + d), 3,35-3,59 (3H, m, enmascarada por el disolvente), 1,74-1,96 (4H, m), 1,19-1,42 (4H, m) ppm.

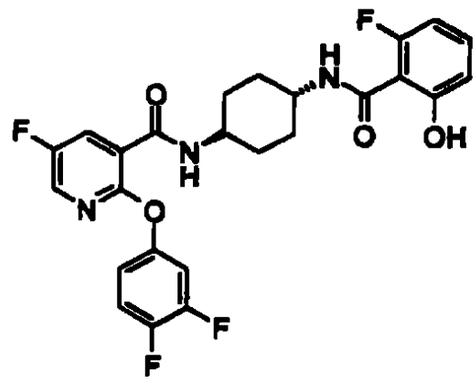
LCMS (termopulverización): m/z $[M+H]^+$ 539.

**Ejemplo 40:**

$^1H$ NMR (300MHz, DMSO-$d^6$): δ = 9,63 (1H, s), 8,25-8,35 (1H, d), 8,19-8,21 (1H, d), 8,00-8,07 (1H, t), 7,93-7,98 (1H, m), 7,58-7,63 (1H, d), 7,15-7,30 (4H, m), 7,00-7,14 (2H, m), 6,77-6,82 (1H, d), 6,70-6,76 (1H, t), 3,60-3,80 (3H, m + d), 3,41-3,58 (3H, m + s), 1,69-1,99 (4H, m), 1,20-1,44 (4H, m) ppm.

LCMS (termopulverización): m/z $[M+H]^+$ 539.

**Ejemplo 41 : anti-5-Fluoro-2-(3,4-difluoro-fenoxi)-N-[4-(2-fluoro-6-hidroxi-benzoilamino)ciclohexil]nicotinamida**

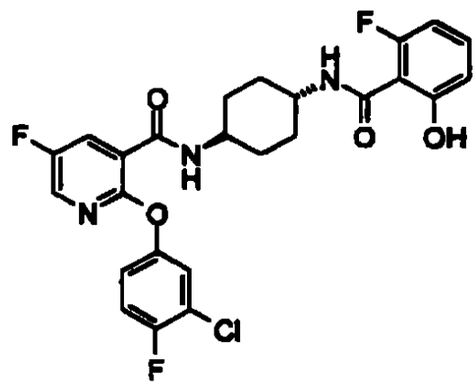


Se agitaron ácido 2-fluoro-6-hidroxibenzoico (115 mg, 0,736 mmol), 1-hidroxibenzotriazol (149 mg, 1,11 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etil-carbodiimida (184 mg, 0,957 mmol), hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(3,4-difluorofenoxi)-nicotinamida (296 g, 0,736 mmol) (véase Preparación 11) y N-metil morfolina (0,16 ml, 1,46 mmol) en N,N-dimetilformamida (6 ml) en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. Se repartió la mezcla entre acetato de etilo (6 ml) y agua (6 ml). La capa orgánica se separó, se lavó con una disolución acuosa saturada de cloruro de sodio (6 ml) y se secó sobre sulfato de magnesio anhidro. Se concentró a vacío, y el residuo se trituró con éter dietílico (3 veces 5 ml) para dar anti-5-fluoro-2-(3,4-difluoro-fenoxi)-N-[4-(2-fluoro-6-hidroxi-benzoilamino)-ciclohexil]-nicotinamida (240 mg) como un sólido blanquecino.

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 10,92 (1H, s ancho) 8,29-8,33 (1H, d), 8,23-8,27 (1H, d), 8,08-8,17 (1H, m), 7,90-8,03 (1H, m), 7,31-7,52 (2H, m), 7,18-7,30 (1H, m), 7,02-7,12 (1H, m), 6,60-6,71 (2H, m), 3,65-3,82 (2H, m), 1,82-2,00 (4H, m), 1,28-1,50 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 504

**Ejemplo 42 : anti-5-Fluoro-2-(3-cloro-4-fluoro-fenoxi)-N-[4-(2-fluoro-6-hidroxi-benzoilamino)-ciclohexil]-nicotinamida**



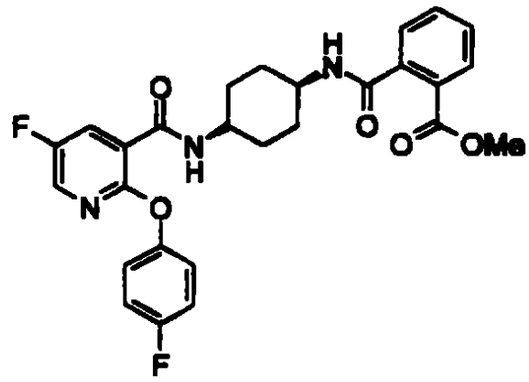
Se agitaron ácido 2-fluoro-6-hidroxibenzoico (117 mg, 0,753 mmol), 1-hidroxibenzotriazol (153 mg, 1,13 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (188 mg, 0,979 mmol), hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(3-cloro-4-fluoro-fenoxi)-nicotinamida (315 mg, 0,736 mmol) (véase Preparación 13) y N-metil morfolina (0,17 ml, 1,51 mmol) en N,N-dimetilformamida (6 ml) en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. La mezcla se repartió entre acetato de etilo (6 ml) y agua (6 ml). La capa orgánica se separó, se lavó con una disolución acuosa saturada de cloruro de sodio (6 ml) y se secó sobre sulfato de magnesio anhidro. Se concentró a vacío, y el residuo se trituró con éter dietílico (3 veces 5 ml) para dar anti-5-fluoro-2-(3-cloro-4-fluoro-fenoxi)-N-[4-(2-fluoro-6-hidroxi-benzoilamino)-ciclohexil]-nicotinamida (250 mg) como un sólido blanquecino.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 10,94 (1H, s ancho) 8,28-8,35 (1H, d), 8,23-8,26 (1H, d), 8,07-8,17 (1H, m), 7,92-8,03 (1H, m), 7,42-7,54 (2H, m), 7,17-7,28 (2H, m), 6,58-6,73 (2H, m), 3,64-3,83 (2H, m), 1,83-2,00 (4H, m), 1,31-1,50 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 520, 522

**Ejemplo 43 : Éster metílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}ci-**

**clohexil)ftalámico**



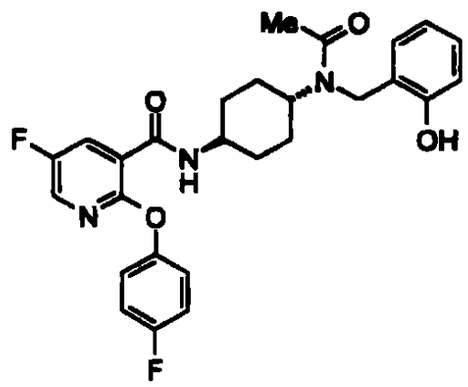
Se agitaron éster monometílico del ácido ftalámico (141 mg, 0,781 mmol), 1-hidroxibenzotriazol hidrato (158 mg, 1,17 mmol) e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (195 mg, 1,02 mmol) en N,N-dimetilformamida (6 ml) a temperatura ambiente y se adicionó hidrocloruro de sin-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (300 mg, 0,781 mmol) (véase Preparación 22) seguido por adición de N-metil morfolina (0,17 ml, 1,56 mmol). Se agitó la mezcla de reacción en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas, se repartió la mezcla de reacción entre acetato de etilo (20 ml) y agua (20 ml), y se separó la capa orgánica. A continuación se lavó la capa orgánica con una disolución acuosa saturada de cloruro de sodio (20 ml) se secó sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. Se trituró el residuo con éter dietílico (5 ml) dando el éster metílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ftalámico (385 mg) como un sólido blanquecino.

$^1$H NMR (300MHz, DMSO-$d^6$): $\delta$ = 8,28-8,35 (1H, d), 8,20-8,24 (1H, d), 8,01-8,08 (2H, m), 7,75-7,80 (1H, d), 7,48-7,64 (2H, m), 7,38-7,43 (1H, d), 7,20-7,38 (4H, m), 4,04-4,16 (1H, m), 3,84-3,99 (1H, m), 3,74 (3H, s), 1,56-1,88 (8H,

m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 510

**Ejemplo 44 : anti-N-{4-[Acetil-(2-hidroxibencil)-amino]-ciclohexil}-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida**



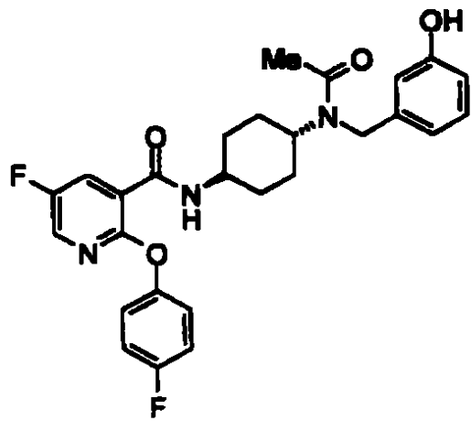

Se disolvieron éster anti-1-{[acetil-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-amino]-metil}-fenílico del ácido acético (275 mg, 0,512 mmol) (véase Preparación 19) e hidróxido de litio (monohidrato, 32 mg, 0,767 mmol) en tetrahidrofurano (10 ml) y agua (10 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Se adicionó ácido clorhídrico 2M (0,4 ml) y se filtró el precipitado resultante y se lavó con agua (30 ml). Se disolvió el sólido en diclorometano/éter dietílico y se secó sobre sulfato de sodio anhidro. Se separó el disolvente a vacío dando anti-N-{4-[acetil-(2-hidroxibencil)amino]-ciclohexil}-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (100 mg) como un sólido blanco.

H NMR (400 MHz, $CDCl_3$): $\delta$ = 9,77 (1H, s), 8,32-8,39 (1H, m), 8,01-8,05 (1H, d), 7,68-7,78 (1H, d), 7,07-7,23 (6H, m), 6,85-6,90 (1H, d), 6,77-6,84 (1H, t), 4,52 (2H, s), 3,92-4,10 (1H, m), 3,59-3,70 (1H, m), 2,22-2,31 (2H, d), 2,18 (3H, s), 1,75-1,98 (4H, m), 1,26-1,43 (2H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 494

**Ejemplo 45 : anti-N-{4-[Acetil-(3-hidroxibencil)-amino]-**

**ciclohexil}-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida**



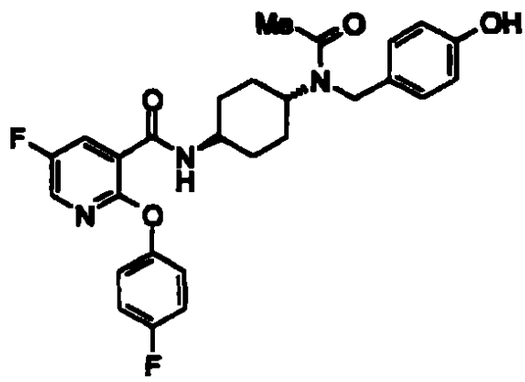

Se disolvió anti-N-{4-(terc-butil-dimetil-silanil-oxi)-bencilamino]ciclohexil}-5-fluoro-2-(4-fluorofenoxi)-nicotinamida (337 mg, 0,512 mmol) (véase Preparación 18) en diclorometano (10 ml) y se adicionó diisopropiletilamina (0,15 ml, 0,831 mmol) seguido por la adición de cloruro de acetilo (0,051 ml, 0,712 mmol). Se mantuvo la mezcla de reacción a temperatura ambiente en una atmósfera de nitrógeno durante 2 horas, y entonces se separó el disolvente a vacío. Se disolvió el disolvente en metanol (15 ml) y se adicionó resina amberlyst 15 (1 g). Se mantuvo la reacción a temperatura ambiente durante otras 18 horas. Se filtró la mezcla a través de una columna corta de celita (5 g) y se lavó la celita con metanol (2 veces 10 ml). Se combinaron los filtrados, se concentraron a vacío y el residuo se destiló azeotrópicamente con éter dietílico. Se suspendió el sólido blanco resultante en pentano y se filtró dando anti-N-{4-[acetil-(3-hidroxibencil)-amino]ciclohexil}-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (290 mg) como un sólido blanco.

H NMR (400 MHz, DMSO-$d^6$): $\delta$ = 9,32 (0,5H, s), 9,18 (0,5H, s), 8,20-8,25 (1H, m), 8,15-8,19 (1H, d), 7,90-7,98 (1H, m), 7,17-7,22 (4H, m), 6,98-7,16 (1H, 2xt), 6,52-6,65 (3H, m), 4,36-4,48 (2H, 2xs), 4,20-4,33 (0,5H, m), 3,57-

3,76 (1,5H, m), 2,13 (1,3H, s), 1,78-1,90 (2,7H, m), 1,25-1,64 (7H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 494

**Ejemplo 46 : anti-N-{4-[Acetil-(4-hidroxibencil)-amino]-ciclohexil}-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida**

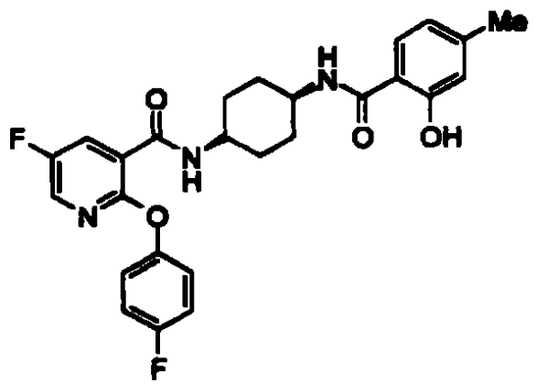



Se disolvió anti-N-{4-[4-(terc-butildimetil-silanil-oxi)bencilamino]ciclohexil}-5-fluoro-2-(4-fluorofenoxi)-nicotinamida (97 mg, 0,171 mmol) (véase Preparación 17) en diclorometano (5 ml) y se adicionó diisopropiletil-amina (0,042 ml, 0,239 mmol) seguido por adición de cloruro de acetilo (0,015 ml, 0,205 mmol). Se mantuvo la mezcla de reacción a temperatura ambiente bajo atmósfera de nitrógeno durante 2 horas, antes de eliminar el disolvente a vacío. Se disolvió el residuo en metanol (10 ml) y se adicionó resina amberlyst 15 (1 g) y ácido trifluoroacético (0,1 ml). Se mantuvo la mezcla de reacción a temperatura ambiente durante otras 18 horas. Se filtró la mezcla a través de una columna corta de celita (5 g) y se lavó la celita con metanol (2 veces 10 ml). Se combinaron los filtrados, se concentraron a vacío y el residuo se destiló azeotrópicamente con éter dietílico. El sólido blanco resultante se suspendió en pentano y se filtró dando anti-N-{4-[acetil-(4-hidroxibencil)-amino]-ciclohexil}-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (46 mg) como un sólido blanco.

$^1$H NMR (400 MHz, DMSO-d$^6$): δ = 8,17-8,21 (1H, m), 8,13-8,16 (1H, d), 7,88-7,95 (1H, m), 7,11-7,21 (4H, m), 6,92-6,99 (2H, d), 6,67-6,73 (1H, d), 6,57-6,63 (1H, d), 4,30-4,41 (2H, 2xs), 4,12-4,22 (1H, m), 3,57-3,72 (1H, m), 2,10 (1H, s), 1,86 (2H, s), 1,76-1,83 (2H, d), 1,43-1,60 (4H, m), 1,20-1,40 (2H, m) ppm.

LRMS (electropulverización): m/z [M+H]$^+$ 496

**Ejemplo 47 : sin-5-Fluoro-2-(4-fluorofenoxi)-N-[4-(2-hidroxi-4-metilbenzoilamino)ciclohexil]nicotinamida**




Se agitaron ácido 2-hidroxi-4-metilbenzoico (91 mg, 0,595 mmol), 1-hidroxibenzotriazol (80 mg, 0,595 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (134 mg, 0,703 mmol), hidrocloruro de sin-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (200 mg, 0,541 mmol) (véase Preparación 22) y N-metil morfolina (0,18 ml, 1,62 mmol) en N,N-dimetilformamida (5 ml) en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. Se separó la N,N-dimetilformamida a vacío, y se repartió el residuo entre diclorometano (15 ml) y agua (15 ml). Se separó la fase orgánica y se lavó secuencialmente con una disolución al 10% de ácido cítrico en agua (15 ml) seguido por una disolución acuosa saturada de hidrógeno carbonato de sodio (15 ml). Se secó la fase orgánica sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. Se trituró

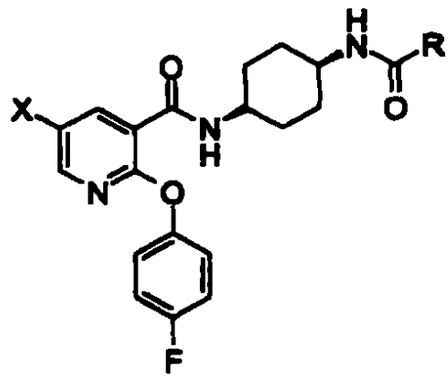
el residuo con acetato de etilo/pentano (1:1, en volumen, 5 ml) dando sin-5-fluoro-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-nicotinamida (130 mg) como un sólido blanco.

$^1$H NMR (400MHz, $CDCl_3$): $\delta$ = 12,17 (1H, s), 8,32-8,38 (1H, m), 8,00-8,08 (2H, m), 7,15-7,22 (4H, d), 6,97-7,01 (1H, d), 6,78 (1H, s), 6,60-6,65 (1H, d), 5,84-5,92 (1H, d), 4,23-4,31 (1H, m), 4,02-4,15 (1H, m), 2,34 (3H, s), 1,80-2,00 (6H, m), 1,49-1,67 (2H, m, parcialmente enmascarada por el disolvente) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 480

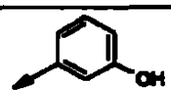
**Ejemplos 48-71**

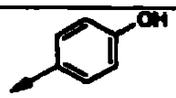
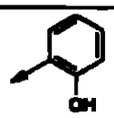
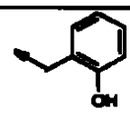
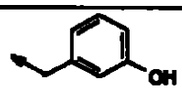
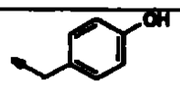
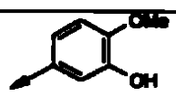
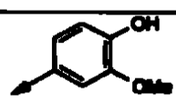
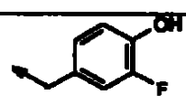
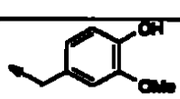
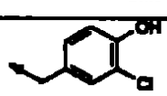
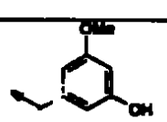
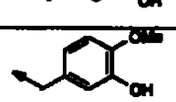
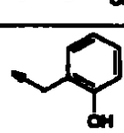
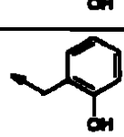
Se prepararon los compuestos de los siguientes ejemplos tabulados (Tabla 3) de fórmula general:

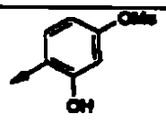
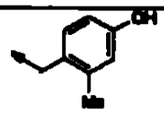
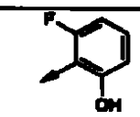
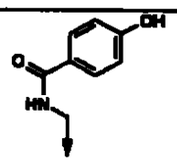
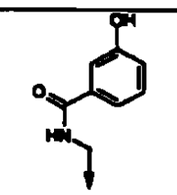
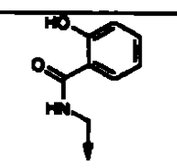
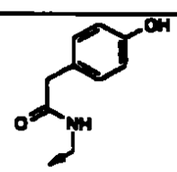
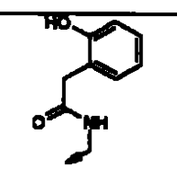
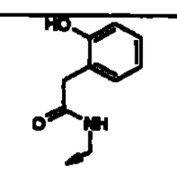



por un método similar al del Ejemplo 47 empleando el ácido carboxílico y la amina apropiados como productos de partida.

**TABLA 3**

| Ejemplo N° | Amina de partida Prep. N° | X | R |
|---|---|---|---|
| 48 | 22 | F |  |

| | | | |
|---|---|---|---|
| 49 | 22 | F |  |
| 50 | 22 | F |  |
| 51 | 22 | F |  |
| 52 | 22 | F |  |
| 53 | 22 | F |  |
| 54 | 22 | F |  |
| 55 | 22 | F |  |
| 56 | 22 | F |  |
| 57 | 22 | F |  |
| 58 | 22 | F |  |
| 59 | 22 | F |  |
| 60 | 22 | F |  |
| 61 | 22 | H |  |
| 62 | 22 | F |  |

| | | | |
|---|---|---|---|
| 63[1] | 22 | F |  |
| 64[1] | 22 | F |  |
| 65[1] | 22 | F |  |
| 66[1,1] | 24 | F |  |
| 67[1,1] | 24 | F |  |
| 68[1,1] | 24 | F |  |
| 69[1,1] | 24 | F |  |
| 70[1,1] | 24 | F |  |
| 71[1,1] | 24 | F |  |

Estos ejemplos se elaboraron repartiendo la masa de reacción entre acetato de etilo y agua, y se lavó la fase

orgánica con una disolución acuosa saturada de cloruro de sodio.

Se purificaron estos ejemplos por cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de diclorometano : metanol (100 : 0 cambiando a 95 : 5 luego a 70 : 30, en volumen). Se disolvió el producto en acetato de etilo, se lavó secuencialmente con agua y una disolución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio anhidro y se concentró bajo presión reducida para dar el compuesto deseado.

Se diluyeron estos compuestos con metanol y acetato de etilo hasta completa disolución antes de secar sobre sulfato de magnesio anhidro.

**Ejemplo 48:**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 9,50 (1H, s), 8,22-8,26 (1H, d), 8,17-8,21 (1H, d), 7,95-7,99 (1H, m), 7,84-7,92 (1H, d), 7,12-7,23 (7H, m), 6,80-6,85 (1H, d), 3,86-3,95 (1H, m), 3,72-3,82 (1H, m), 1,56-1,82 (8H, m) ppm.

LRMS (electropulverización): m/z [M-H]$^-$ 466

**Ejemplo 49:**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 9,83 (1H, s), 8,21-8,24 (1H, m), 8,17-8,20 (1H, d), 7,93-7,97 (1H, m), 7,63-7,67 (1H, d), 7,57-7,62 (1H, d), 7,17-7,24 (4H, m), 6,70-6,77 (1H, d), 3,87-3,92 (1H, m), 3,72-3,80 (1H, m), 1,76-1,83 (2H, m), 1,55-1,72 (6H, m) ppm.

LRMS (electropulverización): m/z [M-H]$^-$ 466

**Ejemplo 50:**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 12,18 (1H, s ancho), 8,34-8,41 (1H, m), 8,16-8,19 (1H, d), 7,93-7,97 (1H, m), 7,80-7,86 (1H, d), 7,28-7,35 (1H, t), 7,15-7,23 (4H, m), 6,78-6,86 (2H, m), 3,89-3,94 (1H, m), 3,80-3,88 (1H, m), 1,58-1,80 (8H, m) ppm.

LRMS (electropulverización): m/z [M-H]$^-$ 466

**Ejemplo 51:**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8,03-8,07 (2H, m), 7,10-7,21 (4H, m), 6,96-7,08 (2H, m), 6,68-6,78 (2H, m), 3,97-4,07 (1H, m), 3,75-3,80 (1H, m), 3,43 (2H, s), 1,63-1,80 (6H, m), 1,52-1,62 (6H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 480

**Ejemplo 52:**

H NMR (400MHz, $CD_3OD$): δ = 8,00-8,08 (2H, m), 7,09-7,19 (4H, m), 7,00-7,08 (1H, t), 6,57-6,72 (3H, m), 4,00-4,09 (1H, m), 3,72-3,81 (1H, m), 3,37 (2H s), 1,66-1,80 (6H, m), 1,51-1,62 (6H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 480

**Ejemplo 53:**

H NMR (400MHz, DMSO-$d^6$): δ = 9,08 (1H, s), 8,22-8,26 (1H, d), 8,14-8,17 (1H, d), 7,92-7,96 (1H, d), 7,63-7,67 (1H, d), 7,16-7,23 (4H, d), 6,94-6,99 (2H, d), 6,57-6,62 (2H, d), 3,78-3,86 (1H, m), 3,52-3,61 (1H, m), 3,23 (2H, s), 1,46-1,86 (8H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 480

**Ejemplo 54:**

H NMR (300MHz, DMSO-$d^6$): δ = 9,08 (1H, s), 8,26-8,32 (1H, d), 8,21-8,25 (1H, d), 8,01-8,07 (1H, m), 7,75-7,82 (1H, m), 7,19-7,38 (6H, m), 6,92-6,97 (1H, d), 3,76-4,01 (5H, m), 1,54-1,80 (8H, m) ppm.

LRMS (termopulverización) m/z $[M+H]^+$ 498

**Ejemplo 55:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9,48 (1H, s ancho), 8,26-8,33 (1H, d), 8,20-8,25 (1H, d), 7,98-8,06 (1H, m), 7,74-7,80 (1H, d), 7,18-7,41 (6H, m), 6,77-6,82 (1H, d), 3,76-4,03 (5H, m), 1,50-1,92 (8H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 498

**Ejemplo 56:**

$^1$H NMR (300MHz, DMSO-$d^6$): δ = 9,58 (1H, s), 8,25-8,30 (1H, d), 8,20-8,24 (1H, d), 8,00-8,07 (1H, m), 7,77-7,83 (1H, d), 7,20-7,30 (4H, d), 6,96-7,03 (1H, d), 6,77-6,83 (2H, m), 3,82-3,93 (1H, m), 3,55-3,64 (1H, m), 3,26 (2H, s,

parcialmente enmascarada por el disolvente), 1,52-1,80 (8H, m) ppm.

LRMS (termopulverización): m/z [M+H]⁺ 500

**Ejemplo 57:**

H NMR (300MHz, DMSO-$d^6$): δ = 8,73 (1H, s), 8,27-8,32 (1H, d), 8,21-8,25 (1H, d), 7,96-8,05 (1H, m), 7,70-7,78 (1H, d), 7,20-7,30 (4H, d), 6,57-6,80 (3H, m), 3,82-3,94 (1H, m), 3,58-3,78 (4H, m), 3,24 (2H, s, parcialmente enmascarada por el disolvente), 1,52-1,78 (8H, m) ppm.

LRMS (termopulverización): m/z [M+H]⁺ 512

**Ejemplo 58:**

H NMR (300MHz, DMSO-$d^6$): δ = 9,92 (1H, s), 8,26-8,32 (1H, d), 8,19-8,24 (1H, d), 7,91-8,05 (1H, m), 7,78-7,84 (1H, d), 7,16-7,30 (5H, m), 6,95-7,02 (1H, m), 6,83-6,88 (1H, d), 3,82-3,96 (1H, m), 3,57-3,69 (1H, m), 3,26 (2H, s, parcialmente enmascarada por el disolvente), 1,53-1,78 (8H, m) ppm.

LRMS (termopulverización): m/z [M+H]⁺ 516

**Ejemplo 59:**

H NMR (300MHz, DMSO-$d^6$): δ = 8,70 (1H, s), 8,28-8,33 (1H, d), 8,20-8,24 (1H, d), 7,96-8,02 (1H, m), 7,70-7,77 (1H, d), 7,20-7,28 (4H, d), 6,57-6,82 (3H, m), 3,81-3,94 (1H, m), 3,60-3,80 (4H, m), 3,24 (2H, s, parcialmente enmascarada por el disolvente), 1,52-1,78 (8H, m) ppm.

LRMS (termopulverización): m/z [M+H]⁺ 512

**Ejemplo 60:**

H NMR (300MHz, DMSO-$d^6$): δ = 8,80 (1H, s ancho), 8,25-8,33 (1H, d), 8,18-8,23 (1H, d), 7,95-8,05 (1H, m), 7,73-7,78 (1H, d), 7,17-7,34 (4H, d), 6,56-6,82 (3H, m), 3,81-3,91 (1H, m), 3,67 (2H, s), 3,50-3,65 (1H, m), 3,22 (3H, s), 1,51-1,78 (8H, m) ppm.

LRMS (termopulverización): m/z [M+H]⁺ 512

**Ejemplo 61:**

H NMR (400MHz, $CDCl_3$): δ = 9,63 (1H, s), 8,68-8,75 (1H, d), 7,79-7,83 (2H, m), 7,16-7,20 (1H, t), 7,11-7,14 (4H,

2xd), 7,00-7,10 (2H, m), 6,92-6,98 (1H, d), 6,78-6,84 (1H, t), 6,23-6,31 (1H, d), 4,00-4,08 (1H, m), 3,58 (2H, s), 2,43-2,54 (1H, m), 1,78-1,90 (6H, m), 1,60-1,75 (2H, m, parcialmente enmascarada por el disolvente) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 462

**Ejemplo 62:**

$^1H$ NMR (300MHz, DMSO-$d^6$): δ = 12,58 (1H, s), 10,00 (1H, s), 8,30-8,36 (1H, d), 8,01-8,03 (1H, d), 8,06-8,13 (1H, m), 7,99-8,06 (1H, m), 7,70-7,76 (1H, d), 7,20-7,29 (4H, d), 6,20-6,30 (2H, d + s), 3,88-3,99 (1H, s ancho), 3,60-3,88 (1H, s ancho), 1,53-1,88 (8H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 484

**Ejemplo 63:**

$^1H$ NMR (300MHz, DMSO-$d^6$): δ = 12,74-12,80 (1H, s ancho), 8,30-8,36 (1H, d), 8,18-8,23 (2H, m), 7,98-8,04 (1H, m), 7,80-7,85 (1H, d), 7,20-7,25 (4H, d), 6,39-6,48 (2H, d + s), 3,93-4,01 (1H, s ancho), 3,80-3,91 (1H, s ancho), 3,77 (3H, s), 1,62-1,90 (8H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 498.

**Ejemplo 64:**

$^1H$ NMR (300MHz, DMSO-$d^6$): δ = 8,26-8,32 (1H, d), 8,01-8,03 (1H, d), 7,98-8,04 (1H, dd), 7,58-7,64 (1H, d), 7,19-7,28 (4H, d), 7,12-7,18 (1H, t), 6,68-6,79 (3H, m), 4,42 (2H, s), 3,85-3,97 (1H, s ancho), 3,70-3,80 (1H, s ancho), 2,24 (3H, s), 1,53-1,79 (8H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 496.

**Ejemplo 65:**

$^1H$ NMR (300MHz, DMSO-$d^6$): δ = 11,00 (1H, s), 8,26-8,31 (1H, d), 8,20-8,21 (1H, d), 7,93-8,03 (2H, m), 7,18-7,34 (5H, m), 6,60-6,73 (2H, m), 3,83-3,99 (2H, s ancho), 1,52-1,80 (8H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 486.

**Ejemplo 66:**

$^1H$ NMR (400MHz, $CD_3OD$): δ = 8,02-8,10 (2H, m), 7,71-7,76 (2H, m), 7,11-7,22 (4H, m), 6,78-6,84 (2H, d), 4,04-4,11

(1H, s ancho), 3,95 (2H, s), 3,80-3,90 (1H, s ancho), 1,73-1,87 (6H, m), 1,60-1,72 (2H, m) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 547, [M-H]⁻ 523.

**Ejemplo 67:**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8,05-8,09 (2H, m), 7,22-7,30 (3H, m), 7,13-7,21 (4H, m), 6,91-6,96 (1H, m), 4,05-4,10 (1H, m), 3,96 (2H, s), 3,82-3,90 (1H, m), 1,73-1,85 (6H, m), 1,60-1,72 (2H, m) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 547, [M-H]⁻ 523.

**Ejemplo 68:**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 8,93-9,00 (1H, s ancho), 8,26-8,32 (1H, d), 8,20 (1H, s), 7,95-8,00 (1H, m), 7,81-7,87 (2H, m), 7,34-7,40 (1H, t), 7,18-7,27 (4H, d), 6,83-6,91 (2H, m), 3,83-3,93 (3H, m), 3,64-3,72 (1H, m), 1,56-1,75 (8H, 2xm) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 547, [M-H]⁻ 523.

**Ejemplo 69:**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8,25-8,35 (1H, s ancho), 8,07-8,12 (2H, m), 7,53-7,63 (1H, m), 7,06-7,22 (6H, 2xm), 6,68-6,73 (2H, d), 3,99-4,08 (1H, s ancho), 3,75-3,85 (3H, m), 3,43 (2H, s), 1,65-1,80 (6H, m), 1,53-1,63 (2H, m) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 561, [M-H]⁻ 537.

**Ejemplo 70:**

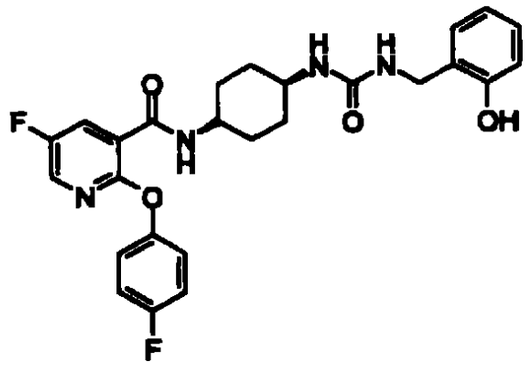
$^1$H NMR (400MHz, $CD_3OD$): δ = 8,05-8,12 (2H, m), 7,52-7,57 (1H, m), 7,09-7,21 (5H, m), 7,00-7,08 (1H, t), 6,73-6,79 (2H, m), 4,00-4,08 (1H, s ancho), 3,74-3,85 (3H, m), 3,52 (2H, s), 1,67-1,82 (6H, m), 1,57-1,66 (2H, m) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 561, [M-H]⁻ 537.

**Ejemplo 71:**

$^1$H NMR (400MHz, $CD_3OD$): δ = 8,25-8,33 (1H, d), 8,04-8,10 (2H, m), 7,53-7,60 (1H, m), 7,11-7,22 (4H, m), 7,06-7,11 (1H, t), 6,72-6,76 (2H, m), 6,59-6,64 (1H, d), 4,00-4,08 (1H, s ancho), 3,74-3,85 (3H, m), 3,47 (2H, s), 1,66-1,83 (6H, m), 1,56-1,65 (2H, m) ppm.

LRMS (electropulverización): m/z [M+Na]⁺ 561, [M-H]⁺ 537.

**Ejemplo 72 : sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[3-(2-hidroxi-bencil)-ureido]-ciclohexil}-nicotinamida**



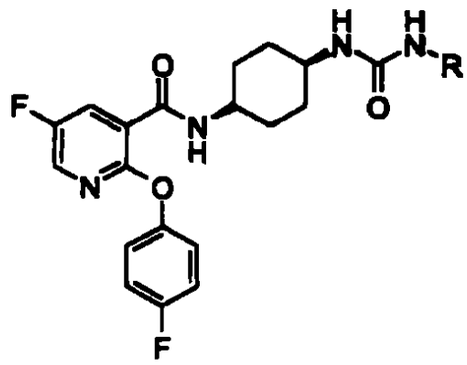
Se agitaron 2-aminometil fenol (62 mg, 0,386 mmol), sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)-amino]-ciclohexil)-nicotinamida (142 mg, 0,322 mmol) (véase Preparación 25) y trietilamina (0,06 ml, 0,386 mmol) en diclorometano (10 ml) en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. Se lavó secuencialmente la mezcla de reacción con agua (6 ml) y una disolución al 10% de ácido cítrico en agua (6 ml). La fase orgánica se separó y se secó sobre sulfato de magnesio anhidro. Se separó el disolvente a vacío y el residuo se trituró con éter dietílico (3 veces 5 ml) para dar sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[3-(2-hidroxi-bencil)-ureido]-ciclohexil}-nicotinamida (102 mg) como un sólido amarillo claro.

H NMR (400MHz, $CDCl_3$): δ = 9,75 (1H, s), 8,29-8,35 (1H, m), 8,00-8,04 (1H, d), 7,88-7,95 (1H, d), 7,05-7,21 (5H, m), 6,97-7,03 (1H, d), 6,85-6,92 (1H, d), 6,74-6,79 (1H, t), 4,76-4,85 (1H, t), 4,27-4,35 (1H, m), 4,21-4,26 (2H, d), 4,07-4,17 (1H, m), 3,56-3,68 (1H, m), 1,62-1,86 (6H, m), 1,35-1,51 (2H, m) ppm.

LRMS (electropulverización): m/z [M-H]⁺ 495

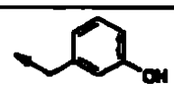
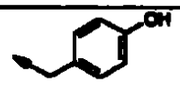
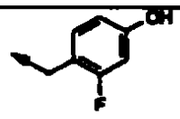
**Ejemplos 73-75**

Se prepararon los compuestos de los siguientes ejemplos tabulados (Tabla 4) de fórmula general:



por un método similar al del Ejemplo 72 empleando la apropiada amina producto de partida.

**TABLA 4**

| Ejemplo N° | Intermedio de partida Prep. N° | R |
|---|---|---|
| 73 | 25 |  |
| 74 | 25 |  |
| 75 | 25 |  |

Este compuesto se aisló por filtrado de la fase acuosa después de elaboración. Se disolvió el sólido en metanol, se secó sobre sulfato de magnesio anhidro y se concentró a presión reducida. Se trituró el residuo con éter dietílico para dar el compuesto deseado.

**Ejemplo 73**

H NMR (400MHz, $CD_3OD$): δ = 8,00-8,06 (2H, m), 7,01-7,20 (5H, m), 6,64-6,70 (2H, m), 6,58-6,63 (1H, d), 4,19 (2H,

s), 3,98-4,06 (1H, s ancho), 3,62-3,71 (1H, s ancho), 1,64-1,82 (6H, m), 1,50-1,61 (2H, m) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 519, [M-H]⁻ 495.

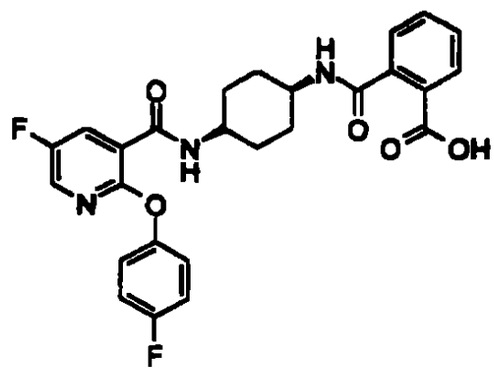
**Ejemplo 74**

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 9,17 (1H, s), 8,21-8,25 (1H, d), 8,16-8,18 (1H, d), 7,93-7,97 (1H, dd), 7,15-7,21 (4H, d), 6,95-7,00 (2H, d), 6,40-6,44 (2H, d), 5,99-6,04 (1H, t), 5,68-5,75 (1H, d), 3,97-4,01 (2H, d), 3,78-3,87 (1H, s ancho), 3,44-3,55 (1H, s ancho), 1,40-1,64 (8H, m) ppm.
LRMS (electropulverización): m/z [M+H]⁺ 497, [M+Na]⁺ 519, [M-H]⁻ 495

**Ejemplo 75**

$^1$H NMR (400MHz, CD$_3$OD): δ = 8,00-8,06 (2H, m), 7,02-7,18 (4H, m), 6,93-6,99 (1H, t), 6,48-6,52 (1H, d), 6,39-6,46 (1H, m), 4,34 (1H, s), 4,18 (1H, s), 3,97-4,06 (1H, s ancho), 3,60-3,72 (1H, m), 1,61-1,82 (6H, m), 1,48-1,60 (2H, m) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 537, [M-H]⁻ 513.

**Ejemplo 76 : Ácido sin-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]amino}ciclohexil)ftalámico**



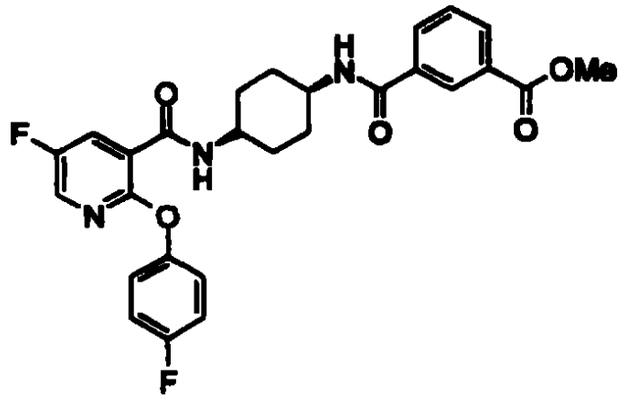
Se disolvieron el éster metílico del ácido sin-N-(4-{[5-Fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-ciclohexil)ftalámico (378 mg, 0,742 mmol) (véase Ejemplo 43) y una disolución 1 M de hidróxido de litio en agua

(1,5 ml, 1,484 mmol) en tetrahidrofurano (5 ml) y se agitó la reacción a temperatura ambiente durante 18 horas. Se adicionó ácido clorhídrico 2 M (0,8 ml), y la mezcla de reacción se extrajo con diclorometano (3 veces 10 ml). Se secaron los extractos orgánicos combinados sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. Se trituró el residuo con éter dietílico (5 ml) dando ácido sin-N-(4-{[5-fluoro-2-(4-fluorofenoxi)piridin-3-carbonil]amino}ciclohexil)ftalámico (235 mg) como un sólido blanquecino.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 12,63 (1H, s ancho), 8,20-8,30 (2H, m), 8,12-8,17 (1H, d), 7,98-8,06 (1H, m), 7,73-7,81 (1H, d), 7,48-7,58 (2H, m), 7,30-7,35 (1H, d), 7,18-7,28 (4H, d), 3,78-3,96 (2H, m), 1,60-1,83 (8H m) ppm.

LRMS (electropulverización): m/z [M-H]$^-$ 494

**Ejemplo 76a : Éster metílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluorofenoxi)piridin-3-carbonil]amino}ciclohexil)isoftalámico**



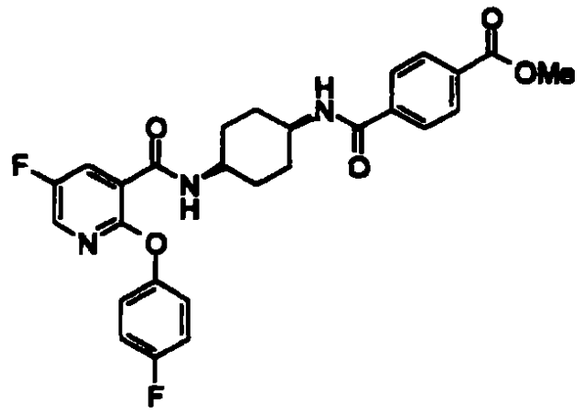

Se disolvieron éster monometílico del ácido isoftalámico (141 mg, 0,781 mmol), 1-hidroxibenzotriazol hidrato (158 mg, 1,17 mmol) e hidrocloruro de 1-(3-dimetilamino-propil)-3-etilcarbodiimida (195 mg, 1,02 mmol) en N,N-dimetilformamida (6 ml) a temperatura ambiente y se adicionó hidrocloruro de sin-N-(4-aminociclohexil)-5-

fluoro-2-(4-fluorofenoxi)nicotinamida (300 mg, 0,781 mmol) (véase Preparación 22) seguido por adición de N-metil morfolina (0,17 ml, 1,56 mmol). La mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 18 horas y entonces se repartió entre acetato de etilo (20 ml) y agua (20 ml) y se separó la capa orgánica. La fase orgánica se lavó con una disolución acuosa saturada de cloruro de sodio (20 ml), se secó sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. Se trituró el residuo con éter dietílico (5 ml) dando el éster metílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluorofenoxi)piridin-3-carbonil]amino}ciclohexil)-isoftalámico (398 mg) como un sólido blanquecino.

H NMR (300MHz, DMSO-$d^6$): $\delta$ = 8,32-8,45 (2H, m), 8,28 (1H, s), 7,92-8,18 (4H, m), 7,60-7,68 (1H, t), 7,20-740 (4H, m), 3,80-4,20 (5H, m), 1,56-1,97 (8H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 510

**Ejemplo 76b : éter metílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluorofenoxi)piridin-3-carbonil]amino}ciclohexil)tereftalámico**




Se disolvieron éster monometílico del ácido tereftálico (141 mg, 0,781 mmol), 1-hidroxibenzotriazol hidrato (158 mg, 1,17 mmol) e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (195 mg, 1,02

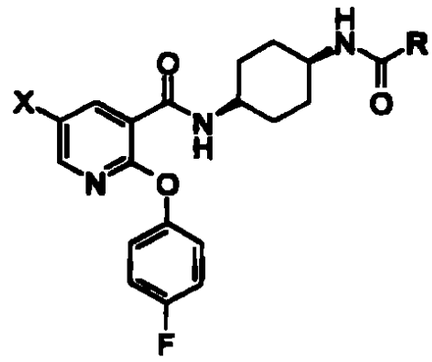
mmol) en N,N-dimetilformamida (6 ml) a temperatura ambiente y se adicionó hidrocloruro de sin-N-(4-aminociclohexil)-5-fluoro-2-(4-fluorofenoxi)nicotinamida (300 mg, 0,781 mmol) (véase Preparación 22) seguido por adición de N-metil morfolina (0,17 ml, 1,56 mmol). Se agitó la mezcla de reacción en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas, y luego se repartió entre acetato de etilo (20 ml) y agua (20 ml) y se separó la capa orgánica. A continuación se lavó la capa orgánica con una disolución acuosa saturada de cloruro de sodio (20 ml), se secó sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. Se trituró el residuo con éter dietílico (5 ml) dando el éster metílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}ciclohexil)tereftalámico (395 mg) como un sólido blanquecino.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8,21-8,37 (3H, m), 8,00-8,16 (3H, d), 7,89-7,94 (2H, d), 7,40-7,34 (4H, d), 3,80-4,08 (5H, m), 1,56-1,95 (8H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 510

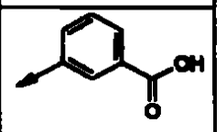
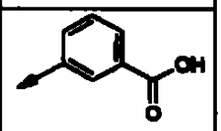
**Ejemplos 77-78**

Se prepararon los compuestos de los siguientes ejemplos tabulados (Tabla 5) de fórmula general:




por un método similar al del Ejemplo 76 empleando el éster apropiado como producto de partida.

**TABLA 5**

| Ejemplo N° | Producto de partida Prep. N° | X | R |
|---|---|---|---|
| 77 | Ejemplo 76a | F |  |
| 78 | Ejemplo 76b | F |  |

**Ejemplo 77**

H NMR (300MHz, DMSO-$d^6$): $\delta$ = 13,14 (1H, s ancho), 8,39 (1H, s), 8,29-8,35 (2H, d), 8,20-8,28 (1H, d), 7,96-8,16 (3H, m), 7,52-7,62 (1H, t), 7,18-7,40 (4H, m), 3,91-4,00 (1H, m), 3,78-3,90 (1H, m), 1,56-1,89 (8H, m) ppm.

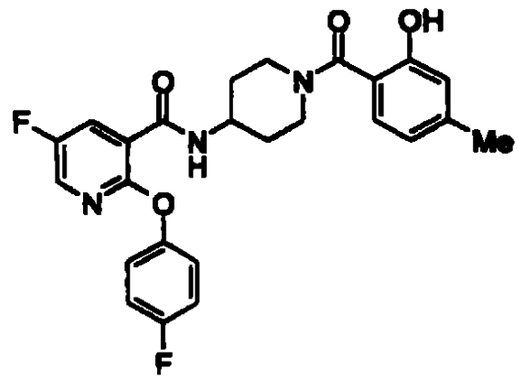
LRMS (electropulverización): m/z $[M-H]^-$ 494

**Ejemplo 78**

H NMR (300MHz, DMSO-$d^6$): $\delta$ = 13,16 (1H, s ancho), 8,30-8,35 (1H, d), 8,20-8,28 (2H, m), 7,97-8,09 (3H, m), 7,85-7,91 (2H, d), 7,20-7,35 (4H, d), 3,91-4,02 (1H, m), 3,80-3,90 (1H, m), 1,60-1,92 (8H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 494

**Ejemplo 79 : 5-fluoro-2-(4-fluoro-fenoxi)-N-[1-(2-hidroxi-4-metil-benzoil)-piperidin-4-il]-nicotinamida**



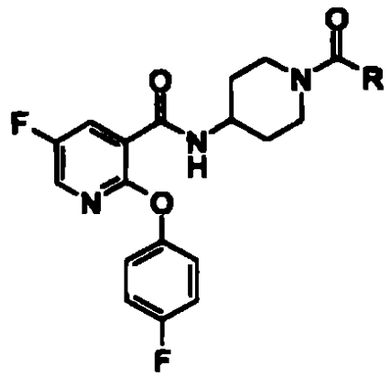
Se agitaron ácido 4-metilsalicílico (91 mg, 0,595 mmol), 1-hidroxibenzotriazol hidrato (110 mg, 0,811 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (135 mg, 0,703 mmol), hidrocloruro de 5-fluoro-2-(4-fluoro-fenoxi)-N-piperidin-4-il-nicotinamida (200 mg, 0,541 mmol) (véase Preparación 29) y N-metil morfolina (0,12 ml, 1,08 mmol) en N,N-dimetilformamida (4 ml) en atmósfera de nitrógeno a temperatura ambiente durante 18 horas. La mezcla de reacción se repartió entre acetato de etilo (10 ml) y agua (10 ml), la capa orgánica se separó, se lavó con una disolución acuosa saturada de cloruro de sodio (10 ml) y se secó sobre sulfato de magnesio anhidro. Se retiró el disolvente a vacío y el residuo se purificó vía cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de 100 % diclorometano cambiando al 99:1, en volumen, diclorometano : metanol. Se trituró la espuma blanca resultante con pentano (5 ml) dando 5-fluoro-2-(4-fluoro-fenoxi)-N-[1-(2-hidroxi-metil-benzoil)-piperidin-4-il]-nicotinamida (169 mg) como un sólido blanco.

H NMR (400MHz, $CDCl_3$): $\delta$ = 8,34-8,38 (1H, m), 8,01-8,03 (1H, d), 7,80-7,84 (1H, d), 7,08-7,18 (5H, m), 7,81 (1H, s), 6,60-6,65 (1H, d), 4,24-4,36 (3H, m), 3,17-3,25 (2H, t), 2,30 (3H, s), 2,10-2,18 (2H, d), 1,50-1,62 (2H, m) ppm.

LRMS (electropulverización): m/z $[M+H]^+$ 468, $[M+Na]^+$ 490

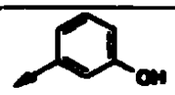
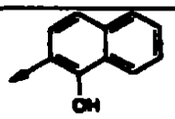
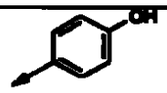
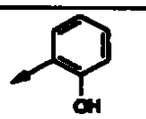
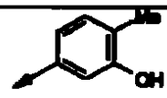
**Ejemplos 80-91**

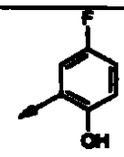
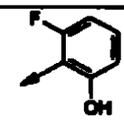
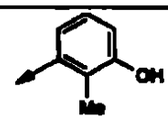
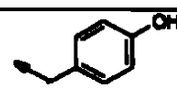
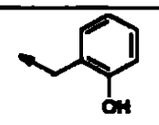
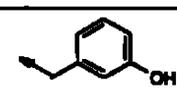
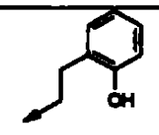
Se prepararon los compuestos de los siguientes ejemplos tabulados (Tabla 6) de fórmula general:



por un método similar al del Ejemplo 79 empleando el ácido carboxílico apropiado como producto de partida.

**TABLA 6**

| Ejemplo N° | Intermedio de partida Prep. N° | R |
|---|---|---|
| 80 | 29 |  |
| 81 | 29 |  |
| 82 | 29 |  |
| 83 | 29 |  |
| 84 | 29 |  |

| | | |
|---|---|---|
| 85 | 29 |  |
| 86 | 29 |  |
| 87 | 29 |  |
| 88 | 29 |  |
| 89 | 29 |  |
| 90 | 29 |  |
| 91 | 29 |  |

**Ejemplo 80:**

H NMR (400MHz, DMSO-$d^6$): δ = 9,55 (1H, s ancho), 8,36-8,41 (1H, d), 8,17 (1H, s), 7,90-7,96 (1H, m) 7,12-7,23 (5H, m), 6,74-6,79 (1H, d), 6,65-6,72 (1H, d), 6,64 (1H, s,, 4,08-4,30 (1H, m), 3,98-4,06 (1H, m), 3,41-3,60 (1H, m,, 2,91-3,20 (2H, m), 1,72-1,91 (2H, d), 1,30-1,54 (2H, m ppm.

LRMS (termopulverización) : m/z [M+H]$^+$ 454, [M+Na]$^+$ 476

**Ejemplo 81**

H NMR (400MHz, $CDCl_3$): δ = 11,16 (1H, s), 8,31-8,37 (2H, m', 7,98-8,02 (1H, d), 7,80-7,85 (1H, d), 7,72-7,77 (1H, d;, 7,44-7,56 (2H, m), 7,19-7,23 (2H, d), 7,04-7,16 (4H, m;, 4,23-4,39 (3H, m), 3,22-3,30 (2H, t), 2,12-2,19 (2H, d;, 1,50-1,63 (2H, m) ppm.

LRMS (electropulverización): m/z [M-H]$^-$ 502

**Ejemplo 82:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,32-8,37 (1H, m), 8,02-8,05 (1H, d), 7,80-7,86 (1H, d), 7,20-7,26 (1H, m, parcialmente enmascarada por el disolvente), 7,08-7,20 (4H, m), 6,71-6,81 (3H, m), 4,00-4,35 (3H, m), 3,08-3,23 (2H, m), 2,05-2,18 (2H, d), 1,40-1,60 (2H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 452

**Ejemplo 83:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9,55 (1H, s), 8,34-8,39 (1H, m), 8,04-8,07 (1H, d), 7,79-7,88 (1H, d), 7,28-7,36 (1H, m), 7,21-7,24 (1H, d), 7,08-7,16 (4H, m), 6,96-7,02 (1H, d), 6,78-6,85 (1H, t), 4,24-4,37 (3H, m), 3,18-3,28 (2H, t), 2,12-2,21 (2H, d), 1,69-1,83 (2H, m, parcialmente enmascarada por el disolvente) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 452

Encontrado C, 61,85; H, 4,68; N, 9,19. $C_{24}H_{21}F_2N_3O_4$. 0,7 moles $H_2O$ requiere C, 61,85 H, 4,84; N, 9,02%.

**Ejemplo 84:**

H NMR (400MHz, $CDCl_3$): δ = 8,33-8,37 (1H, m), 8,04 (1H, s), 7,79-7,85 (1H, d), 7,08-7,18 (4H, m), 7,02-7,07 (1H, d), 6,85-6,92 (1H, s ancho), 6,74-6,78 (1H, d), 4,38-4,65 (1H, m), 4,21-4,36 (1H, m), 3,78-3,94 (1H, m), 3,01-3,24 (2H, m), 2,21 (3H, s), 1,98-2,19 (2H, d), 1,38-1,60 (2H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 466

**Ejemplo 85:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9,18 (1H, s), 8,32-8,37 (1H, m), 8,02-8,04 (1H, d), 7,80-7,86 (1H, d), 7,02-7,18 (2H, m), 7,08-7,20 (5H, m), 6,86-6,97 (2H, m), 4,22-4,37 (3H, m), 3,18-3,22 (2H, t), 2,13-2,22 (2H, d), 1,50-1,63 (2H, m, parcialmente enmascarada por el disolvente) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 470

**Ejemplo 86:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,28-8,36 (1H, m), 8,01-8,04 (1H, d), 7,75-7,84 (1H, d), 7,18-7,27 (1H, m, parcialmen-

te enmascarada por el disolvente), 7,04-7,17 (4H, m), 6,75-6,80 (1H, d), 6,52-6,60 (1H, t), 4,35-4,63 (1H, m), 4,18-4,33 (1H, m), 3,60-3,90 (1H, m), 3,03-3,30 (2H, m), 2,02-2,19 (2H, d), 1,40-1,70 (2H, m, parcialmente enmascarada por el disolvente) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 470

**Ejemplo 87**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,26-8,32 (1H, m), 7,99-8,02 (1H, d), 7,77-7,84 (1H, d), 7,04-7,16 (4H, m), 6,93-7,02 (1H, m), 6,62-6,73 (2H, m), 5,88-6,00 (1H, d), 4,52-4,68 (1H, dd), 4,16-4,27 (1H, m), 3,41-3,48 (1H, d), 2,96-3,16 (1H, m), 2,10-2,19 (1H, m), 2,09 (3H, s), 1,88-2,02 (1H, m), 1,68-1,80 (1H, m, parcialmente enmascarada por el disolvente), 1,24-1,39 (1H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 466

**Ejemplo 88:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,25-8,31 (1H, m), 7,98-8,02 (1H, d), 7,71-7,78 (1H, d), 6,96-7,18 (6H, m), 6,67-6,75 (2H, m), 5,84 (1H, s), 4,37-4,47 (1H, m), 4,10-4,22 (1H, m), 3,72-3,83 (1H, d), 3,62 (2H, s), 3,08-3,21 (1H, t), 2,82-2,95 (1H, t), 1,90-2,05 (2H, t), 1,35-1,46 (1H, m), 1,13-1,23 (1H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 466

**Ejemplo 89:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9,57 (1H, s), 8,30-8,36 (1H, m), 8,01-8,04 (1H, d), 7,72-7,80 (1H, d), 7,05-7,20 (5H, m), 6,90-7,02 (2H, m), 6,76-6,84 (1H, t), 4,43-4,55 (1H, d), 4,20-4,32 (1H, m), 4,08-4,18 (1H, d), 3,71 (2H, s), 3,32-3,44 (1H, t), 2,86-2,95 (1H, t), 2,15-2,24 (1H, d), 2,02-2,14 (1H, d), 1,37-1,50 (2H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 466

**Ejemplo 90:**

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,28-8,31 (1H, m), 8,01-8,04 (1H, d), 7,72-7,79 (1H, d), 7,22 (1H, s), 7,05-7,17 (5H, m), 6,84 (1H, s), 6,65-6,70 (2H, d), 4,37-4,47 (1H, d),

4,12-4,22 (1H, m), 3,77-3,84 (1H, d), 3,64 (2H, s), 3,12-3,21 (1H, t), 2,81-2,88 (1H, t), 1,90-2,03 (2H, 2xd), 1,38-1,51 (1H, m), 1,10-1,20 (1H, m) ppm.

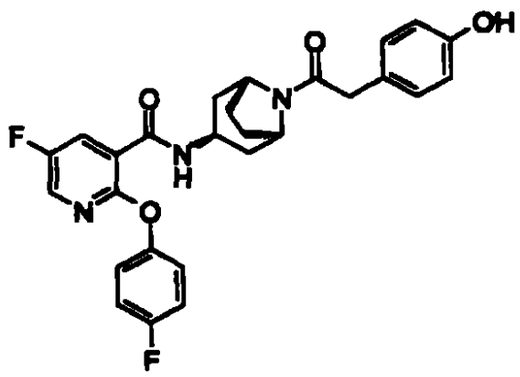
LRMS (electropulverización): m/z $[M-H]^-$ 466

**Ejemplo 91:**

$^1H$ NMR (400MHz, $CDCl_3$): δ = 9,36 (1H, s), 8,30-8,35 (1H, m), 8,02-8,04 (1H, d), 7,75-7,81 (1H, d), 7,00-7,16 (6H, m), 6,65-6,89 (1H, d), 6,76-6,82 (1H, t), 4,44-4,53 (1H, d), 4,17-4,27 (1H, m), 3,72-3,81 (1H, d), 3,13-3,24 (1H, t), 2,82-2,96 (3H, m), 2,68-2,75 (2H, m), 1,97-2,16 (2H, 2xd), 1,28-1,46 (2H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^-$ 480

**Ejemplo 92 : endo-5-Fluoro-2-(4-fluoro-fenoxi)-N-{8-[2-(4-hidroxi-fenil)-4-acetil]-8-aza-biciclo[3.2.1]oct-3-il}nicotinamida**




Se agitaron ácido 4-hidroxi-fenil-acético (88 mg, 0,57 mmol), 1-hidroxibenzotriazol (84 mg, 0,62 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (122 mg, 0,62 mmol), endo-N-(8-aza-biciclo[3.2.1]-oct-3-il)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (204 mg, 0,57 mmol) (véase Preparación 32) y N-metil morfolina (0,07 ml, 0,62 mmol) en diclorometano (5 ml) en una atmósfera de nitrógeno a temperatura ambiente durante 18 horas. La mezcla de reacción se lavó con una disolución acuosa saturada de cloruro de sodio (6 ml), se separó la

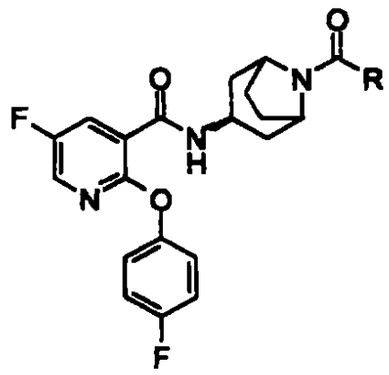
capa orgánica y se secó sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío. El residuo se purificó por cromatografía instantánea en columna sobre gel de sílice eluyendo con un gradiente de disolvente de diclorometano : pentano (50 : 50, en volumen) cambiando a diclorometano : metanol (100 : 0 luego 97 : 3, en volumen) para dar endo-5-fluoro-2-(4-fluoro-fenoxi)-N-{8-[2-(4-hidroxi-fenil)-acetil]-8-aza-biciclo[3.2.1]oct-3-il}-nicotinamida (50 mg) como una espuma blanca.

H NMR (400MHz, $CDCl_3$): δ = 8,48-8,57 (1H, d), 8,29-8,33 (1H, dd), 7,98-8,00 (1H, d), 7,00-7,14 (6H, m), 6,70-6,75 (2H, d), 5,88 (1H, s), 4,68-4,74 (1H, m), 4,28-4,35 (1H, m), 4,18-4,23 (1H, s ancho), 3,48-3,62 (2H, cuarteto), 2,24-2,29 (1H, m), 1,72-1,92 (7H, m) ppm.

LRMS (electropulverización): m/z $[M+H]^+$ 494, $[M+Na]^+$ 516, $[M-H]^-$ 492.

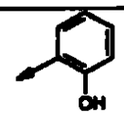
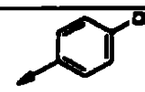
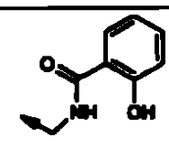
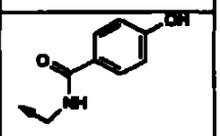
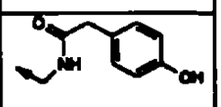
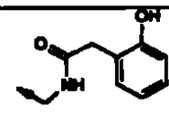
**Ejemplos 93-98**

Los compuestos de los siguientes ejemplos tabulados (Tabla 7) de fórmula general:



se prepararon por un método similar al del Ejemplo 92 empleando el ácido carboxílico y la amina apropiados como producto de partida.

**TABLA 7**

| Ejemplo N° | Amina de partida Prep. N° | Estereoq. anillo | R |
|---|---|---|---|
| 93[1,2] | 35 | exo |  |
| 94[1,2,4] | 35 | exo |  |
| 95[3] | 37 | exo |  |
| 96[3] | 37 | exo |  |
| 97 | 37 | exo |  |
| 98 | 37 | exo |  |

[1] El eluyente para cromatografía instantánea en columna fue diclorometano : metanol (100 : 0 cambiando al 98 : 2, en volumen).

[2] El compuesto se suspendió en acetato de etilo al 20% en pentano después cromatografía, y se filtró, se lavó con pentano y se secó a vacío para dar el producto deseado.

[3] El compuesto se trituró con éter dietílico después cromatografía para dar el producto deseado.

**Ejemplo 93**

$^1$H NMR (400MHz, $CDCl_3$): δ = 10,42 (1H, s), 8,30-8,35 (1H, dd), 8,00-8,02 (1H, d), 7,64-7,73 (1H, d), 7,29-7,38 (2H, m), 7,05-7,19 (4H, m), 6,97-7,01 (1H, d), 6,80-6,85 (1H, t), 4,73-4,83 (2H, s ancho), 4,60-4,72 (1H, m), 2,15-2,24 (2H, d), 2,00-2,14 (2H, m), 1,92-2,00 (2H, d), 1,69-1,80

(2H, t) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 502, [M-H]⁺ 478.

**Ejemplo 94**

$^1$H NMR (400MHz, DMSO-$d^6$): δ = 9,91 (1H, s), 8,30-8,37 (1H, dd), 8,08-8,10 (1H, d), 7,90-7,97 (1H, dd), 7,27-7,33 (2H, d), 7,16-7,25 (4H, m), 6,74-6,80 (2H, d), 4,02-4,64 (3H, 2x s ancho + m), 1,48-2,01 (8H, m) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 502, [M-H]⁺ 478.

**Ejemplo 95**

H NMR (400MHz, $CDCl_3$): δ = 12,08 (1H, s), 8,28-8,36 (1H, d), 8,02 (1H, 8), 7,60-7,70 (1H, d), 7,16-7,30 (3H, m), 7,03-7,16 (4H, m), 6,94-6,99 (1H, d), 6,81-6,88 (1H, t), 4,77-4,84 (1H, s ancho), 4,60-4,75 (1H, m), 4,10-4,30 (3H, m), 2,22-2,30 (1H, d), 1,99-2,20 (3H, m), 1,87-1,98 (1H, d), 1,60-1,72 (1H, t), 1,46-1,60 (2H, m, parcialmente enmascarada por el disolvente) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 559, [M-H]⁺ 535.

**Ejemplo 96**

H NMR (400MHz, $CDCl_3$): δ = 8,30-8,36 (1H, dd), 8,00-8,02 (1H, d), 7,62-7,73 (3H, d), 7,06-7,16 (4H, m), 7,01 (1H, s), 6,86-7,00 (1H, s ancho), 6,80-6,86 (2H, d), 4,77-4,81 (1H, s ancho), 4,60-4,76 (1H, m), 4,16-4,33 (3H, m), 3,67-3,77 (1H, m), 2,20-2,37 (1H, d), 1,98-2,20 (4H, m), 1,88-1,98 (1H, d), 1,51-1,70 (1H, m, parcialmente enmascarada por el disolvente) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 559, [M-H]⁺ 535.

**Ejemplo 97**

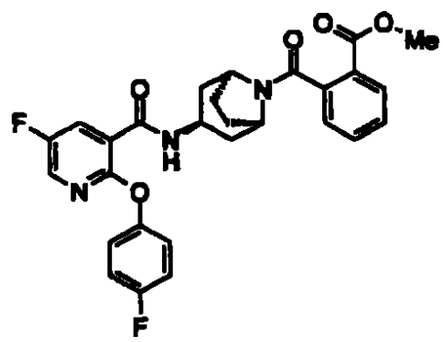
$^1$H NMR (400MHz, $CDCl_3$): δ = 8,27-8,32 (1H, d), 8,01 (1H, s), 7,58-7,65 (1H, d), 7,07-7,18 (6H, m), 6,71-6,79 (2H, d), 6,43-6,49 (1H, s ancho), 6,04-6,13 (1H, s ancho), 4,66-4,74 (1H, s ancho), 4,56-4,66 (1H, m), 4,16-4,23 (1H, m), 3,92-4,07 (2H, m), 3,53 (2H, s), 2,14-2,23 (1H, d), 1,81-2,13 (5H, m), 1,50-1,64 (1H, m, parcialmente enmascarada por el disolvente), 1,40-1,50 (1H, t) ppm.
LRMS (electropulverización): m/z [M+Na]⁺ 573, [M-H]⁺ 549.

**Ejemplo 98**

$^1$H NMR (400MHz, $CDCl_3$): δ = 9,40 (1H, s), 8,27-8,35 (1H, d), 8,02 (1H, s), 7,57-7,64 (1H, d), 6,92-7,20 (8H, m), 6,79-6,87 (1H, t), 4,72-4,79 (1H, s ancho), 4,58-4,70 (1H, m), 4,14-4,21 (1H, m), 3,95-4,05 (2H, m), 3,61 (2H, s), 2,17-2,24 (1H, d), 1,83-2,17 (5H, m), 1,57-1,64 (1H, t, parcialmente enmascarada por el disolvente), 1,40-1,51 (1H, t) ppm.

LRMS (electropulverización): m/z $[M+Na]^+$ 573, $[M-H]^+$ 549.

**Ejemplo 99 : Éster metílico del ácido exo-2-(3-{[5-Fluoro-2-(4-fluoro-fenoxi)-piridina-3-carbonil]-amino}-8-azo-biciclo[3.2.1]octano-8-carbonil)-benzoico**



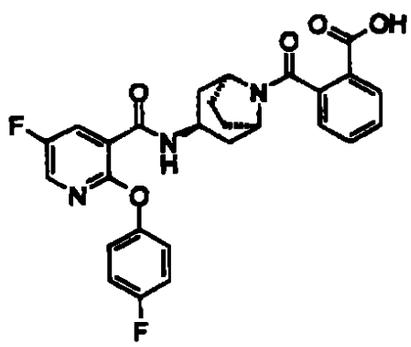

Se agitaron éster monometílico del ácido ftálico (155 mg, 0,83 mmol), 1-hidroxibenzotriazol (135 mg, 1 mmol) e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (196 mg, 1 mmol) en diclorometano (5 ml) a temperatura ambiente y se adicionó exo-N-(8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (299 mg, 0,83 mmol) (véase Preparación 35) seguido por adición de N-metil morfolina (0,11 ml, 1 mmol). La mezcla reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 18 horas, entonces se lavó con una disolución acuosa saturada de cloruro de sodio (5 ml) y se separó la fase orgánica. Se concentró la fase orgánica a vacío y el residuo se purificó por cromatogra-

fía en columna de gel de sílice eluyendo con diclorometano : metanol 100 : 0 cambiando al 97:3, en volumen dando éster metílico del ácido exo-2-(3-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]-amino}-8-azo-biciclo[3.2.1]-octano-8-carbonil)-benzoico (298 mg) como una espuma blanca.

H NMR (400MHz, $CDCl_3$): δ = 8,30-8,36 (1H, dd), 8,00-8,01 (1H, d), 7,93-7,98 (1H, d), 7,75-7,82 (1H, d), 7,49-7,56 (1H, t), 7,40-7,47 (1H, t), 7,28-7,33 (1H, d), 7,12-7,19 (4H, d), 4,93-4,98 (1H, m), 4,59-4,71 (1H, m), 3,76-3,81 (1H, m), 3,63 (3H, s), 1,83-2,21 (6H, m), 1,39-1,49 (2H, t) ppm.

LRMS (electropulverización): m/z $[M+Na]^+$ 544, $[M-H]^-$ 520

**Ejemplo 100 : ácido exo-2-(3-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-8-aza-biciclo[3.2.1]octano-8-carbonil}-benzoico**



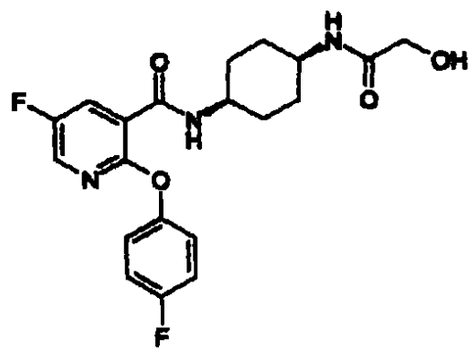
Se agitaron éster metílico del ácido exo-2-(3-{[5-Fluoro-2-(4-fluoro-fenoxi)-piridin-carbonil]-amino}-8-aza-biciclo[3,2,1]octano-8-carbonil}-4-benzoico (véase Ejemplo 99) (225 mg, 0,43 mmol) e hidróxido de litio acuoso 1 N (0,5 ml, 0,5 mmol) en metanol (5 ml) a temperatura ambiente durante 18 horas. Al quedar producto de partida, la reacción se calentó a reflujo y se agitó durante otras 5 horas. Se enfrió la mezcla de reacción y se adicionó ácido acético glacial hasta que el pH llegó a 5. Se retiró el metanol a presión reducida, y se extrajo el

residuo con acetato de etilo (10 ml). La fase orgánica se separó, se lavó con una disolución acuosa saturada de cloruro de sodio (10 ml), se concentró a vacío y se trituró el residuo con éter dietílico (5 ml) para dar ácido exo-2-(3-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}-8-aza-biciclo[3.2.1]octano-8-carbonil}-benzoico (103 mg) como un sólido blanco.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8,26-8,38 (1H, s ancho), 8,18-8,20 (1H, d), 7,91-7,97 (1H, dd), 7,70-7,88 (1H, s ancho), 7,55-7,63 (1H, m), 7,43-7,53 (1H, m), 7,16-7,31 (5H, m), 4,63-4,72 (1H, s ancho), 4,27-4,40 (1H, m), 3,52-3,62 (1H, s ancho), 1,84-2,00 (4H, m), 1,63-1,82 (4H, m) ppm.

LRMS (electropulverización): m/z [M-H]$^-$ 506.

**Ejemplo 101: Sin-5-Fluoro-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-acetilamino)ciclohexil]nicotinamida**




Se disolvieron ácido glicólico (40 mg, 0,52 mmol), hidrato de 1-hidroxibenzotriazol (80 mg, 0,52 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-(etilcarbodiimida) (100 mg, 0,52 mmol), trietilamina (181 µl, 1,3 mmol) e hidrocloruro de sin-N-(4-aminociclohexil)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (150 mg, 0,39 mmol) (véase Preparación 22) en N,N-dimetilformamida y se agitaron durante 18 horas a temperatura ambiente. La mezcla se repartió entre acetato de etilo y agua, la fase

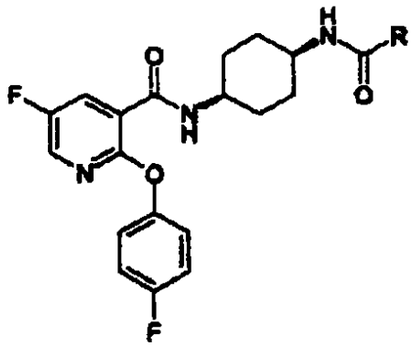
orgánica se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano (5:95) y después se purificó mediante cromatografía sobre gel de sílice utilizando metanol en acetato de etilo (gradiente de 0:100 a 5:95) para dar sin-5-Fluoro-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-acetilamino)ciclohexil]nicotinamida (100 mg).

H NMR (400MHz, $CDCl_3$): δ 8,33 (1H, d), 8,03 (1H, s), 7,99 (1H, d), 7,12 (4H, m), 6,22 (1H, d), 4,22 (1H, m), 4,09 (2H, s), 4,00 (1H, m), 2,20 (1H, s), 1,86 (5H, m), 1,79 (3H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 404

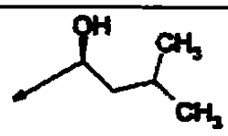
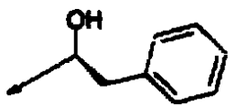
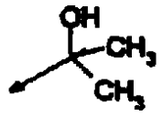
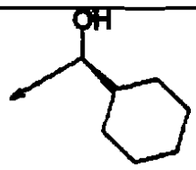
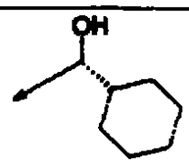
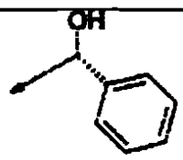
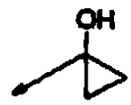
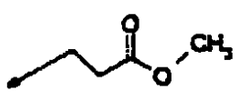
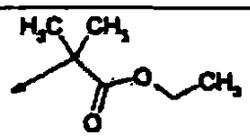
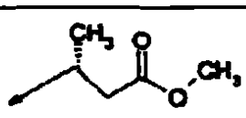
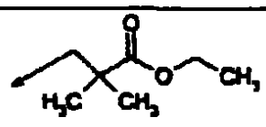
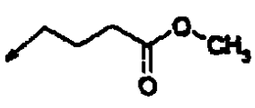
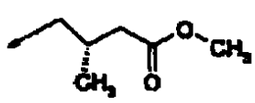
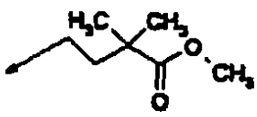
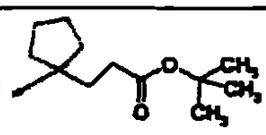
**Ejemplos 102-125**

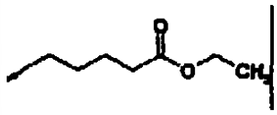
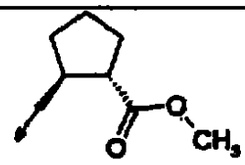
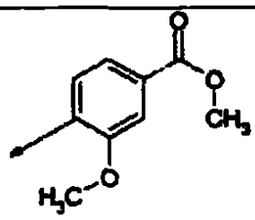
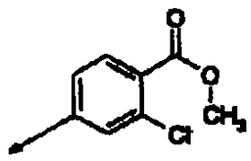
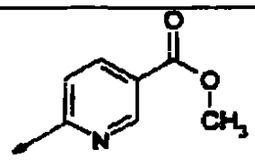
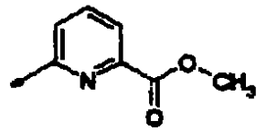
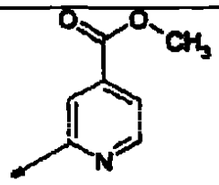
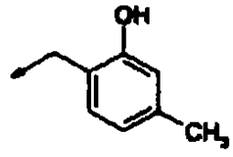
Los compuestos de los siguientes ejemplos tabulados (Tabla 8) de la fórmula general:



se prepararon por un método similar al del ejemplo 101 utilizando la amina de la Preparación 22 y el ácido carboxílico apropiado.

**TABLA 8**

| Ejemplo N° | grupo R | Ejemplo N° | grupo R |
|---|---|---|---|
| 102[1] |  | 103[2] |  |
| 104[1] |  | 105[2] |  |
| 106[1] |  | 107[2] |  |
| 108[1,4] |  | 109[2] |  |
| 110 |  | 111 |  |
| 112 |  | 113 |  |
| 114 |  | 115 |  |
| 116 |  | 117 |  |

| | | | |
|---|---|---|---|
| 118 |  | 119 |  |
| 120 |  | 121 |  |
| 122 |  | 123 |  |
| 124 |  | 125 |  |

Purificación por cromatografía utilizando un gradiente desde 95:5:0,5 hasta 90:10:0,5 de acetato de etilo: metanol: disolución de hidróxido amónico, después diclorometano: metanol: disolución de hidróxido amónico 95:5:0,5.

La trietilamina se remplazó con N-metilmorfolina.

Las soluciones acuosa se extrajeron además cuatro veces con diclorometano (5 ml)

Se utilizó purificación mediante cromatografía sobre gel de sílice diclorometano: metanol: disolución de hidróxido amónico 99:1:0,1, después diclorometano: metanol: disolución de hidróxido amónico 97:3:0,1.

El compuesto se pre-adsorbió sobre gel de sílice antes de la purificación mediante cromatografía en gel de sílice utilizando metanol en diclorometano al 1%.

Tras 18 horas de agitación se adicionó ácido L-mandélico (10 mg, 0,065 mmol) y la mezcla se dejó agitar 24 horas.

**Ejemplo 102**

$^1$H NMR (400MHz, DMSO-d6): δ 8,20 (1H, m), 7,99 (1H, m), 7,70 (1H, d), 7,21 (4H, m), 4,18 (1H, m), 3,84 (1H, m), 3,63 (1H, m), 3,52 (2H, m), 2,40 (1H, m), 2,28 (2H, m), 1,63-1,56 (8H, m).

LCMS (electropulverización): m/z[M-H]$^-$ 418

**Ejemplo 103**

$^1$H NMR (400MHz, $CDCl_3$) δ 8,35 (1H, d), 8,04 (1H, d), 7,93 (1H, d), 7,13 (4H m), 6,40 (1H, s), 4,20 (1H, s), 4,08 (1H, m), 3,91 (1H, m), 2,05 (1H, m), 1,82 (8H, m), 1,60 (1H, m), 1,45 (2H, m) 0,90 (6H, m).

LCMS (electropulverización): m/z [M+Na]$^-$ 484

**Ejemplo 104**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,38 (1H, m), 8,04 (1H, s), 7,97 (1H, d), 7,20 (9H m), 6,25 (1H, d), 4,29 (1H, m), 4,18 (1H, m), 3,91 (1H, m), 3,91 (1H, m), 3,18 (1H m), 2,92 (1H, m), 1,79 (4H, m), 1,61 (2H, m), 1,42 (2H, m).

LCMS (electropulverización): m/z [M-H]$^-$ 494

**Ejemplo 105**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,33 (1H, m), 8,04 (1H, d), 7,93 (1H, d), 7,18 (4H m), 6,59 (1H, s), 4,21 (1H, s), 3,96 (2H, m), 1,84 (4H, m), 1,77 (2H, m), 1,60 (6H, s), 1,48 (2H, m).

LCMS (electropulverización): m/z [M+H]$^-$ 434

**Ejemplo 106**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,33 (1H, m), 8,02 (2H, m), 7,16 (4H, m), 6,40 (1H, d), 4,20 (1H, s), 3,90 (2H, m), 1,74 (12H, m), 1,43 (3H, m), 1,14 (5H, m).

LCMS (electropulverización): m/z [M-H]$^-$ 486

**Ejemplo 107**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, m), 8,02 (2H, m), 7,16 (4H, m), 6,40 (1H, d), 4,20 (1H, s), 3,90 (2H, m), 1,75 (12H, m), 1,43 (3H, m), 1,18 (5H, m).

LCMS (electropulverización): m/z [M-H]$^-$ 486

**Ejemplo 108**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,31 (1 H, m), 8,04 (1 H, s), 7 94 (1H, s), 7,25 (6H, m), 7,14 (4H, m), 6,21 (1H, d), 4,98 (1H, s), 4,14 (1H, m), 3,96 (1H, m), 1,79 (4H, m), 1,63 (2H, s), 1,24 (2H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 504

**Ejemplo 109**

H NMR (400MHz, $CD_3OD$): δ 8,32 (1H, m), 8,01 (1H, m), 7,14 (4H, m), 6,81 (1H, d), 4,18 (1H, s), 3,90 (1H, m), 1,81 (6H, m), 1,51 (2H, m), 1,25 (2H, m), 1,19 (2H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 454

**Ejemplo 110**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,38 (1H, m), 8,04 (1H, s), 7,97 (1H, d), 7,14 (4H, m), 5,56 (1H, d), 4,20 (1H, s), 3,92 (1H, m), 3,89 (3H, s), 2,66 (2H, m), 2,41 (2H, m), 1,82 (4H, m), 1,73 (2H, m), 1,48 (2H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 486

**Ejemplo 111**

H NMR (400MHz, $CDCl_3$): δ 8,38 (1H, d), 8,06 (1H, s), 7,98 (1H, d), 7,16 (4H, m), 6,50 (1H, d), 4,20 (1H, s), 4,11 (2H, c), 3,89 (1H, m), 1,93 (4H, m), 1,71 (2H, m), 1,48 (2H, m), 1,40 (6H, s), 1,22 (3H, t).

LCMS (electropulverización): m/z $[M-H]^-$ 488

**Ejemplo 112**

H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, d), 8,04 (1H, s), 7,98 (1H, d), 7,17 (4H, m), 5,79 (1H, d), 4,20 (1H, m), 3,90, (1H, m), 3,60, (3H, s), 2,71 (1H, m), 2,60 (1H, m), 2,36 (1H, m), 1,83 (4H, m), 1,74 (2H, m), 1,49 (2H, m), 1,14 (3H, d).

LCMS (electropulverización): m/z $[M+Na]^+$ 498

**Ejemplo 113**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, d), 8,04 (1H, s), 7,96 (1H, d), 7,17 (4H, m), 5,85 (1H, d), 4,19 (1H, s), 4,04 (2H, c), 3,90 (1H, s), 2,40 (2H, s), 1,82 (4H, m), 1,70 (2H, m), 1,43 (2H, m), 1,24 (6H, s), 1,21 (3H, t).

LCMS (electropulverización): m/z $[M+Na]^+$ 526

**Ejemplo 114**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, d), 8,04 (1H, s), 7,96 (1H, d), 7,14 (4H, m), 5,38 (1H, s), 4,20 (1H, s), 3,91 (1H, s), 3,66 (3H, s), 2,18 (2H, t), 2,19 (2H, t), 1,91 (2H, m), 1,81 (4H, m), 1,76 (2H, m), 1,23 (2H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 474

**Ejemplo 115**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,18 (2H, s), 7,20 (4H, m), 4,10 (1H, s), 3,80 (1H, s), 3,66 (3H, s), 2,39 (2H, m), 2,20 (2H, m), 2,19 (1H, m), 1,80 (6H, m), 1,60 (2H, m), 0,95 (3H, d).

LCMS (termopulverización): m/z [M-H] 488

**Ejemplo 116**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, d), 8,04 (1H, s), 7,97 (1H, d), 7,16 (4H, m), 5,25 (1H, d), 4,20 (1H, s), 3,91 (1H, s), 3,68 (3H, s), 2,07 (2H, m), 1,84 (6H, m), 1,77 (2H, m), 1,44 (2H, m), 1,20 (6H, s).

LCMS (electropulverización): m/z $[M-H]^-$ 502

**Ejemplo 117**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, d), 8,05 (1H, s), 7,99 (1H, d), 7,17 (4H, m), 5,38 (1H, d), 4,22 (1H, s), 3,88 (1H, s), 2,15 (2H, t), 1,92 (2H, m), 1,81 (6H, m), 1,60 (4H, m), 1,18 (15H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 570

**Ejemplo 118**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, d), 8,04 (1H, s), 7,96 (1H, d), 7,18 (4H, m), 5,30 (1H, d), 4,20 (1H, s), 4,10 (2H, c), 3,93 (1H, s), 2,31 (2H, m), 2,13 (2H, m), 1,91 (6H, m), 1,76 (2H, m), 1,64 (2H, m), 1,43 (2H, m), 1,24 (3H, t).

LCMS (electropulverización): m/z $[M-H]^-$ 502

**Ejemplo 119**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,17 (2H, s), 7,20 (4H, m), 4,09 (1H, s), 3,80 (1H, s), 3,60 (3H, s), 3,03 (1H, m), 2,86 (1H, m), 2,04 (1H, m), 1,98 (1H, m), 1,70 (14H, m).

LCMS (electropulverización): m/z [M-H]⁻ 500

**Ejemplo 120**

¹H NMR (400MHz, $CD_3OD$): δ 8,08 (2H, m), 7,88 (1H, d), 7,70 (2H, m), (2H, m), 7,16 (2H, m), 4,10 (2H, s), 3,93 (3H, s), 3,90 (3H, s), 1,83 (8H, m).

LCMS (electropulverización): m/z [M-H]⁻ 538

**Ejemplo 121**

¹H NMR (400MHz, $CDCl_3$): δ 8,38 (1H, d), 8,04 (1H, s), 8,00 (1H, d), 7,85 (1H, d), 7,74 (1H, s), 7,57 (1H, d), 7,18 (4H, m), 5,80 (1H, d), 4,28 (1H, s), 4,10 (1H, m), 3,98 (3H, s), 1,93 (6H, m), 1,58 (2H, m).

LCMS (electropulverización): m/z [M-H] 542, 544

Encontrado; C, 59,57; H, 4,50: N, 7,51;, $C_{27}H_{24}ClF_2N_3O_5$ requiere; C, 59,62; H, 4,45; N, 7,72%.

**Ejemplo 122**

¹H NMR (400MHz, $CD_3OD$): δ 9,13 (1H, s) 8,50 (1H, d), 8,19 (1H, d), 8,10 (1H, m), 8,06 (1H, m), 7,22 (2H, m), 7,16 (2H, m), 4,18 (1H, m), 4,06 (1H, s), 3,93 (3H, s), 3,90 (6H, s), 1,79 (2H, m).

LCMS (electropulverización): m/z [M-H]⁻ 509

**Ejemplo 123**

¹H NMR (400MHz $CDCl_3$): δ 8,37 (2H, m), 8,20 (1H, d), 8,02 (4H, m), 7,08 (4H, m), 4,29 (1H, s), 4,10 (1H, m), 3,99 (3H, s), 1,90 (6H, m), 2,69 (2H, m).

LCMS (electropulverización): m/z [M-H] 509

**Ejemplo 124**

¹H NMR (400MHz, $CD_3OD$): δ 8,79 (1H, d) 8,57 (1H, s), 8,07 (3H, m), 720 (4H, m,, 4,19 (1H, m), 4,05 (1H, m) 3,99 (3H, s), 1,90 (6H, s;, 1,78 (2H, m)

LCMS (electropulverización): m/z [M-H] 509

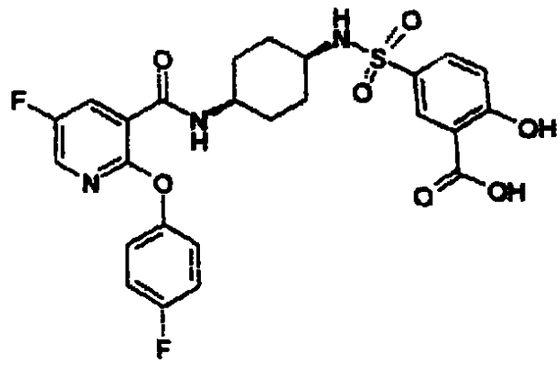
**Ejemplo 125**

¹H NMR (300MHz, $CD_3OD$): δ 8,10 (2H, m), 7,19 (7H, m), 4,07 (2H, m), 359 (2H, m), 2,22 (3H, s), 1,75 (8H, m).

LCMS (electropulverización): m/z [M+H]⁻ 496

**Ejemplo 126: Ácido sin-5-(4-{[5-fluoro-2-(4-flu ro-feno-**

**xi)-piridin-3-carbonil]-amino}-ciclohexilsulfamoil)-2-hidroxibenzoico**

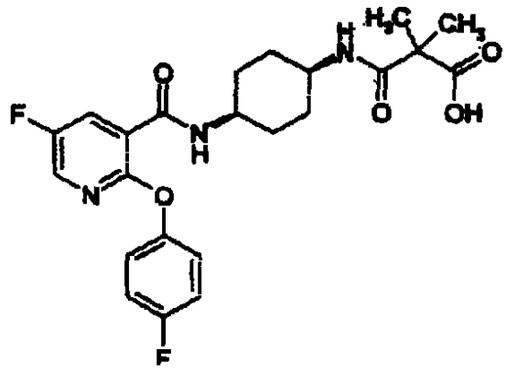


Se añadió ácido 5-clorosulfonil-2-hidroxibenzoico (123 mg, 0,52 mmol) a una suspensión agitada de hidrocloruro de hidrocloruro de sin-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (200 mg, 0,521 mmol, véase Preparación 22) en diclorometano (5 ml) conteniendo trietilamina (220 µl, 1,58 mmol) y se agitó bajo una atmósfera de nitrógeno durante 18 horas a temperatura ambiente. La mezcla se repartió entre diclorometano y agua. La capa de diclorometano se lavó con una disolución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio anhidro y se evaporó a vacío. El residuo se trituró con éter dietílico para dar ácido sin-5-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexilsulfamoil)-2-hidroxibenzoico (170 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,12 (3H, m), 7,92 (3H, m), 7,59 (1H, m), 7,07 (4H, m), 6,79 (1H, m), 5,53 (1H, s), 4,08 (1H, s), 3,97 (1H, m), 1,78 (8H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 546

**Ejemplo 127: Ácido Sin-N-(4-{[5-Fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-2,2-dimetilmalonámico**



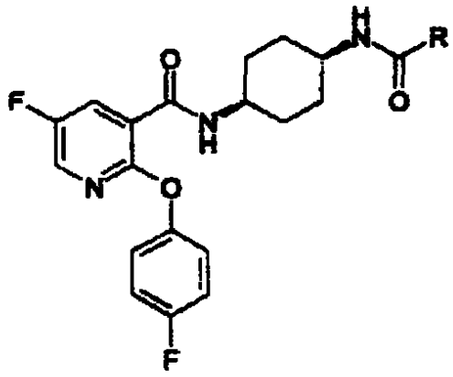
Se disolvió en tetrahidrofurano (4 ml) el éster etílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-2,2-dimetilmalonámico (125 mg, 0,26 mmol, véase Ejemplo 111) y se añadió una disolución de hidróxido de litio 1M (600 µl, 0,6 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas y después se diluyó con diclorometano (5 ml). La capa de diclorometano se separó con una pipeta y la capa acuosa se repartió entre ácido clorhídrico 1N y diclorometano (5 ml). La fase acuosa se extrajo con diclorometano (5 x 5 ml) y las capas de diclorometano combinadas se evaporaron a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice utilizando metanol en diclorometano conteniendo una disolución de hidróxido de amonio (escalonado desde 10:90:1 hasta 20:80:3) para dar el ácido Sin-N-(4-{[5-Fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-2,2-dimetilmalonámico (90 mg).

H NMR (400MHz, $CD_3OD$): δ 8,07 (1H, s), 8,01 (1H, d), 7,19 (4H, m), 4,06 (1H, s), 3,83 (1H, s), 1,78 (8H, m), 1,34 (6H, s).

LCMS (electropulverización): m/z $[M-H]^-$ 460

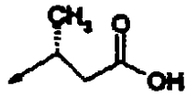
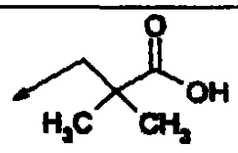
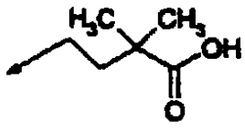
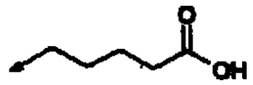
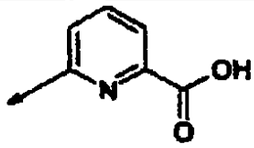
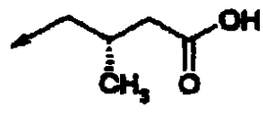
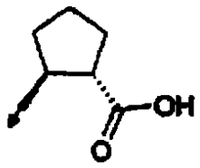
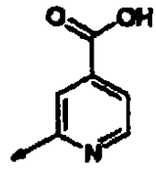
**Ejemplos 128-133**

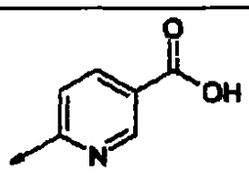
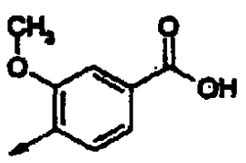
Los compuestos de los siguientes ejemplos tabulados (Tabla 9) de la fórmula general:



se prepararon por un método similar al del ejemplo 127, utilizando el éster apropiado procedente de los compuestos de la Tabla 9

**TABLA 9**

| Ejemplo N° | grupo R | Ejemplo N° | grupo R |
|---|---|---|---|
| 128 |  | 129 |  |
| 130 |  | 131 |  |
| 132 |  | 133 |  |
| 134 |  | 135 |  |

| | | | |
|---|---|---|---|
| 136 |  | 137 |  |

**Ejemplo 128**

H NMR (400MHz, CD3OD): δ 8,04 (1H, s), 8,03 (1H, d), 7,19 (4H, m), 4,14 (1H, t), 3,79 (1H, s), 2,72 (1H, m), 2,50 (1H, m), 2,21 (1H, m), 1,70 (8H, m), 1,11 (3H, m)

LCMS (electropulverización): m/z [M+Na]⁺ 484

**Ejemplo 129**

H NMR (400MHz, CD3OD): δ 8,07 (1H, m), 8,02 (1H, m), 7,20 (4H, m), 458 (1H, s), 3,79 (1H, s), 2,26 (2H, d), 1,79 (8H, m), 1,17 (6H, m).

LCMS (electropulverización): m/z [M+Na]⁺ 498

**Ejemplo 130**

H NMR (400MHz, CD3OD): δ 8,07 (2H, m), 7,20 (4H, m), 4,07 (1H, s), 3,78 (1H, m), 2,18 (2H, m), 1,77 (8H, m), 1,59 (2H, m), 1,18 (6H, s).

LCMS (electropulverización): m/z [M+Na]⁺ 512

**Ejemplo 131**

H NMR (400MHz, CD3OD): δ 8,07 (2H, m), 7,18 (4H, m), 4,08 (1H, m), 3,80 1H, m), 2,25 (2H, m), 2,18 (2H, m), 1,78 (6H, m), 1,60 (6H, m).

LCMS (electropulverización) m/z [M+Na]⁺ 498

**Ejemplo 132**

H NMR (400MHz CD3OD): δ 8,19 (2H, m), 8,10 (3H, m), 7,19 (4H, m), 4,16 (1H, m), 4,02 (1H, m), 1,85 (8H, m).

LCMS (electropulverización): m/z [M+H] 495

**Ejemplo 133**

H NMR (400MHz, CD3OD): δ 8,07 (2H, m), 7,19 (4H, m), 4,08 (1H, s), 3,82 (1H, s), 2,29 (2H, m), 2,15 (2H, m), 2,00 (1H, m), 1,79 (6H, m), 1,63 (2H, m), 0,97 (3H, d).

LCMS (electropulverización): m/z [M-H]⁻ 474

**Ejemplo 134**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,08 (1H, d), 8,02 (1H, m), 7,19 (4H, m), 4,04 (1H, s), 3,86 (1H, s), 2,86 (2H, m), 2,03 (1H, m), 1,98 (1H, m), 1,74 (12H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 486

**Ejemplo 135**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,64 (1H, d), 8,53 (1H, s), 8,09 (1H, m), 8,06 (1H, m), 7,95 (1H, m) 7,22 (2H, m), 7,16 (2H, m), 4,14 (1H, s) 4,06 (1H, s), 1,89 (6H, s), 1,78 (2H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 495

**Ejemplo 136**

$^1$H NMR (400MHz, $CD_3OD$): δ 9,07 (1H, s) 8,39 (1H, d), 8,05 (3H, m), 7,21 (2H, m), 7,15 (2H, s), 4,06 (1H, s), 1,88 (6H, s), 1,79 (2H, m).

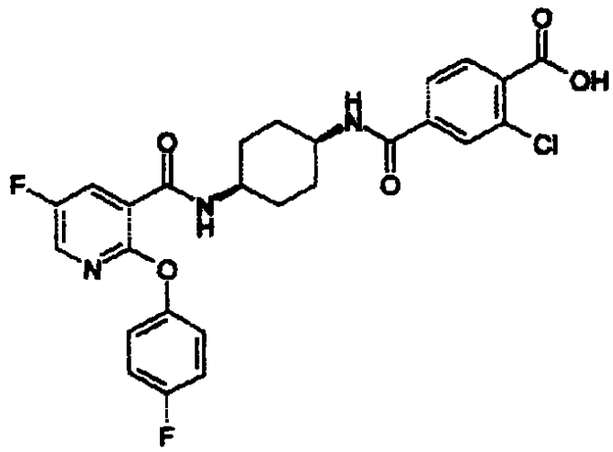
LCMS (electropulverización): m/z $[M-H]^-$ 495

**Ejemplo 137**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,30 (1H, d), 8,06 (2H, m), 7,86 (1H, d), 7,68 (1H, s), 7,61 (1H, d), 7,19 (4H, m), 4,08 (2H, s), 3,89 (3H, s), 1,84 (8H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 524

**Ejemplo 138: Ácido sin-2-cloro-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-tereftalámico**

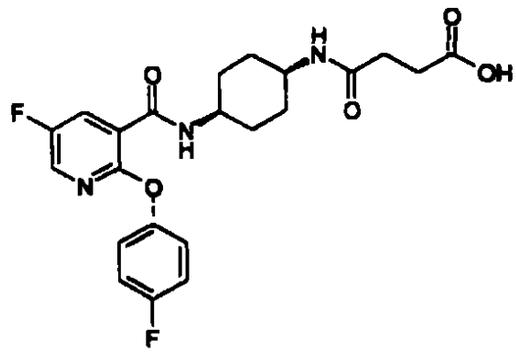


El éster metílico del ácido sin-2-cloro-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-tereftalámico (95 mg, 0,18 mmol, véase Ejemplo 121) se suspendió en 1,4-dioxano (3 ml) y se añadió una disolución de hidróxido de litio 1M (350 µl, 0,35 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas, después de lo cual se añadieron 1,4-dioxano (3 ml) y una disolución de hidróxido de litio 1M (500 µl, 0,5 mmol) y la mezcla se agitó 24 horas más. La mezcla de reacción se diluyó con ácido clorhídrico 1M (20ml) y se extrajo con diclorometano (4 x 200 ml) y las capas de diclorometano combinadas se secaron sobre sulfato de magnesio y se evaporaron a vacío para dar el ácido sin-2-cloro-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-tereftalámico como un sólido blanco (66 mg).

H NMR (400MHz, DMSO-$d_6$): δ 8,32 (2H, m), 8,20 (1H, s), 7,99 (1H, d), 7,90 (1H, s), 7,79 (1H, s), 7,22 (4H, m), 3,95 (1H, s), 3,91 (1H, s), 1,78 (8H, m).

LCMS (electropulverización): m/z [M-H] 528, 530

**Ejemplo 139: Ácido sin-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-succinámico**



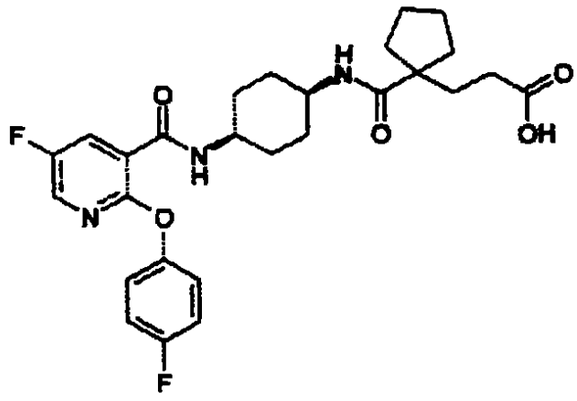
Se disolvió en tetrahidrofurano (3 ml) el éster metílico del ácido sin-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-

piridin-3-carbonil]-amino}-ciclohexil)-succinámico (65 mg, 0,14 mmol, véase Ejemplo 110) y se añadió una disolución de hidróxido de litio 1M (750 µl, 0,75 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas después de lo cual se evaporó el disolvente a vacío. El residuo se diluyó con ácido clorhídrico 1M (20 ml) y se extrajo con diclorometano (3 x 150 ml), las capas de diclorometano combinadas se secaron sobre sulfato de magnesio y se evaporaron a vacío para dar el ácido sin-N-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-succinámico como un sólido blanco (60 mg).

H NMR (400MHz, DMSO-$d_6$): δ 8,26 (1H, d), 8,20 (1H, s), 7,98 (1H, d), 7,63 (1H, d), 7,22 (4H, m), 3,86 (1H, s), 3,63 (1H, d), 2,39 (2H, t), 2,30 (3H, t), 1,60 (8H, m).

LCMS (electropulverización): m/z [M-H]⁻ 446

**Ejemplo 140: Ácido sin-3-[1-(4-{[5-fluoro-2-(4-fluor -fenoxi)-piridin-3-carbonil]-amino}-ciclohexilcarbamoil)-ciclopentil]propiónico**



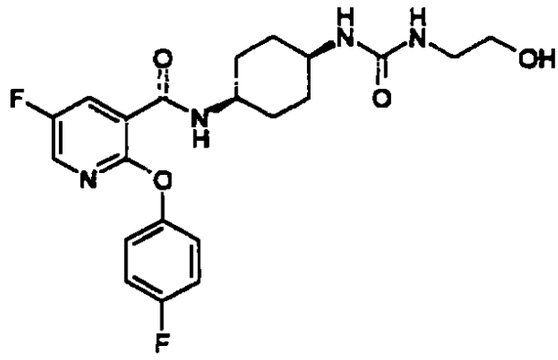
Se disolvió en 1,4-dioxano el éster terc-butílico del ácido Sin-3-[1-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexilcarbamoil)-ciclopentil]propiónico (170 mg, 0,3 mmol, véase Ejemplo 117) y se añadió cloruro de hidrógeno (disolución 4M en 1,4 dioxa-

no). La mezcla se agitó a temperatura ambiente durante 18 horas después de lo cual se evaporó el disolvente a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano conteniendo una disolución de hidróxido de amonio (desde 10:90:1 hasta 15:85:2 hasta 20:80:3) para dar el ácido sin-3-[1-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexilcarbamoil)-ciclopentil]propiónico (60 mg).

H NMR (400MHz, CD,OD): δ 8,06 (2H, m), 7,19 (4H, m), 7,04 (1H, d), 4,13 (1H, s), 3,78 (1H, s), 2,10 (2H, m), 2,01 (2H, m), 1,88 (4H, m), 1,77 (4H, m), 1,61 (6H, m) 1,31 (2H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 514

**Ejemplo 141: sin-5-Fluoro-2-(4-fluoro-fenoxi)-N-{4-[3-(2-hidroxi-etil)-ureido]-ciclohexil}-nicotinamida**



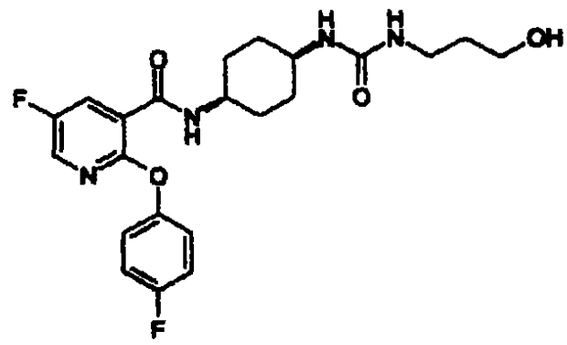
Se disolvió la sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)-amino]-ciclohexil}-nicotinamida (110 mg, 0,25 mmol, ver Preparación 25) en diclorometano (7 ml) conteniendo trietilamina (42 µl, 0,3 mmol) y 2-aminoetanol (46 µl, 0,75 mmol) y se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con agua (200 ml) y la disolución acuosa se extrajo con diclorometano (5 x 200 ml). Las capas de diclorometa-

no combinadas se secaron sobre sulfato de magnesio y se evaporaron a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano (gradiente desde 4:96 hasta 10:90) para dar la sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[3-(2-hidroxietil)-ureido]-ciclohexil}-nicotinamida como un sólido blanco (40 mg).

$^1$H NMR (400MHz, CD$_3$OD): δ 8,07 (2H, m), 7,17 (4H, m), 4,04 (1H, s), 3,68 (1 H, s), 3,57 (2H, t), 3,21 (2H, t), 1,79 (6H, m), 1,59 (2H, m).

LCMS (electropulverización): m/z [M-H]$^-$ 434

**Ejemplo 142: sin-5-Fluoro-2-(4-fluoro-fenoxi)-N-{4-[3-(3-hidroxi-propil)-ureido]-ciclohexil}-nicotinamida**



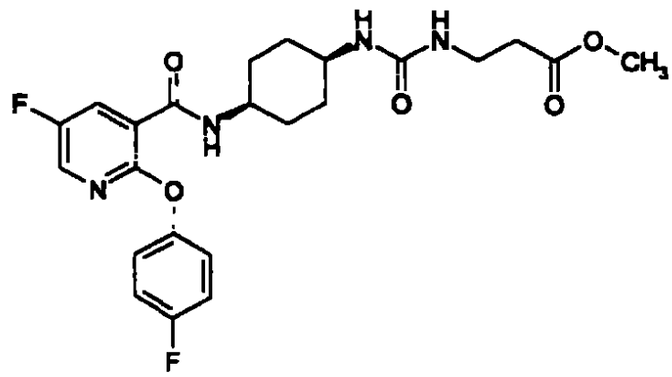
Se disolvió la sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)-amino]-ciclohexil}-nicotinamida (150 mg, 0,34 mmol, ver Preparación 25) en diclorometano (10 ml) conteniendo trietilamina (57 µl, 0,41 mmol) y 3-amino-1-propanol (78 µl, 1,02 mmol) y se agitó a temperatura ambiente bajo atmósfera de nitrógeno durante 66 horas. La mezcla de reacción se lavó con agua (2 x 50 ml) y la capa de diclorometano se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano y disolución de hidróxido de amonio (gra-

diente desde 4:96:0 hasta 10:90:1) para dar la sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[3-(3-hidroxi-propil)-ureido]-ciclohexil}-nicotinamida como un sólido blanco (90 mg).

H NMR (400MHz, $CD_3OD$): δ 8,07 (2H, m), 7,20 (4H, m), 4,04 (1H, s), 3,66 (1H, s), 3,59 (2H, t), 3,19 (2H, t), 1,79 (6H, m), 1,60 (4H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 447

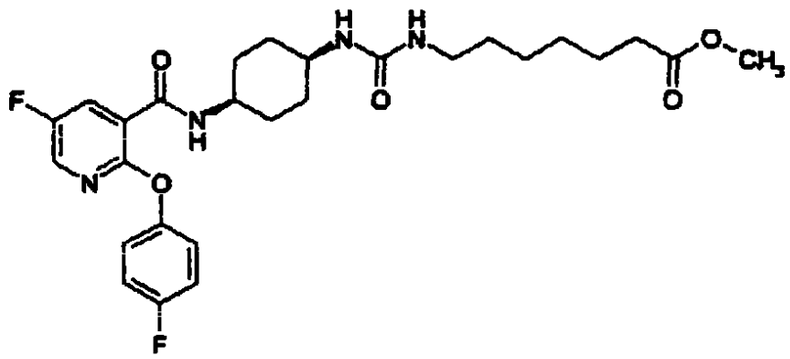
**Ejemplo 143: Éster metílico del ácido sin-3-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-propiónico**



Se disolvió la sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)-amino]-ciclohexil}-nicotinamida (150 mg, 0,34 mmol, véase Preparación 25) en diclorometano (10 ml) conteniendo trietilamina (57 µl, 0,41 mmol) y éster metílico del ácido 3-aminopropiónico (48 mg, 0,41 mmol) y se agitó a temperatura ambiente bajo atmósfera de nitrógeno a 66 horas. La mezcla de reacción se lavó con ácido clorhídrico 1M (50 ml), la capa de diclorometano se secó sobre sulfato de magnesio y se evaporó a vacío para dar el éster metílico del ácido sin-3-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-propiónico como un sólido blanco (130 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,37 (1H, d), 8,04 (1H, s), 7,96 (1H, d), 7,18 (4H, m), 4,19 (1H, s), 3,70 (4H, m), 3,47 (2H, t), 2,55 (2H, t), 1,79 (8H, m), 1,50 (2H, m).
LCMS (electropulverización): m/z $[M-H]^-$ 475

**Ejemplo 144: Éster metílico del ácido sin-7-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-heptanoico**

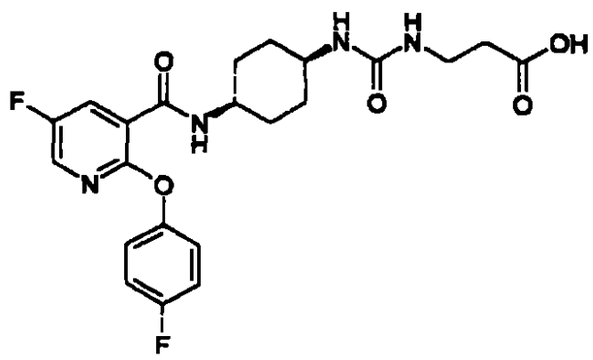


Se disolvió la sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)-amino]-ciclohexil}-nicotinamida (150 mg, 0,34 mmol, véase Preparación 25) en diclorometano (10 ml) conteniendo trietilamina (57 µl, 0,41 mmol) y éster metílico del ácido 7-aminoheptanoico (68 mg, 0,43 mmol) y se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se lavó con agua (2 x 50 ml) y después con ácido clorhídrico 1M (2 x 50 ml). la capa de diclorometano se secó sobre sulfato de magnesio y se evaporó a vacío para dar el éster metílico del ácido sin-7-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-heptanoico como un sólido blanco (168 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,36 (1H, d), 8,02 (1H, s), 7,96 (1H, d), 7,16 (4H, m), 4,19 (1H, s), 3,67 (4H, m), 3,13 (2H, t), 2,30 (2H, t), 1,82 (4H, m), 1,76 (3H, m), 1,61 (4H, m), 1,44 (4H, m), 1,36 (3H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 555

**Ejemplo 145: Ácido sin-3-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-propiónico**



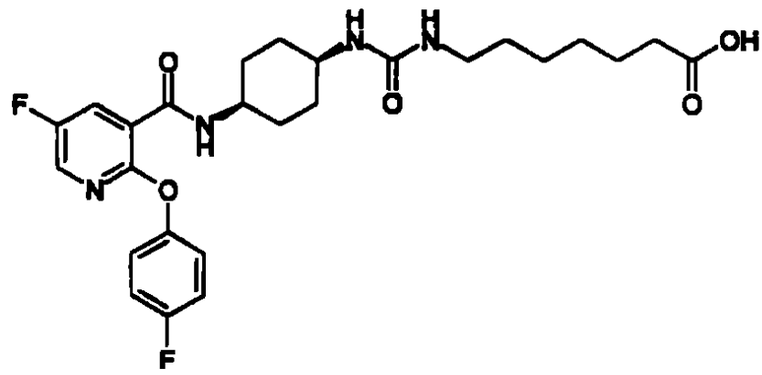
El éster metílico del ácido sin-3-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-propiónico (110 mg, 0,23 mmol, véase Ejemplo 143) se disolvió en tetrahidrofurano (1,5 ml). Se añadió una disolución de hidróxido de litio 1M (460 µl, 0,46 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se disolvió en agua y se lavó con diclorometano (2 x 50 ml). La capa acuosa se diluyó con ácido clorhídrico 1M (20 ml) y se extrajo con diclorometano (4 x 150 ml). Las capas de diclorometano combinadas se evaporaron a vacío. El residuo se redisolvió en diclorometano y se lavó con una disolución de carbonato de potasio al 10% (300 ml). La disolución acuosa se aciduló con ácido clorhídrico 1M y se extrajo con diclorometano (2 x 200 ml). Estas capas de diclorometano combinadas se secaron sobre sulfato de magnesio y se evaporaron a vacío para dar el ácido sin-3-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-propiónico (30 mg).

H NMR (400MHz, $CD_3OD$): δ 8,09 (2H, m), 7,04 (4H, m), 4,19

(1H, s), 3,66 1H, s), 2,42 (2H, t), 1,79 (8H, m), 1,59 2H, m).

LCMS: (electropulverización) m/z [M-H] 461

**Ejemplo 146: Ácido sin-7-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-heptanoico**

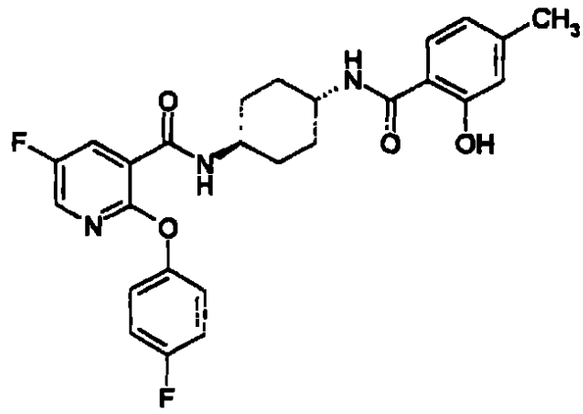


El éster metílico del ácido sin-7-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-heptanoico (130 mg, 0,24 mmol, véase Ejemplo 144) se disolvió en tetrahidrofurano (1,5 ml) conteniendo una disolución de hidróxido de litio 1M (500 µl, 0,5 mmol) y la mezcla se agitó a temperatura ambiente durante 66 horas. La mezcla de reacción se disolvió en agua (200 ml) y se lavó con diclorometano (2 x 200 ml). La capa acuosa se aciduló con ácido clorhídrico 1M (50 ml) y se extrajo con diclorometano (3 x 150 ml). Las capas de diclorometano combinadas se evaporaron a vacío para dar el ácido sin-7-[3-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-ureido]-heptanoico (60 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,36 (1H, d), 8,01 (2H, m), 7,04 (4H, m), 4,99 (1H, s), 4,50 (1H, s), 4,13 (1H, m), 3,74 (1H, m), 3,06 (2H, t), 2,33 (2H, t), 1,79 (6H, s), 1,63 (2H, m) 1,44 (4H, m), 1,37 (5H, s).

LCMS (electropulverización): m/z $[M-H]^-$ 517

**Ejemplo 147: anti-5-Fluoro-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-4-metilbenzoilamino)-ciclohexil]-nicotinamida**

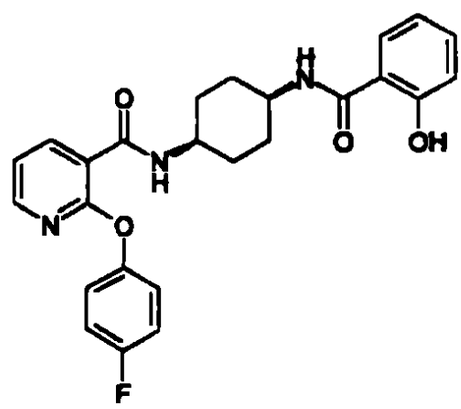


Se disolvieron ácido 2-hidroxi-4-metilbenzoico (119 mg, 0,78 mmol), hidrato de 1-hidroxibenzotriazol (158 mg, 1,17 mmol) e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (100 mg, 0,52 mmol), en N,N-dimetilformamida (6 ml) bajo atmósfera de nitrógeno y se agitaron 30 minutos. Se añadieron hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluorofenoxi)nicotinamida (300 mg, 0,782 mmol, véase Preparación 7) y 4-metil morfolina (170 µl, 1,56 mmol) y la mezcla se agitó durante 18 horas a temperatura ambiente. La mezcla se repartió entre acetato de etilo y agua y la fase orgánica se lavó con una disolución saturada de cloruro de sodio , se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se trituró con éter dietílico para dar la anti-5-Fluoro-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-4-metilbenzoilamino)-ciclohexil]-nicotinamida (210 mg).

$^1$H NMR (300MHz, $CDCl_3$): δ 8,34 (1H, m), 8,03 (1H, m), 7,77 (1H, m), 7,22 (1H, m), 7,12 (5H, m), 6,79 (1H, s), 6,63 (1H, d), 6,19 (1H, d), 4,00 (2H, s), 2,34 (3H, s), 2,19 (4H, m), 1,42 (4H, m).

LCMS (termopulverización): $[M+H]^+$ m/z 482

**Ejemplo 148: sin-2-(4-Fluoro-fenoxi)-N-[4-(2-hidroxi-benzoilamino)-ciclohexil]-nicotinamida**



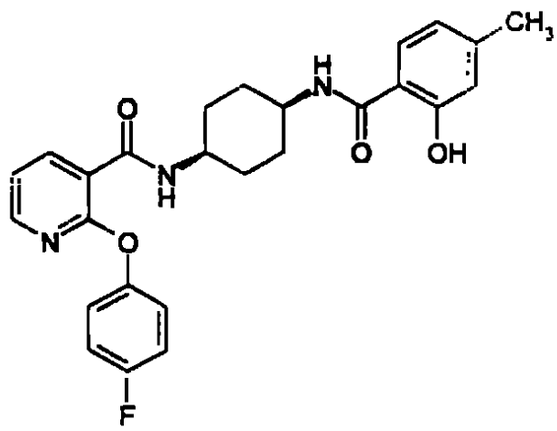
Se añadió hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (225 mg, 1,17 mmol) a una suspensión de ácido 2-hidroxibenzoico (108 mg, 0,78 mmol), hidrocloruro de sin-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)-nicotinamida (300 mg, 0,78 mmol, véase Preparación 47), e hidrato de 1-hidroxibenzotriazol (115 mg, 0,85 mmol) en N,N-dimetilformamida (5 ml) conteniendo trietilamina (545 µl, 3,9 mmol) y la mezcla se agitó durante 18 horas. El disolvente se separó a vacío y el residuo se repartió entre acetato de etilo y ácido clorhídrico 2N. La capa de acetato de etilo se lavó con agua, después se concentró la disolución de cloruro de sodio, después se secó sobre sulfato de magnesio y el disolvente se separó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando acetato de etilo en ciclohexano como eluyente (gradiente desde 10:90 hasta 60:40) para dar sin-2-(4-Fluoro-fenoxi)-N-[4-(2-hidroxi-benzoilamino)-ciclohexil]-nicotinamida (150 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8,26 (1H, m), 8,18 (1H, m) 7,76 (1H, d), 7,36 (1H, t), 7,23 (3H, m), 7,15 (2H, m), 6,88 (2H, m), 4,17, (1H, m), 4,03 (1H, m), 1,88 (6H, m), 1,77

:2H, m).

LCMS (electropulverización): m/z [M-H] 449

**Ejemplo 149: Sin-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-4-metil-benzoil-amino)-ciclohexil]-nicotinamida**

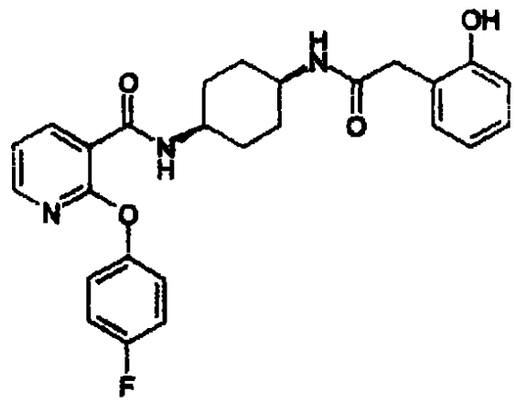


El compuesto del título se obtuvo a partir del hidrocloruro de sin-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)-nicotinamida y ácido 2-hidroxi-4-metilbenzoico con un rendimiento del 35% siguiendo el procedimiento descrito en el ejemplo 148.

$^1$H NMR (400MHz, $CD_2OD$): δ 8,27 (1H, m), 8,19 (1H, m), 7,63 (1H, d), 7,23 (3H, m), 7,16 (2H, m), 6,73 (2H, m), 4,16, (1H, m), 4,01 (1H, m), 2,31 (3H, s), 1,88 (6H, m), 1,75 (2H, m).

LCMS (electropulverización): m/z [M+Na]$^+$ 486

**Ejemplo 150: sin-2-(4-Fluoro-fenoxi)-N-{4-[2-(2-hidroxi-fenil)acetilamino]-ciclohexil}-nicotinamida**

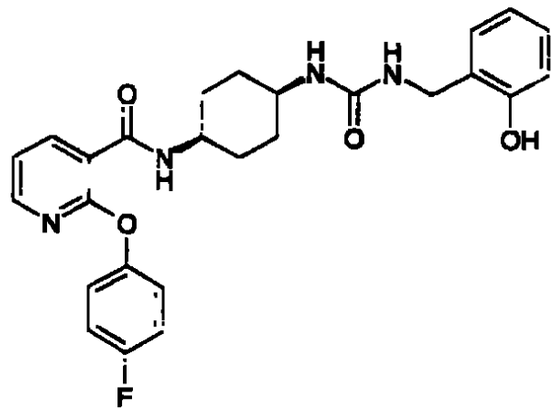


Se añadió hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (234 mg, 0,49 mmol) a una suspensión de ácido (2-hidroxifenil)acético (74,9 mg, 0,49 mmol) e hidrocloruro de sin-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)nicotinamida (150 mg, 0,41 mmol, véase Preparación 47), en N,N-dimetilformamida (2,7 ml) conteniendo base de Hünigs (820 µl, 0,82 mmol) y la mezcla se agitó durante 18 horas. La mezcla de reacción se diluyó con agua (10 ml) y se extrajo con éter dietílico (2 x 12,5 ml). Las capas orgánicas combinadas se lavaron con una disolución concentrada de cloruro de sodio, después se secaron sobre sulfato de magnesio y el disolvente se separó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol y una disolución de hidróxido amónico en diclorometano como eluyente (5:0,5:95) seguido por una purificación adicional mediante cromatografía sobre gel de sílice utilizando ciclohexano en acetato de etilo (33:67) como eluyente para dar sin-2-(4-fluoro-fenoxi)-N-{4-[2-(2-hidroxi-fenil)acetil-amino]-ciclohexil}-nicotinamida como una espuma blanquecina (25,1 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 9,68 (1H, s), 8,62 (1H, d), 8,21 (1H, d), 7,97 (1H, m), 7,19 (6H, m), 6,98 (2H, m), 6,82 (1H, m), 5,78 (1H, m), 4,16, (1H, m), 3,89 (1H, m), 3,48 (2H, s), 1,80 (6H, m), 1,51 (2H, m).

LCMS (electropulverización): m/z [M+Na]$^+$ 486

**Ejemplo 151: Sin-2-(4-fluoro-fenoxi)-N-{4-[3-(2-hidroxi-bencil)-ureido]-ciclohexil}-nicotinamida**

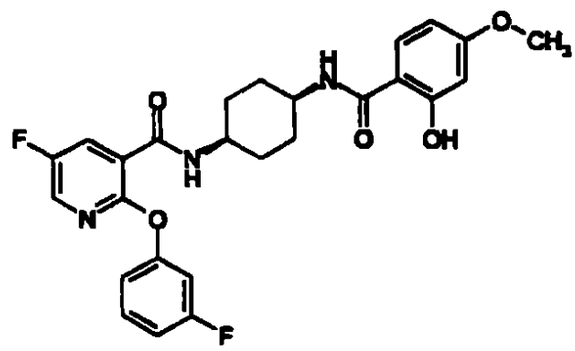


Se añadió 2-aminometilfenol (65 mg, 0,53 mmol) a una disolución de 2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)-amino]-ciclohexil}-nicotinamida (150 mg, 0,35 mmol, véase Preparación 47) y 4-dimetilaminopiridina (43,3 mg, 0,35 mmol) en diclorometano (3 ml) a temperatura ambiente bajo una atmósfera de nitrógeno. La mezcla se agitó durante 18 horas y después se lavó con agua (20 ml) y después se diluyó con una disolución de ácido cítrico al 10% (20 ml). La mezcla se extrajo con diclorometano (2 x 10 ml) y las capas orgánicas combinadas se lavaron con una disolución saturada de cloruro de sodio (20 ml) y se secaron sobre sulfato de magnesio. El disolvente se separó a vacío y el residuo se purificó por cromatografía sobre gel de sílice utilizando ciclohexano en acetato de etilo (33,3:66,6) para dar sin-2-(4-fluoro-fenoxi)-N-{4-[3-(2-hidroxi-bencil)-ureido]-ciclohexil}-nicotinamida como una espuma blanquecina (96 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 9,75 (1H, s), 8,60 (1H, d), 8,20 (1H, d), 7,91 (1H, d), 7,18 (6H, m), 7,02 (1H, d), 6,98 (2H, m), 6,79 (1H, m), 4,84 (1H, m), 4,29, (2H, d), 3,71

1H, m), 1,82 (6H, m), 1,49 (2H, m).
LCMS (electropulverización): m/z [M+Na]⁺ 501

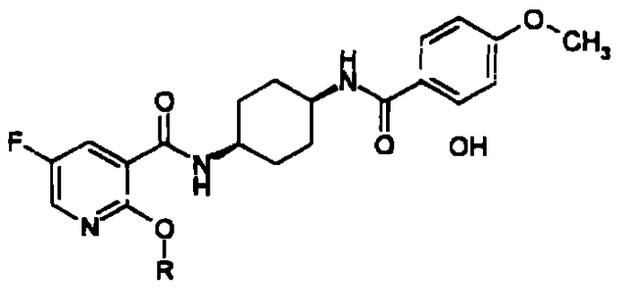
**Ejemplo 152: Sin-2-(3-fluoro-fenoxi)-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-nicotinamida**



Se añadió carbonato de cesio (170 mg, 0,52 mmol) a una disolución de sin-2-cloro-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-nicotinamida (110 mg, 0,26 mmol, véase Preparación 45) y 3-fluorofenol (35 mg, 0,31 mmol) en N,N-dimetilformamida (2 ml) y se agitó a 65°C durante 18 horas. La mezcla se repartió entre acetato de etilo y agua y la disolución orgánica se secó utilizando un cartucho Chem Elut® y se evaporó a vacío. El residuo se purificó por cromatografía sobre un cartucho de Biotage™ para dar sin-2-(3-fluoro-fenoxi)-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-nicotinamida (19 mg).
$^1$H NMR (400MHz, $CDCl_3$): δ 12,56 (1H, s), 8,38 (1H, d), 8,09 (1H, s), 7,94 (1H, d), 7,44 (1H, m), 7,00 (4H, m), 6,46 (1H, s), 6,39 (1H, d), 5,78 (1H, d), 4,26 (1H, m), 4,07 (1H, m), 3,82 (3H, s), 1,90 (8H, m).
LCMS (electropulverización): m/z [M+Na]⁺ 520

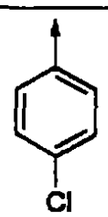
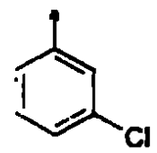
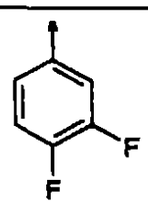
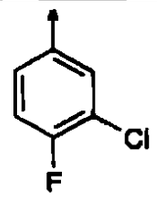
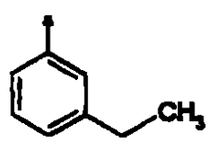
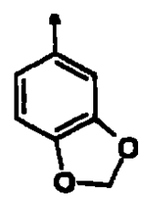
**Ejemplos 153-159**

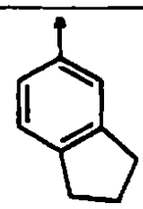
Los compuestos de los siguientes ejemplos tabulados (Tabla 10) de la fórmula general:



se prepararon por un método similar al del ejemplo 152 utilizando 2-cloro-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]nicotinamida (véase Preparación 45) y el fenol apropiado.

**Tabla 10**

| Ejemplo N° | grupo R | Ejemplo N° | grupo R |
|---|---|---|---|
| 153 |  | 154 |  |
| 155 |  | 156 |  |
| 157 |  | 158 |  |

| | |
|---|---|
| 159 |  |

**Ejemplo 153**

H NMR (400MHz, $CDCl_3$): δ 12,54 (1H, s), 8,37 (1H, d), 8,06 (1H, s), 7,97 (1H, d), 7,44 (2H, d), 7,14 (2H, d), 7,00 (1H, d), 6,43 (2H, m), 5,74 (1H, d), 4,28 (1H, m), 4,07 (1H, m), 3,82 (3H, s), 1,91 (8H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 536, 538

**Ejemplo 154**

H NMR (400MHz, $CDCl_3$): δ 12,54 (1H, s), 8,38 (1H, d), 8,09 (1H, s), 7,93 (1H, d), 7,40 (1H, m), 7,30 (1H, m), 7,21 (1H, m), 7,07 (2H, m), 6,44 (1H, s), 6,39 (1H, d), 5,79 (1H, d), 4,26 (1H, s), 4,08 (1H, m), 3,81 (3H, s), 1,90 (8H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 536, 538

**Ejemplo 155**

$^1$H NMR (400MHz, $CDCl_3$): δ 12,54 (1H, s), 8,37 (1H, d), 8,08 (1H, s), 7,87 (1H, d), 7,24 (1H, m), 7,14 (2H, d), 6,93 (1H, m), 6,46 (1H, s), 6,40 (1H, d), 5,84 (1H, d), 4,28 (1H, m), 4,09 (1H, m), 3,82 (3H, s), 1,91 (8H, m),

LCMS (electropulverización): m/z $[M+Na]^+$ 538

**Ejemplo 156**

$^1$H NMR (400MHz, $CDCl_3$): δ 12,53 (1H, s), 8,37 (1H, d), 8,06 (1H, s), 7,87 (1H, d), 7,24 (2H, m), 7,10 (2H, m), 6,46 (1H, s), 6,39 (1H, d), 5,84 (1H, d), 4,28 (1H, m), 4,11 (1H, m), 3,82 (3H, s), 1,90 (8H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 554, 556

**Ejemplo 157**

H NMR (400MHz, $CDCl_3$): δ 12,59 (1H, s), 8,38 (1H, d), 8,08 (1H, d), 8,08 (1H, s), 7,39 (1H, t), 7,17 (1H, d), 6,99 (3H, m), 6,44 (1H, s), 6,38 (1H, d), 5,70 (1H, d),

4,29 (1H, s), 4,08 (1H, m), 3,82 (3H, s), 2,70 (2H, c), 1,90 (8H, m) 1,25 (3H, t).

LCMS (electropulverización): m/z [M+Na]⁺ 530

**Ejemplo 158**

$^1$H NMR (400MHz, $CDCl_3$): δ 12,59 (1H, s), 8,34 (1H, d), 8,08 (2H, m), 7,07 (1H, d), 6,88 (1H, d), 6,71 (1H, s), 6,64 (1H, d), 6,46 (1H, s), 6,39 (1H, d), 6,03 (2H, s), 5,78 (1H, d), 4,30 (1H, m), 4,08 (1H, m), 3,83 (3H, s), 1,93 (1H, m).

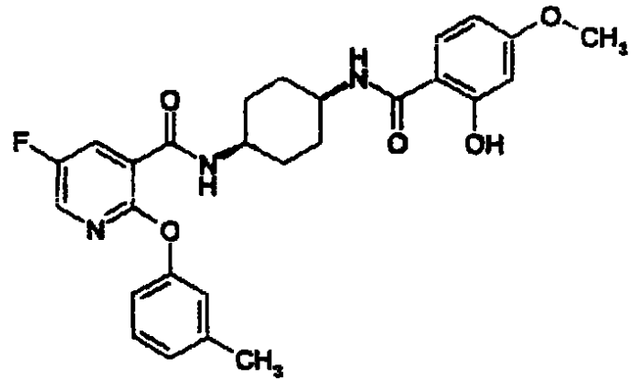
LCMS (electropulverización): m/z 546 [M+Na]⁺

**Ejemplo 159**

H NMR (400MHz, $CDCl_3$): δ 12,59 (1H, s), 8,37 (1H, d), 8,19 (1H, d), 8,07 (1H, s), 7,30 (1H, d), 7,02 (2H, m), 6,94 (1H, d), 6,46 (1H, s), 6,38 (1H, d), 5,74 (1H, d), 4,30 (1H, m), 4,08 (1H, m), 3,83 (3H, s), 2,94 (4H, m), 2,17 (2H, m), 1,93 (8H, m).

LCMS (electropulverización): m/z [M+Na]⁺ 542

**Ejemplo 160: sin-5-Fluoro-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-2-toliloxi-nicotinamida**



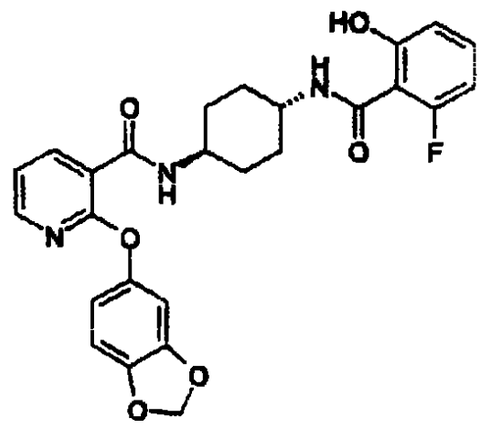
Se añadió carbonato de cesio (116 mg, 036 mmol) a una disolución de sin-2-cloro-5-fluoro-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-nicotinamida (100 mg, 0,24 mmol, ver Preparación 45) y 3-hidroxitolueno (28 mg, 0, 26 mmol) en dimetilformamida (3 ml) y se agitó a 55°C

durante 18 horas. Se añadió una porción adicional de carbonato de cesio (30 mg, 0,16 mmol) y de 3-hidroxitolueno (10 mg, 0,9 mmol) y la mezcla se calentó a 65°C durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente y se repartió entre acetato de etilo y agua. La capa de acetato de etilo se lavó con agua y después con una disolución acuosa saturada de cloruro de sodio, se secó sobre sulfato de magnesio anhidro y se evaporó a vacío. El residuo se purificó mediante cromatografía sobre gel de sílice utilizando acetato de etilo en pentano (50:50) como eluyente para dar sin-5-fluoro-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-2-toliloxi-nicotinamida (36 mg).

H NMR (400MHz, $CDCl_3$): δ 12,56 (1H, s), 8,37 (1H, d), 8,16 (1H, d), 8,10 (1H, s), 7,36 (1H, m), 7,14 (1H, d), 6,97 (3H, d), 7,07 (2H, m), 6,48 (1H, s), 6,39 (1H, d), 5,70 (1H, d), 4,30 (1H, s), 4,06 (1H, m), 3,83 (3H, s), 2,40 (3H, s), 1,90 (8H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 493

**Ejemplo 161: Anti-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(2-fluoro-6-hidroxibenzoilamino)-ciclohexil]-nicotinamida**



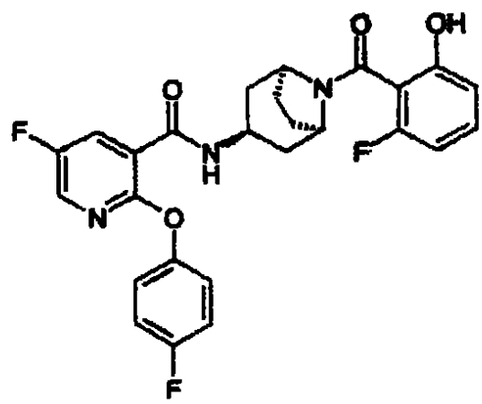

Se añadió ácido 2-fluoro-6-hidroxi-benzoico (119 mg, 0,77 mmol) a hidrato de 1-benzotriazol (155 mg, 0,77

mmol) e hidrocloruro de 1-(3-dimetilaminopropil-3-etil-carbodiimida) (220 mg, 0,77 mmol) en N,N-dimetilformamida (5 ml) y la mezcla se agitó durante 1,5 horas. Se añadieron hidrocloruro de anti-N-(4-amino-ciclohexil)-2-'benzo[1,3]dioxol-5-iloxi)-nicotinamida (300 mg, 0,77 mmol, véase Preparación 39) y 4-metilmorfolina (167 µl, 0,77 mmol) y la mezcla se agitó durante 18 horas y después se repartió entre diclorometano y una disolución de ácido cítrico al 10% (10 ml). La capa orgánica se separó, se pasó a través de una frita hidrofóbica y se evaporó a vacío. El residuo se trituró con metanol y el sólido obtenido se aisló por filtración para dar anti-2-(Benzo[1,3]dioxol-5-iloxi)-N-[4-(2-fluoro-6-hidroxibenzoilamino)-ciclohexil]-nicotinamida (26 mg).

H NMR (400MHz, $CDCl_3$): δ 13,36 (1H, s), 8,60 (1H, d), 8,21 (1H, d), 7,73 (1H, d), 7,27 (1H, m), 7,14 (1H, m), 6,93 (1H, m), 6,88 (1H, d), 6,79 (1H, d), 6,72 (1H, s), 6,60 (2H, m), 6,61 (2H, s), 4,02 (2H, m), 2,20 (4H, m), 1,46 (4H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 492

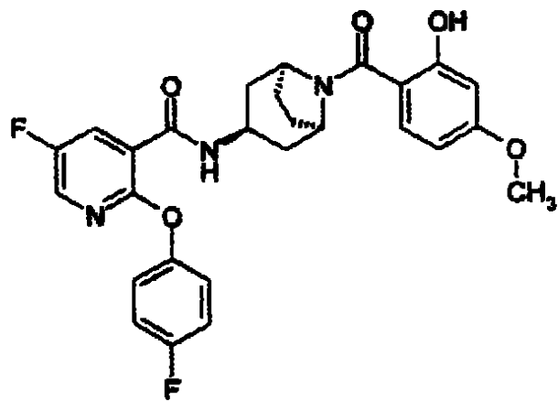
**Ejemplo 162: exo-5-Fluoro-N-[8-(2-fluoro-6-hidroxi-benzoil)-8-aza-biciclo[3.2.1]oct-3-il]-2-(4-fluoro-fenoxi)-nicotinamida**



Se añadió exo-N-(8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (155 mg, 0,43 mmol, véase Preparación 35) a hidrocloruro de 1-(3-dimetilaminopropil-3-etilcarbodiimida) (101 mg, 0,52 mmol), ácido 2-fluoro-6-hidroxibenzoico (69 mg, 0,43 mmol) e hidrato de 1-hidroxibenzotriazol (70 mg, 0,52 mmol) en diclorometano (5 ml) conteniendo 4-metilmorfolina (57 µl, 0,52 mmol) y la mezcla se agitó a temperatura ambiente durante 24 horas. Se añadió agua y la mezcla se concentró a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano (5:95) como eluyente, para dar la exo-5-Fluoro-N-[8-(2-fluoro-6-hidroxi-benzoil)-8-aza-biciclo[3.2.1]oct-3-il]-2-(4-fluoro-fenoxi)-nicotinamida (85 mg). RMN-$^1$H (400MHz, DMSO-$d_6$): δ 10,10 (1H, s), 8,19 (1H, d), 8,18 (1H, s), 7,92 (1H, d), 7,19 (5H, m), 6,86 (2H, m), 4,67 (1H, s), 4,33 (1H, m), 3,72 (1H, s), 1,79 (7H, m), 1,46 (1H, m).

LCMS: m/z AP$^-$ 498 $[M+H]^-$

**Ejemplo 163: Exo-5-Fluoro-2-(4-fluoro-fenoxi)-N-[8-(2-hidroxi-4-metoxi-benzoil)-8-aza-biciclo[3.2.1]oct-3-il]-nicotinamida**



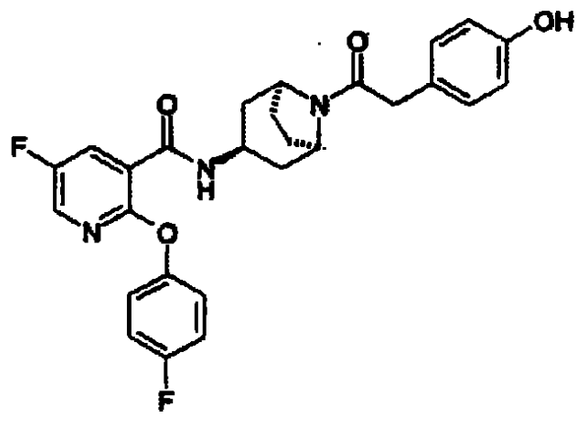
Se añadió exo-N-(8-aza-biciclo[3.2.1]oct-3-il)-5-

fluoro-2-(4-fluoro-fenoxi)nicotinamida (155 mg, 0,43 mmol, véase Preparación 35) a hidrocloruro de 1-(3-dimetilaminopropil-3-etilcarbodiimida (101 mg, 0,52 mmol), ácido 2-hidroxi-4-metoxibenzoico 73 mg, 0,43 mmol) e hidrato de 1-hidroxibenzotriazol (70 mg, 0,52 mmol) en diclorometano (5 ml) conteniendo 4-metilmorfolina (57 µl, 0,52 mmol) y la mezcla se agitó a temperatura ambiente durante 24 horas. Se añadió agua y la mezcla se concentró a vacío, el residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano (5:95) como eluyente, para dar la exo-5-fluoro-2-(4-fluoro-fenoxi)-N-[8-(2-hidroxi-4-metoxi-benzoil)-8-aza-biciclo[3.2.1]oct-3-il]-nicotinamida (165 mg).

H NMR (400MHz, DMSO-$d_6$): δ 10,13 (1H, s), 8,34 (1H, d), 8,19 (1H, s), 7,92 (1H, m), 7,19 (5H, m), 6,40 (2H, m), 4,36 (3H, m), 3,74 (3H, s), 1,79 (8H, m).

LCMS: m/z AP$^-$ 510 [M+H]$^+$

**Ejemplo 164: Exo-5-fluoro-2-(4-fluoro-fenoxi)-N-{8-[2-(4-hidroxi-fenil)-acetil]-8-aza-biciclo[3.2.1]oct-3-il}-nicotinamida**



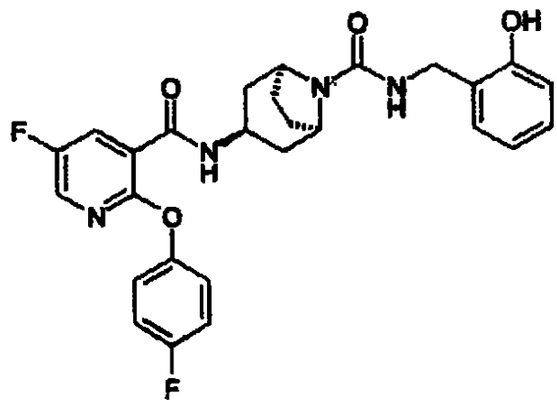
Se añadió exo-N-(8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (310 mg, 0,86 mmol, ver Preparación 35) a hidrocloruro de 1-(3-

dimetilaminopropil-3-etilcarbodiimida) (185 mg, 0,95 mmol), ácido 4-hidroxifenilacético (134 mg, 0,86 mmol) e hidrato de 1-hidroxibenzotriazol (128 mg, 0,95 mmol) en diclorometano (5 ml) conteniendo 4-metilmorfolina (104 µl, 0,95 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con agua y la fase orgánica se concentró a vacío y después se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano conteniendo una disolución de hidróxido de amonio como eluyente (gradiente desde 1:99:0,1 hasta 5:95:0,5). El material obtenido se trituró con metanol y se aisló por filtración, después se secó a vacío para dar exo-5-fluoro-2-(4-fluoro-fenoxi)-N-{8-[2-(4-hidroxi-fenil)-acetil]-8-aza-biciclo[3.2.1]oct-3-il}-nicotinamida (270 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 9,21 (1H, s), 8,31 (1H, d), 8,19 (1H, s), 7,94 (1H, d), 7,20 (4H, m), 7,00 (2H, d), 6,66 (2H, d), 446 (1H, m), 4,35 (2H, m), 3,56 (1H, d), 3,40 (1H, d), 1,79 (6H, m), 1,48 (2H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 516

**Ejemplo 165: 2-Hidroxi-bencil-amida del ácido exo-3-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-8-aza-biciclo[3.2.1]octano-8-carboxílico**



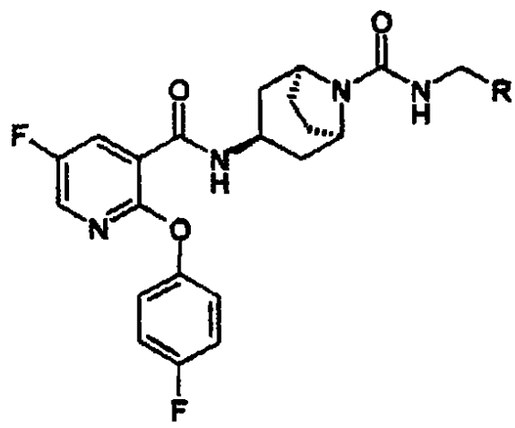
Se preparó en el momento una disolución de cloruro de exo-3-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-8-aza-biciclo[3.2.1]octano-8-carbonilo por adición de exo-N-(8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (625 mg, 1,74 mmol, ver Preparación 35) en porciones durante 10 minutos a una disolución de trifosgeno (175 mg, 0,56 mmol) en diclorometano (10 ml) y agitando durante 18 horas a temperatura ambiente. Se añadieron trietilamina 218 µl, 1,5 mmol) e hidrocloruro de 2-aminometilfenol (96 mg, 0,6 mmol, véase Tet. Lett. 2001, 41(49), 8665) a la disolución anterior (3 ml, 0,52 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se lavó con una disolución saturada de cloruro de sodio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente desde 0:100 hasta 5:95), el material aislado se trituró con éter dietílico y se secó a vacío para dar la 2-hidroxi-bencil-amida del ácido exo-3-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-8-aza-biciclo[3.2.1]octano-8-carboxílico (22 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,30 (1H, m), 8,01 (1H, s), 7,60 (1H, d), 7,10 (7H, m), 6,90 (1H, d), 6,80 (1H, m), 5,03 (1H, s), 4,54 (2H, m), 4,34 (1H, s), 4,21 (1H, s), 4,19 (2H, s), 1,86 (8H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 531

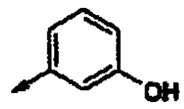
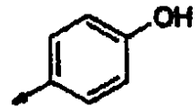
**Ejemplos 166-167**

Los compuestos de los siguientes ejemplos tabulados (Tabla 11) de la fórmula general:



se prepararon por un método similar al del ejemplo 165 utilizando el mismo cloruro de carbamoilo y la amina apropiada.

**Tabla 12**

| Ejemplo N° | grupo R |
|---|---|
| 166[1] |  |
| 167[2] |  |

[1]Para la amina, véase la referencia Tet. Lett. 1995, 36(8), 1279

[2]Para la amina, véase la referencia DE 2552423

**Ejemplo 166**

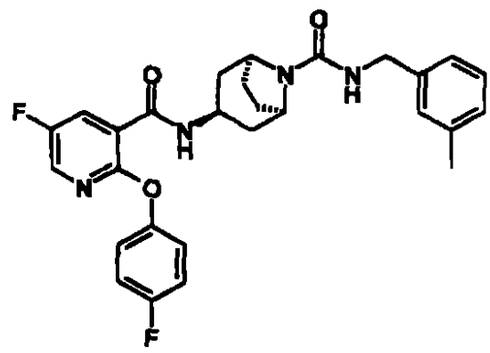
$^1$H NMR (400MHz, $CDCl_3$): δ 8,31 (1H, d) 8,02 (1H, s), 7,80 (1H, d), 713 (7H, m), 6,92 (1H, s), 6,80 (1H, m), 6,74 (1H, d), 4,41 (3H, m), 4,26 (2H, m), 2,10 (2H, m), 1,19 (4H, m), 188 (2H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 531

**Ejemplo 167**

H NMR (400MHz, DMSO-$d_6$): δ 9,13 (1H, s), 8,32 (1H, d), 8,14 (1H, s), 7,93 (1H, m), 7,19 (4H, m), 7,03 (2H, d), 6,87 (1H, m), 6,67 (2H, m) 4,33 (1H, m), 4,24 (2H, s), 4,13 (2H, m), 1,86 (2H, m), 1,72 (4H, m), 1,60 (2H, m).
LCMS (electropulverización): m/z $[M+Na]^+$ 531

**Ejemplo 168: Sin-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[4-(2-hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida**



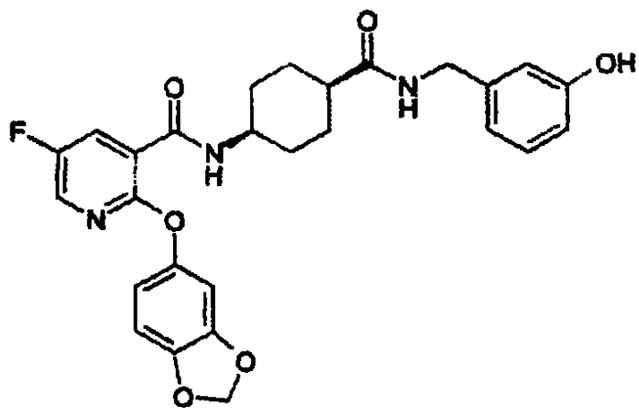
Se mezclaron ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]-amino}-ciclohexano-carboxílico (150 mg, 0,37 mmol, véase Preparación 58), hidrocloruro de 2-aminometilfenol (65 mg, 0,41 mmol, véase Tet. Lett. 2001, 41(49), 8665), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (156 mg, 0,41 mmol) y 4-metilmorfolina (50 µl, 0,41 mmol) en N,N-dimetilformamida (4 ml) y se agitaron a temperatura ambiente bajo atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre agua (10 ml) y diclorometano (10 ml). La capa de diclorometano se secó sobre sulfato de magnesio y se evaporó a vacío y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente desde 0:100 hasta 2:98). El material aislado se trituró con acetato de etilo en pentano (10:90) para dar sin-2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[4-(2-

hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida como un polvo blanco (61 mg).

H NMR (400MHz, $CDCl_3$): δ 8,04 (1H, m), 8,01 (1H, m), 7,04 (2H, m), 6,79 (1H, d), 6,72 (3H, m), 6,61 (1H, d), 5,96 (2H, s), 4,27 (2H, s), 4,13 (1H, m), 2,33 (1H, m), 1,89 (2H, m), 1,71 (6H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 530

**Ejemplo 169: Sin-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[4-(3-hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida**



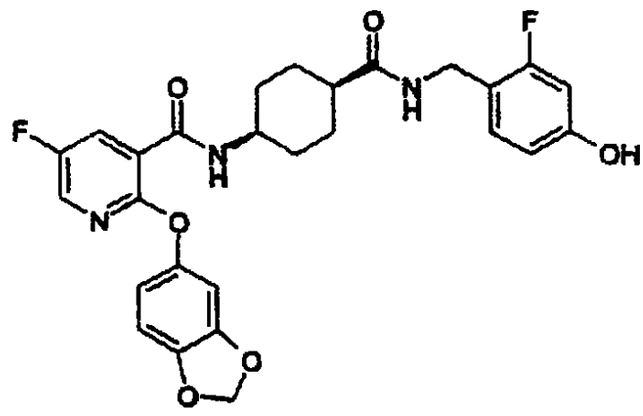

Se mezclaron ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]-amino}-ciclohexano-carboxílico (144 mg, 0,36 mmol, véase Preparación 58), hidrocloruro de 3-aminometilfenol (225 mg, 0,39 mmol, véase Tet. Lett. 1995, 36(8), 1279), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (149 mg, 0,39 mmol) y 4-metilmorfolina (50 µl, 0,39 mmol) en N,N-dimetilformamida (4 ml) y se agitaron a temperatura ambiente bajo atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre agua (10 ml) y acetato de etilo (10 ml). La capa de acetato de etilo se lavó con disolución saturada de cloruro de sodio, se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se trituró con acetato de etilo en pentano (10:90),

el sólido formado se asiló por filtración y se trituró con éter dietílico. El producto se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente desde 2:98 hasta 3:97 para dar sin-2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[4-(3-hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida como una espuma blanca (83 mg).

H NMR (400MHz, CD$_3$OD): δ 8,08 (2H, m), 7,09 (1H, t), 6,80 1H, d), 6,76 (1H, m), 6,66 (4H, m), 5,98 (2H, s), 4,27 2H, s), 4,19 (1H, m), 2,38 (1H, m), 1,93 (2H, m), 1,75 6H, m).

LCMS (electropulverización): m/z $[M+H]^+$ 508

**Ejemplo 170: Sin-2-(Benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[4-(2-fluoro-4-hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida**



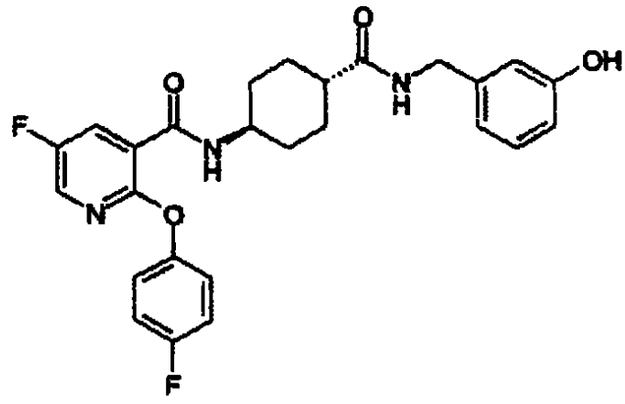
Se mezclaron ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]-amino}-ciclohexanocarboxílico (200 mg, 0,50 mmol, véase Preparación 58), hidrocloruro de aminometil-3-fluoro-fenol (97 mg, 0,55 mmol, véase Preparación 49), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (189 mg, 0,55 mmol) y 4-metilmorfolina (60 µl, 0,55 mmol) en N,N-dimetilformamida (5 ml) y se agitaron a temperatura am-

biente bajo atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre agua (10 ml) y diclorometano (10 ml). La capa de diclorometano se secó sobre sulfato de magnesio y se evaporó a vacío y el residuo se purificó mediante cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente desde 0:100 hasta 2:98). El material aislado se trituró con acetato de etilo en pentano (10:90) para dar sin-2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-N-[4-(2-fluoro-4-hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida como un sólido blanco (83 mg).

H NMR (400MHz, CD$_3$OD): δ 8,01 (2H, m), 7,04 (1H, m), 6,80 (1H, d), 6,74 (1H, m), 6,62 (1H, d), 6,48 (2H, m), 5,97 (2H, s), 4,23, (2H, s), 4,17 (1H, m), 2,13 (1H, m), 1,90 (2H, m), 1,72 (6H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 548

**Ejemplo 171: Anti-5-Fluoro-2-(4-fluoro-fenoxi)-N-[4-(3-hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida**



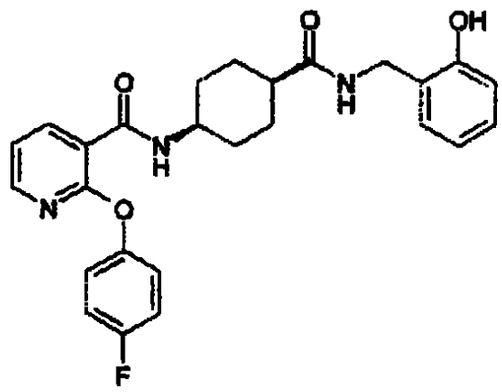
Se mezclaron ácido anti-4-{[5-Fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]-amino}-ciclohexanocarboxílico (200 mg, 0,53 mmol, véase Preparación 52), hidrocloruro de 3-aminometilfenol (334 mg, 0,58 mmol, véase Tet. Lett. 1995, 36(8), 1279), hexafluorofosfato de O-(7-azabenzo-

triazol-1-il)-N,N,N',N'-tetrametiluronio (222 mg, 0,58 mmol) y 4-metilmorfolina (70 µl, 0,58 mmol) en N,N-dimetilformamida (5 ml) y se agitaron a temperatura ambiente bajo atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre agua (10 ml) y diclorometano (10 ml). La capa de diclorometano se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente desde 0:100 hasta 2:98). El material aislado se secó a vacío para dar para dar anti-5-fluoro-2-(4-fluoro-fenoxi)-N-[4-(3-hidroxi-bencilcarbamoil)-ciclohexil]-nicotinamida como un polvo blanco (127 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8,21 (1H, m), 8,07 (1H, d), 8,00 (1H, m), 7,13 (5H, m), 6,70 (3H, m), 4,29, (2H, d), 3,89 (1H, m), 2,26 (1H, m), 2,12 (2H, m), 1,95 (2H, m), 1,68 (2H, m), 1,39 (2H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 504

**Ejemplo 172: Sin-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-bencil-carbamoil)-ciclohexil]-nicotinamida**



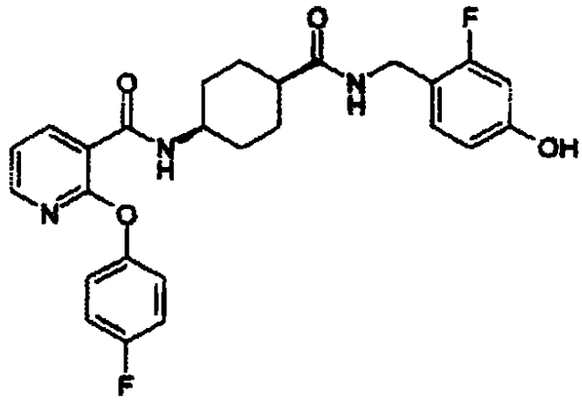
Se mezclaron ácido sin-4-{[2-(4-fluoro-fenoxi)piridin-3-carbonil]-amino}-ciclohexanocarboxílico (164 mg, 0,46 mmol, véase Preparación 55), hidrocloruro de 2-

aminometilfenol (80 mg, 0,50 mmol, véase referencia Tet. Lett. 1995, 36(8), 1279), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (149 mg, 0,50 mmol) y 4-metilmorfolina (60 µl, 0,50 mmol) en N,N-dimetilformamida (4 ml) y se agitaron a temperatura ambiente bajo atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre agua (10 ml) y acetato de etilo (10 ml). La capa de acetato de etilo se lavó con una disolución saturada de cloruro de sodio, se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se trituró con éter dietílico, el sólido formado se aisló por filtración y se lavó con éter dietílico. Este producto se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (2:98) para dar sin-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-bencil-carbamoil)-ciclohexil]-nicotinamida

$^1$H NMR (400MHz, $CD_3OD$): δ 8,26 (1H, d), 8,18 (1H, m), 7,21 (3H, m), 7,11 (4H, m), 6,78 (2H, m), 4,32 (2H, s), 4,20 (1H, m), 2,38 (1H, m), 1,92 (2H, m), 1,76 (6H, m).

LCMS (termopulverización): m/z [M+H]+ 464

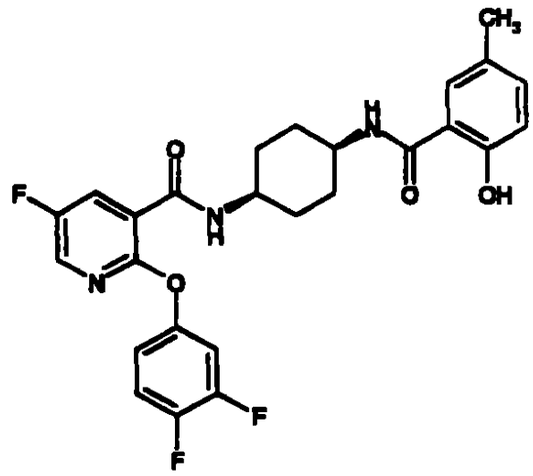
**Ejemplo 173: Sin-N-[4-(2-Fluoro-4-hidroxi-bencil-carbamoil)-ciclohexil]-2-(4-fluoro-fenoxi)-nicotinamida**



Se mezclaron ácido sin-4-{[2-(benzo[1,3]dioxol-5-il-

oxi)-5-fluoro-piridin-3-carbonil]-amino}-ciclohexanocarboxílico (200 mg, 0,56 mmol, véase Preparación 55), hidrocloruro de 4-aminometil-3-fluoro-fenol (109 mg, 0,61 mmol, véase Preparación 49), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (189 mg, 0,61 mmol) y 4-metilmorfolina (70 µl, 0,61 mmol) en N,N-dimetilformamida (5 ml) y se agitaron a temperatura ambiente bajo atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre agua (10 ml) y diclorometano (10 ml). La capa de diclorometano se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente desde 0:100 hasta 2:98). El producto aislado se trituró con éster dietílico en pentano (20:80) para dar sin-N-[4-(2-fluoro-4-hidroxi-bencil-carbamoil)-ciclohexil]-2-(4-fluoro-fenoxi)-nicotinamida como un polvo blanco (83 mg).
$^1$H NMR (400MHz, $CD_3OD$): δ 8,40 (1H, d), 8,21 (1H, d), 8,14 (1H, d), 7,19 (3H, m), 7,09 (3H, m), 6,48 (2H, m), 4,22 (2H, s), 4,16 (1H, m), 2,31 (1H, m), 1,89 (2H, m), 1,70 (6H, m).
LCMS (electropulverización): m/z $[M+Na]^+$ 505

**Ejemplo 174: sin-2-(3,4-Difluoro-fenoxi)-5-fluoro-N-[4-(2-hidroxi-5-metil-benzoilamino)-ciclohexil]-nicotinamida**

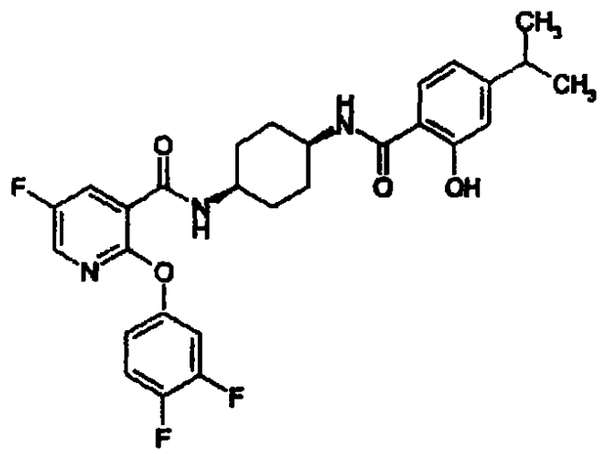


Se adicionó hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (9,45, 50 mmol) a una solución del ácido procedente de la preparación 60 (10,3 g, 38 mmol) e hidrato de 1-hidroxibenzotriazol (5,65 g, 42 mmol) en 1-metil-2-pirrolidinona (150 ml) y la solución se agitó durante 10 minutos. Después se añadió una solución de la amina procedente de la preparación 62 (11,8 g, 40 mmol) y de base de Hünig (17,5 ml, 100 mmol) en 1-metil-2-pirrolidinona (50 ml) y la reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró a vacío, y el residuo se repartió entre acetato de etilo (1,25 L) y ácido clorhídrico 1N (800 ml). Las capas se separaron, la fase orgánica se lavó con ácido clorhídrico 2N (2 veces), agua (2 veces) y salmuera, después se secó sobre sulfato de magnesio y se evaporó a vacío. El producto bruto se recristalizó de metanol, para proporcionar el compuesto del título como un sólido cristalino blanco (15,6 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 1,56-1,66 (2H, m), 1,80-2,02 (6H, m), 2,26 (3H, s), 4,05 (1H, m), 4,25 (1H, m), 6,06 (1H, m), 6,90 (1H, d), 6,95 (1H, m), 6,99 (1H, s), 7,08 (1H, m), 7,19-7,30 (2H, m), 7,89 (1H, m), 8,05 (1H, s), 8,40 (1H, d), 11,98 (1H, s).

LCMS (APCI): m/z $[M+H]^+$ 500

**Ejemplo 175: Sin-2-(3,4-Difluoro-fenoxi)-5-fluoro-N-[4-(2-hidroxi-4-isopropil-benzoilamino)-ciclohexil]-nicotinamida**



Se adicionó sin-N-(4-amino-ciclohexil)-2-(3,4-difluoro-fenoxi)-5-fluoro-nicotinamida (200 mg, 0,55 mmol, véase Preparación 64) a hidrocloruro de 1-(3-dimetilaminopropil-3-etilcarbodiimida) (115 mg, 0,6 mmol), hidrato de 1-hidroxibenzotriazol (81 mg, 0,6 mmol), 4-metilmorfolina (120 µl, 1,1 mmol) y ácido 2-hidroxi-4-isopropil-benzoico (109 mg, 0,6 mmol) en diclorometano (10 ml) y la mezcla se agitó a temperatura ambiente durante 16 horas. Se añadió diclorometano y la mezcla se lavó con una disolución saturada de hidrógeno carbonato de sodio. Las fases se separaron y la fase orgánica se filtró a través de tubos de separación de fase Whatman® y se concentró a vacío. El residuo se trituró con éter dietílico y diclorometano para dar sin-2-(3,4-difluoro-fenoxi)-5-fluoro-N-[4-(2-hidroxi-4-isopropil-benzoilamino)-ciclohexil]-nicotinamida como un sólido blanco (145 mg).

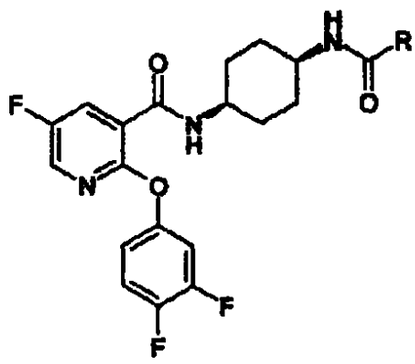
$^1H$ NMR (400MHz, DMSO-$d_6$): δ 8,33 (m, 2H), 8,25 (d, 1H),

8,00 (m, 1H), 7,80 .d, 1H), 7,45 (m, 3H), 7,08 (m, 1H), 6,75 (m, 1H), 3,94 m, 1H), 3,88 (m, 1H), 2,82 (m, 1H), 1,70 (m, 8H), 1,16 (d, 6H)

LCMS (electropulverización): m/z $[M-H]^-$ 526

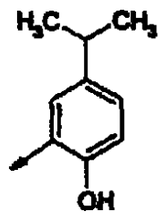
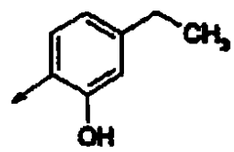
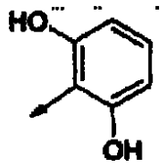
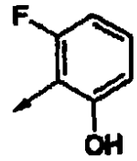
**Ejemplos 176-194**

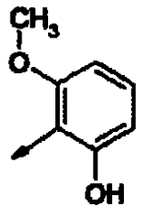
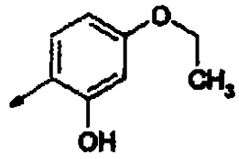
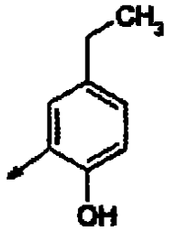
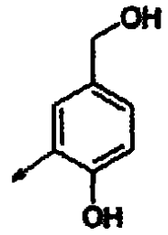
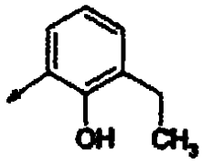
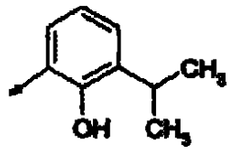
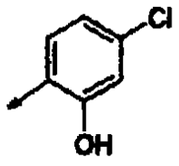
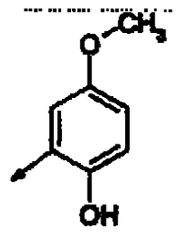
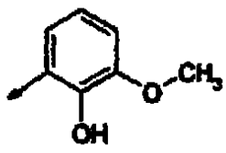
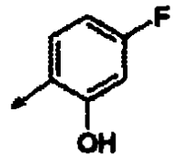
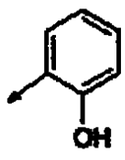
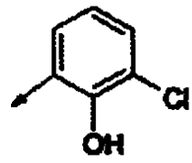
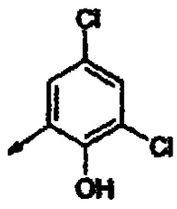
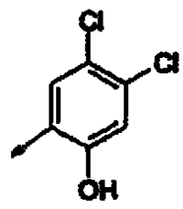
Los compuestos de los siguientes ejemplos tabulados (Tabla 13) de la fórmula general:

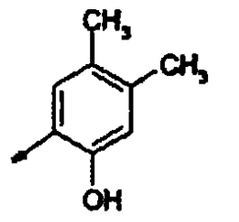


se prepararon por un método similar al del ejemplo 175 utilizando la amina de la Preparación 64 y el ácido carboxílico apropiado.

**Tabla 13**

| Ejemplo N° | R | Ejemplo N° | R |
|---|---|---|---|
| 176 |  | 177 |  |
| 178 |  | 179 |  |

| | | | |
|---|---|---|---|
| 180 |  | 181 |  |
| 182 |  | 183 |  |
| 184 |  | 185 |  |
| 186[A] |  | 187[A] |  |
| 188[A] |  | 189[A] |  |
| 190[A] |  | 191[A] |  |
| 192[A] |  | 193[AB] |  |

| | |
|---|---|
| 194 |  |

Se utilizó como base diisopropiletilamina

Véase referencia Chem. and Pharm. Bull, 1996, 44(4), 734 para el ácido carboxílico de partida.

Véase referencia Synthesis 1984, (9), 758 para el ácido carboxílico de partida.

**Ejemplo 176**

H NMR (400MHz, DMSO-$d_6$): δ 8,35 (m, 3H), 8,00 (m, 1H), 7,70 (s, 1H), 7,45 (m, 3H), 7,25 (d, 1H), 7,08 (m, 1H), 6,83 (d, 1H), 3,90 (m, 2H), 2,81 (m, 1H), 1,70 (m, 8H), 1,15 (d, 6H)

LCMS (electropulverización): m/z $[M-H]^-$ 526

**Ejemplo 177**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,26 (s, 1H), 8,32 (m, 2H), 8,25 (d, 1H), 8,00 (m, 1H), 7,79 (d, 1H), 7,43 (m, 2H), 7,07 (m 1H), 6,72 (m, 2H), 3,90 (m, 2H), 2,55 (c, 2H), 1,73 (m, 8H), 1,14 (t, 3H)

LCMS (electropulverización): m/z $[M-H]^-$ 512

**Ejemplo 178**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,55 (s, 2H), 8,88 (d, 1H), 8,41 (d, 1H), 8,22 (d, 1H), 8,22 (d, 1H), 7,45 (m, 1H), 7,18 (m, 1H), 7,16 (m, 1H), 7,04 (m, 1H), 6,35 (d, 2H), 3,94 (m, 2H), 1,70 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 500

**Ejemplo 179**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 9,95 (s, 1H), 8,29 (d, 1H), 8,22 (d, 1H), 7,99 (m, 2H), 7,41 (m, 2H), 7,22 (m, 1H), 7,06 (m, 1H), 6,68 (m, 2H), 3,88 (m, 2H), 1,66 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 502

**Ejemplo 180**

H NMR (400MHz, DMSO-$d_6$): δ 1,60 (m, 2H), 1,73 (m, 6H), 3,75 (s, 3H), 3,95 (m, 2H), 6,51 (d, 1H), 6,58 (d, 1H), 7,09 (m, 1H), 7,31 (m, 1H), 7,45 (m, 2H), 8,00 (m, 1H), 8,23 (m, 1H), 8,39 (d, 1H), 8,48 (d, 1H), 13,59 (s, 1H)

LCMS (electropulverización): m/z $[M-H]^-$ 514

**Ejemplo 181**

H NMR (400MHz, DMSO-$d_6$): δ 8,84 (d, 1H), 8,24 (m, 2H), 8,00 (d, 1H), 7,80 (d, 1H), 7,46 (m, 3H), 7,09 (m, 1H), 6,44 (d, 1H), 3,98 (m, 5H), 1,71 (m, 8H), 1,30 (t, 3H)

LCMS (electropulverización): m/z $[M-H]^-$ 528

**Ejemplo 182**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 8,39 (m, 2H), 8,26 (s, 1H), 8,02 (d, 1H), 7,71 (s, 1H), 7,45 (m, 3H), 7,20 (m, 1H), 7,06 (m, 1H), 6,81 (d, 1H), 3,90 (m, 2H), 2,50 (c, 2H), 1,72 (m, 8H), 1,15 (t, 3H)

LCMS (electropulverización): m/z $[M-H]^-$ 512

**Ejemplo 183**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,40 (m, 1H), 8,12 (s, 1H), m 8,03 (m, 1H), 7,79 (s, 1H), 7,30 (m, 3H), 6,86 (d, 1H), 4,52 (s, 2H), 4,13 (m, 1H), 4,05 (m, 1H), 1,83 (8H)

LCMS (APCI): m/z $[M-H]^-$ 514

**Ejemplo 184**

H NMR (400MHz, $CD_3OD$): δ 8,11 (d, 1H), 8,07 (m, 1H), 7,48 (d, 1H), 7,30 (m, 3H), 7,04 (m, 1H), 6,78 (m, 1H), 4,15 (m, 1H), 3,98 (m, 1H), 2,63 (c, 2H), 1,88 (m, 8H), 1,09 (t, 3H)

LCMS (APCI): m/z $[M-H]^-$ 514

**Ejemplo 185**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,13 (s, 1H), 8,08 (d, 1H), 7,48 (d, 1H), 7,34 (d, 2H), 7,26 (m, 1H), 7,05 (m, 1H), 6,80 (m, 1H), 4,18 (m, 1H), 3,98 (m, 1H), 3,36 (m, 1H), 1,90 (m, 8H), 1,20 (d, 6H)

LCMS (APCI): m/z $[M+H]^+$ 528

**Ejemplo 186**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,58 (s, 1H), 8,40 (d, 1H),

8,33 (d, 1H), 8,23 (d, 1H), 8,00 (m, 1H), 7,92 (d, 1H), 7,43 (m, 2H), 7,07 (m, 1H), 6,98 (m, 2H), 3,90 (m, 2H), 1,72 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 518

**Ejemplo 187**

H NMR (400MHz, DMSO-$d_6$): δ 12,60 (s, 1H), 8,45 (d, 1H), 8,39 (d, 1H), 8,23 (d, 1H), 7,99 (m, 1H), 7,41 (m, 3H), 7,06 (m, 1H), 6,99 (m, 1H), 6,84 (d, 1H), 3,96 (m, 1H), 3,87 (m, 1H), 3,72 (s, 3H), 1,72 (m, 8H)

LCMS (electropulverización): m/z $[M+Na]^-$ 538

**Ejemplo 188**

H NMR (400MHz, DMSO-$d_6$): δ 12,42 (s, 1H), 8,39 (d, 1H), 8,37 (d, 1H), 8,26 (d, 1H), 8,01 (m, 1H), 8,46 (m, 3H), 7,10 (d, 2H), 6,80 (m, 1H), 3,97 (m, 1H), 3,88 (m, 1H), 3,79 (s, 3H), 2,73 (m, 8H)

LCMS (electropulverización): m/z $[M+Na]^-$ 538

**Ejemplo 189**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,84 (s, 1H), 8,40 (d, 1H), 8,36 (d, 1H), 8,25 (s, 1H), 7,99 (m, 2H), 7,45 (m, 2H), 7,08 (d, 1H), 6,73 (m, 2H), 3,97 (m, 1H), 3,85 (m, 1H), 1,72 (m, 8H)

LCMS (APCI): m/z $[M+H]^-$ 504

**Ejemplo 190**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,22 (s, 1H), 8,40 (d, 1H), 8,35 (d, 1H), 8,22 (d, 1H), 8,00 (m, 1H), 7,89 (d, 1H), 7,40 (m, 3H), 7,08 (m, 1H), 6,90 (m, 2H), 3,93 (m, 2H), 1,75 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 484

**Ejemplo 191**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 13,55 (s, 1H), 8,63 (s, 1H), 8,31 (d, 1H), 8,23 (d, 1H), 8,00 (m, 1H), 7,89 (d, 1H), 7,59 (d, 1H), 7,41 (m, 2H), 7,08 (m, 1H), 6,88 (m, 1H), 3,98 (m, 1H), 3,84 (m, 1H), 1,74 (m, 8H)

LCMS (electropulverización): m/z $[M+Na]^-$ 542

**Ejemplo 192**

H NMR (400MHz, $CDCl_3$): δ (rotámeros) 12,68 (s, 1H), 8,36 (m, 1H), 8,05 (d, 1H), 7,86, 7,80 (2xd, 1H), 7,48 (d, 1H), 7,20 (m, 2H), 7,06 (m, 1H), 6,92 (d, 1H), 6,21, 6,10 (2xd, 1H), 4,22 (m, 1H), 4,10 (m, 1H), 1,93 (m, 6H), 1,62 (m, 2H)

LCMS (electropulverización): m/z $[M-H]^-$ 552

**Ejemplo 193**

H NMR (400MHz, $CDCl_3$): δ 12,28 (s, 1H), 8,35 (m, 1H), 8,05 (d, 1H), 7,88 (d, 1H), 7,27 (m, 2H), 7,05 (m, 2H), 6,96 (d, 1H), 6,07 (d, 1H), 4,23 (m, 1H), 4,12 (m, 1H), 1,90 (m, 6H), 1,62 (m, 2H)

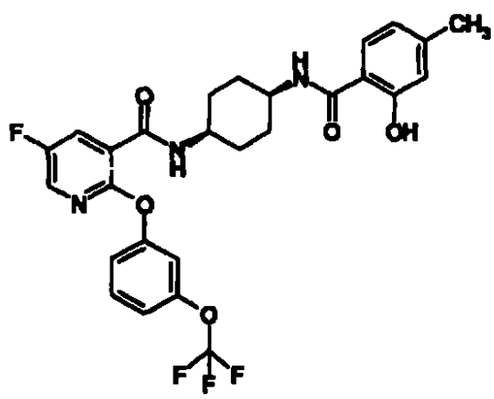
LCMS (electropulverización): m/z $[M-H]^-$ 552

**Ejemplo 194**

H NMR (400MHz, DMSO-$d_6$): δ 12,04 (s, 1H), 8,36 (d, 1H), 8,26 (m, 2H), 8,00 (d, 1H), 7,62 (s, 1H), 7,45 (m, 2H), 7,07 (m, 1H), 6,68 (s, 1H), 3,96 (m, 1H), 3,85 (m, 1H), 2,18 (s, 3H), 2,14 (s, 3H), 1,71 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 512

**Ejemplo 195: Sin-5-fluoro-N-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-2-(3-trifluorometoxi-fenoxi)-nicotinamida**



Se mezcló sin-2-cloro-5-fluoro-N-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-nicotinamida (150 mg, 0,37

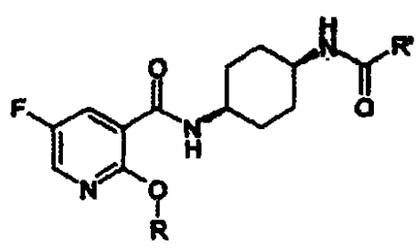
mmol, véase Preparación 67) con carbonato de cesio (602 mg, 1,85 mmol) y 3-trifluorometoxifenol (240 µl, 1,85 mmol) en N,N-dimetilformamida (5 ml) y la mezcla de reacción se calentó a 65°C bajo atmósfera de nitrógeno durante 16 horas. La mezcla de reacción se enfrió a temperatura ambiente y se repartió entre acetato de etilo y agua. La capa acuosa se ajustó a pH por adición de ácido cítrico y las capas se separaron. La capa orgánica se lavó con agua y se secó sobre sulfato de magnesio y se concentró a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente desde 0:100 hasta 1:99). El material aislado se purificó adicionalmente por cromatografía sobre gel de sílice utilizando metanol en diclorometano (0,5:99,5). El producto obtenido se resuspendió en éter dietílico y el sólido formado se aisló por filtración para dar la sin-5-fluoro-N-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-2-(3-trifluorometoxi-fenoxi)-nicotinamida como un sólido blanco (54 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 1,70 (m, 8H), 2,26 (s, 3H), 3,90 (m, 2H), 6,70 (m, 2H), 7,24 (m, 3H), 7,52 (m, 1H), 7,77 (d, 1H), 8,01 (d, 1H), 8,28 (s, 1H), 8,34 (m, 2H), 12,32 (s, 1H)

LCMS (electropulverización): m/z $[M-H]^-$ 546

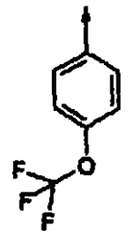
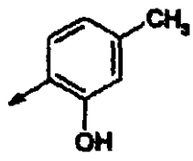
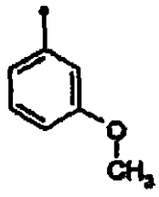
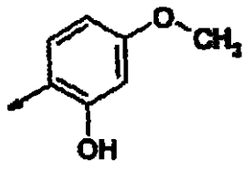
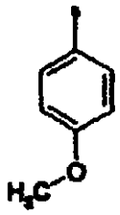
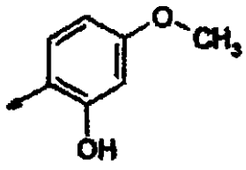
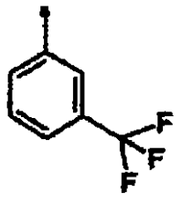
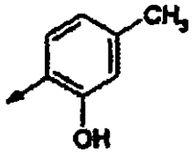
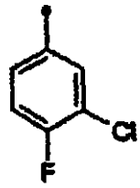
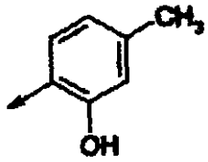
**Ejemplos 196-215**

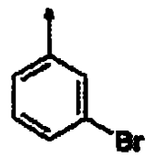
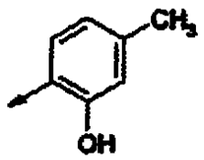
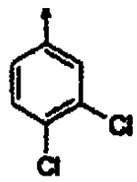
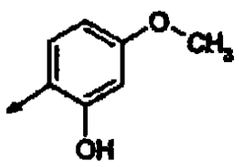
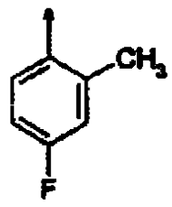
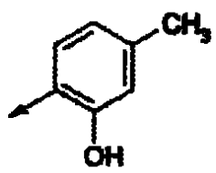
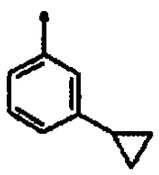
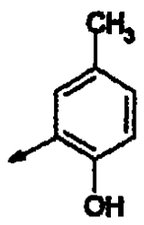
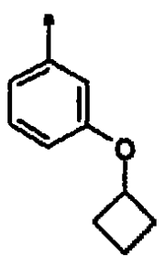
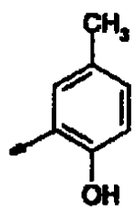
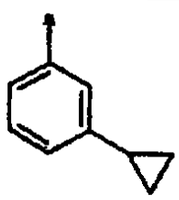
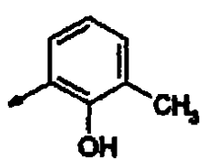
Los compuestos de los siguientes ejemplos tabulados (Tabla 14) de la fórmula general:

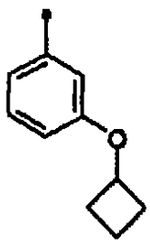
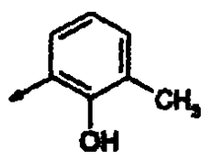
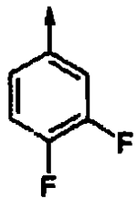
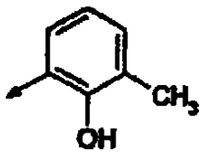
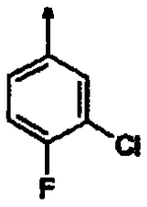
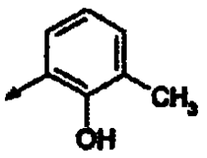
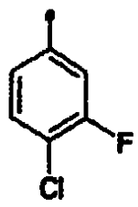
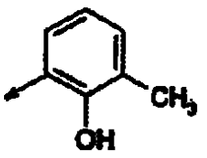
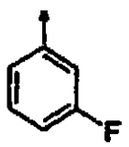
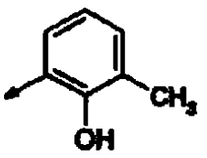
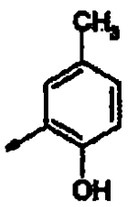


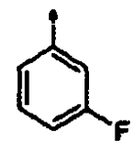
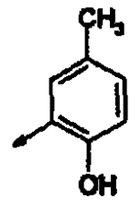
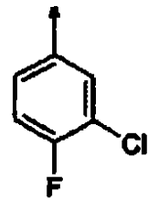
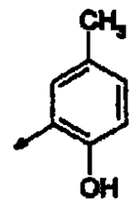
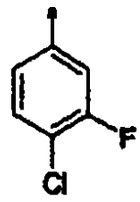
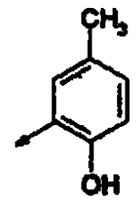
se prepararon por un método similar al del ejemplo 195 utilizando el cloruro de arilo y el fenol apropiados.

**Tabla 14**

| Ejemplo N° | R | R' |
|---|---|---|
| 196 |  |  |
| 197 |  |  |
| 198 |  |  |
| 199 |  |  |
| 200 |  |  |

| | | |
|---|---|---|
| 201 |  |  |
| 202 |  |  |
| 203 |  |  |
| 204[A] |  |  |
| 205[A] |  |  |
| 206[A] |  |  |

| | | |
|---|---|---|
| 207[A] |  |  |
| 208[A] |  |  |
| 209[AB] |  |  |
| 210[AB] |  |  |
| 211[AB] |  |  |
| 212[AB] |  |  |

| | | |
|---|---|---|
| 213[nb] |  |  |
| 214[nb] |  |  |
| 215[nb] |  |  |

Se utilizó acetonitrilo como disolvente

Purificado por cromatografía sobre gel de sílice utilizando acetato de etilo en ciclohexano como eluyente

**Ejemplo 196**

H NMR (400MHz, DMSO-$d_6$): δ 12,31 (s, 1H), 8,35 (m, 2H), 8,25 (d, 1H), 8,00 (m, 1H), 7,78 (d, 1H), 7,40 (d, 2H), 7,31 (d, 2H), 6,69 (m, 2H), 3,90 (m, 2H), 2,26 (s, 3H), 1,70 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 546

**Ejemplo 197**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,35 (m, 1H), 8,08 (m, 2H), 7,36 (m, 1H), 7,03 (d, 1H), 6,85 (d, 1H), 6,76 (m, 2H), 6,44 (s, 1H), 6,39 (d, 1H), 7,74 (d, 1H), 4,28 (m, 1H), 4,06 (m, 1H), 3,80 (2xs, 6H), 1,90 (m, 6H), 1,50 (m, 2H)

LCMS (APCI): m/z $[M-H]^-$ 508

**EJEMPLO 198**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,35 (d, 1H), 8,20 (d, 1H), 8,08 (d, 1H), 7,12 (d, 2H), 6,98 (m, 3H), 6,45 (s, 1H), 6,39

(d, 1H), 5,72 (d, 1H), 4,30 (m, 1H), 4,07 (m, 1H), 3,82 (2xs, 6H), 1,90 (m, 6H), 1,53 (m, 2H)

LCMS (APCI): m/z [M-H] 508

**Ejemplo 199**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,28 (s, 1H), 8,40 (d, 1H), 8,32 (d, 1H), 8,26 (s, 1H), 8,01 (m, 1H), 7,76 (d, 1H), 7,60 (m, 4H), 6,69 (m, 2H), 3,95 (m, 1H), 3,46 (m, 1H), 2,50 (s, 3H), 1,72 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 530

**Ejemplo 200**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,30 (s, 1H), 8,33 (m, 2H), 8,23 (d, 1H), 8,00 (d, 1H), 7,77 (d, 1H), 7,53 (d, 1H), 7,46 (m, 1H), 7,24 (m, 1H), 6,70 (m, 2H), 3,97 (m, 1H), 3,86 (m, 1H), 2,28 (s, 3H), 1,74 (m, 8H)

LCMS (electropulverización): m/z [M-H[ 514

**Ejemplo 201**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,30 (s, 1H), 8,37 (m, 2H), 8,24 (d, 1H), 8,00 (d, 1H), 7,78 (d, 1H), 7,45 (s, 1H), 7,38 (m, 2H), 7,20 (d, 1H), 6,70 (m, 2H), 3,91 (m, 2H), 2,26 (s, 3H), 1,70 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 542

**Ejemplo 202**

$^1$H NMR (400MHz, $CDCl_3$): δ 7,32 (m, 5H), 7,13 (d, 1H), 7,04 (d, 1H), 6,44 (s, 1H), 6,39 (d, 1H), 6,14 (m, 1H), 4,42 (m, 1H), 4,29 (m, 1H), 3,79 (s, 3H), 1,90 (m, 8H)

LCMS (APCI): m/z $[M+H]^+$ 548

**Ejemplo 203**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,38 (d, 1H), 8,10 (m, 1H), 8,00 (s, 1H), 7,02 (m, 4H), 6,79 (s, 1H), 6,62 (m, 1H), 5,92 (s, 1H), 4,26 (m, 1H), 4,08 (m, 1H), 2,38 (s, 3H), 2,20 (s, 3H), 2,02-1,80 (m, 6H), 1,59 (m, 2H).

**Ejemplo 204**

$^1$H NMR (400MHz, $CDCl_3$): δ 12,00 (s, 1H), 8,35 (m, 1H), 8,13 (d, 1H), 8,08 (d, 1H), 7,35 (m, 1H), 7,20 (d, 1H), 7,00 (d, 1H), 6,95 (m, 2H), 6,86 (m, 2H), 5,91 (d, 1H),

4,28 (m, 1H), 4,07 (m, 1H), 2,31 (s, 3H), 1,90 (m, 6H), 1,52 (m, 3H), 0,97 (m, 2H), 0,68 (m, 2H)

LCMS (electropulverización): m/z [M+Na]$^+$ 526

**Ejemplo 205**

$^1$H NMR (400MHz, $CDCl_3$): δ 12,00 (s, 1H), 8,18 (m, 1H), 8,09 (s, 1H), 7,33 (m, 1H), 7,20 (d, 1H), 6,95 (s, 1H), 6,87 (d, 1H), 6,72 (m, 2H), 6,61 (s, 1H), 5,92 (d, 1H), 4,59 (m, 1H), 4,27 (m, 1H), 4,05 (m, 1H), 2,34 (m, 6H), 1,80 (m, 11H)

LCMS (electropulverización): m/z [M+H]$^+$ 534

**Ejemplo 206**

$^1$H NMR (400MHz, $CDCl_3$): δ 12,47 (s, 1H), 8,37 (m, 1H), 8,16 (d, 1H), 8,07 (s, 1H), 7,14 (m, 1H), 7,00 (d, 1H), 6,94 (m, 2H), 6,88 (s, 1H), 6,72 (m, 1H), 5,88 (d, 1H), 4,36 (m, 1H), 4,08 (m, 1H), 2,27 (s, 3H), 1,90 (m, 7H), 1,50 (m, 2H), 0,98 (m, 2H), 0,69 (m, 2H)

LCMS (electropulverización): m/z [M+H]$^+$ 504

**Ejemplo 207**

$^1$H NMR (400MHz, $CDCl_3$): δ 12,49 (s, 1H), 8,38 (m, 1H), 8,16 (m, 2H), 7,34 (m, 1H), 6,99 (d, 1H), 6,73 (m, 3H), 6,63 (s, 1H), 5,90 (d, 1H), 4,60 (m, 1H), 4,29 (m, 1H), 4,08 (m, 1H), 2,39 (m, 2H), 2,26 (s, 3H), 2,15 (m, 2H), 1,80 (m, 11H)

LCMS (electropulverización): m/z [M+Na]$^+$ 556

**Ejemplo 208**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,11 (s, 1H), 8,06 (d, 1H), 7,49 (d, 1H), 7,30 (m, 3H), 7,05 (d, 1H), 6,75 (m, 1H), 4,16 (m, 1H), 3,99 (m, 1H), 2,20 (s, 3H), 1,86 (m, 8H)

LCMS (APCI): m/z [M-H]$^-$ 498

**Ejemplo 209**

$^1$H NMR (400MHz, $CD_3OD$): δ 8,13 (d, 1H), 8,08 (d, 1H), 7,49 (d, 1H), 7,42 (m, 1H), 7,27 (m, 3H), 6,75 (m, 1H), 4,17 (m, 1H), 3,99 (m, 1H), 2,19 (s, 3H), 1,85 (m, 8H)

LCMS (electropulverización): m/z [M+Na]$^-$ 538

**Ejemplo 210**

H NMR (400MHz, $CD_3OD$): δ 8,15 (d, 1H), 8,06 (d, 1H), 7,50 (m, 2H), 7,22 (m, 2H), 7,06 (d, 1H), 6,75 (m, 1H), 4,16 (m, 1H), 3,99 (m, 1H), 2,20 (s, 3H), 1,85 (m, 8H)

LCMS (electropulverización): m/z [M+Na]⁺ 538

**Ejemplo 211**

H NMR (400MHz, $CD_3OD$): δ 8,15 (d, 1H), 8,07 (m, 1H), 7,48 (d, 1H), 7,42 (m, 1H), 7,25 (d, 1H), 7,01 M, 3H), 6,75 (m, 1H), 4,16 (m, 1H), 3,99 (m, 1H), 2,19 (s, 3H), 1,83 (m, 8H)

LCMS (electropulverización): m/z [M+Na]⁺ 504

**Ejemplo 212**

H NMR (400MHz, $CDCl_3$): δ 12,00 (s, 1H), 8,39 (m, 1H), 8,06 (m, 2H), 7,18 (m, 4H), 6,96 (s, 1H), 6,90 (m, 1H), 5,99 (d, 1H), 4,30 (m, 1H), 4,08 (m, 1H), 2,32 (s, 3H), 1,95 (m, 6H), 1,60 (m, 2H)

LCMS (electropulverización): m/z [M+Na]⁺ 504

**Ejemplo 213**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,39 (m, 1H), 8,06 (d, 1H), 7,98 (d, 1H), 7,42 (m, 1H), 7,20 (d, 1H), 6,98 (m, 3H), 6,89 (d, 1H), 5,99 (d, 1H), 4,29 (m, 1H), 4,08 (m, 1H), 2,31 (s, 3H), 1,92 (m, 6H), 1,57 (m, 2H)

LCMS (electropulverización): m/z [M+Na]⁺ 504

**Ejemplo 214**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,38 (m, 1H), 8,06 (d, 1H), 7,88 (d, 1H), 7,22 (m, 3H), 7,10 (m, 1H), 7,00 (s, 1H), 6,89 (d, 1H), 6,07 (d, 1H), 4,24 (m, 1H), 4,09 (m, 1H), 2,29 (s, 3H), 1,90 (m, 6H), 1,62 (m, 2H)

LCMS (electropulverización): m/z [M+Na]⁺ 538

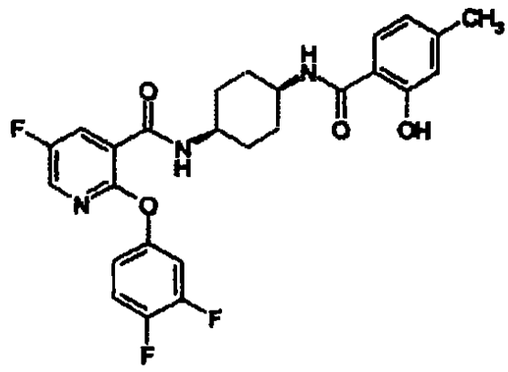
**Ejemplo 215**

$^1$H NMR (400MHz, $CDCl_3$): δ 8,38 (m, 1H), 8,06 (d, 1H), 7,80 (m, 1H), 7,49 (m, 1H), 7,21 (d, 1H), 7,00 (m, 3H), 6,05 (d, 1H), 4,23 (m, 1H), 4,06 (m, 1H), 2,32 (s, 3H), 1,90 (m, 6H), 1,56 (m, 2H)

LCMS (electropulverización): m/z [M+Na]⁺ 538

**Ejemplo 216: Sin-2-(3,4-Difluoro-fenoxi)-5-fluoro-N-[4-**

**(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-nicotinamida**



Se añadió hidrato de 1-hidroxibenzotriazol (6,06 g, 44,85 mmol) a ácido 2-(3,4-difluoro-fenoxi)-5-fluoro-nicotínico (10,5 g, 39 mmol, véase Preparación 60) en 4-metilmorfolina (100 ml). Se añadió en porciones hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (9,71 g, 50,7 mmol) y la mezcla se agitó durante 20 minutos a temperatura ambiente. Se disolvió hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-4-metil-benzamida (11,66 g, 40,9 mmol, véase Preparación 66) en 4-metilmorfolina (100 ml) y diisopropilamina (12,6 g, 97,5 mmol). La mezcla se agitó a temperatura ambiente durante 15 minutos y después se añadió a la mezcla que contenía el ácido carboxílico. La mezcla de reacción se agitó a temperatura ambiente durante 17 horas y después se repartió entre acetato de etilo (1 l) y agua (1,5 l). Las fases se separaron y la fase orgánica se lavó con disolución de ácido cítrico al 10% (300 ml, después 200 ml), hidrógeno carbonato de sodio saturado (3-veces, 500 ml) y después se diluyó con acetato de etilo (500 ml). La disolución orgánica se lavó con agua (3 veces, 500 ml), se secó sobre sulfato de magnesio y se concentró a vacío. El residuo se trituró con metanol y el producto obtenido se aisló por filtración y se lavó con metanol y éter dietílico. El

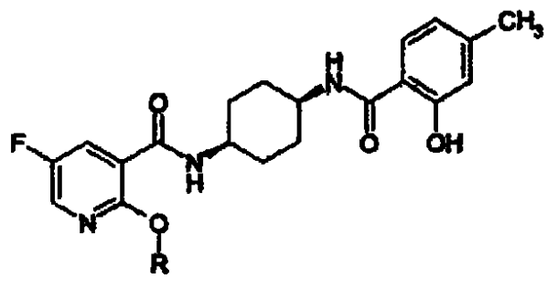
producto obtenido se secó a vacío a 50°C durante 17 horas y se recristalizó de acetato de etilo/propan-2-ol. El producto obtenido se trituró con propan-2-ol y el residuo se aisló por filtración y se lavó con propan-2-ol y éter dietílico, después se secó a vacío a 50°C durante 17 horas para dar sin-2-(3,4-difluoro-fenoxi)-5-fluoro-N-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-nicotinamida como un sólido blanco (15,3 g).

H NMR (400MHz, DMSO-$d_6$): δ 12,25 (s, 1H), 8,33 (m, 2H), 8,23 (s, 1H), 7,99 (m, 1H), 7,75 (d, 1H), 7,42 (m, 2H), 7,08 (d, 1H), 6,68 (m, 2H), 3,97 (m, 1H), 3,86 (m, 1H), 2,26 (s, 3H), 1,72 (m, 8H)

LCMS (APCI): m/z $[M-H]^-$ 498

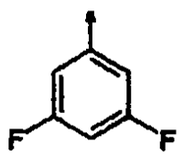
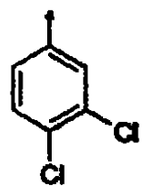
**Ejemplos 217-218**

Los compuestos de los siguientes ejemplos tabulados (Tabla 15) de la fórmula general:




se prepararon por un método similar al del ejemplo 216 utilizando hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-4-metil-benzamida (véase Preparación 66) y el ácido carboxílico apropiado.

**Tabla 15**

| Ejemplo N° | R | Ejemplo N° | R |
|---|---|---|---|
| 217 |  | 218 |  |

**Ejemplo 217**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,28 (s, 1H), 8,30 (m, 3H), 8,00 (m, 1H), 7,75 (d, 1H), 7,08 (m, 1H), 6,99 (m, 2H), 6,68 (m, 2H), 3,89 (m, 2H), 2,27 (s, 3H), 1,72 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 498

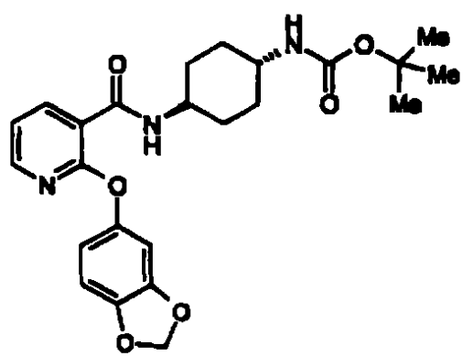
**Ejemplo 218**

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,28 (s, 1H), 8,31 (m, 2H), 8,27 (s, 1H), 8,00 (m, 1H), 7,75 (d, 1H), 7,67 (d, 1H), 7,57 (s, 1H), 7,22 (d, 1H), 6,68 (m, 2H), 3,90 (m, 2H), 2,26 (s, 3H), 1,73 (m, 8H)

LCMS (electropulverización): m/z $[M-H]^-$ 530

**PREPARACIONES**

**Preparación 1 : Éster terc-butílico del ácido anti-(4-{[2-(Benzo[1,3]dioxol-5-iloxi)-piridin-3-carbonil]-amino}-ciclohexil)-carbámico**

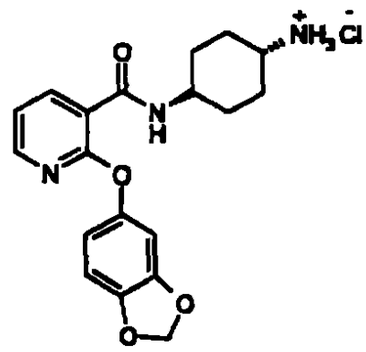


Se agitaron ácido 2-(4-benzo[1,3]dioxol-5-iloxi)-nicotínico (5,0 g, 19,3 mmol) (véase referencia WO 98/45268), éster terc-butílico del ácido anti-(4-amino-ciclohexil)-carbámico (4,13 g, 19,3 mmol) (véase Preparación 40), 1-hidroxibenzotriazol (3,91 g, 29 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (4,81 g, 25,1 mmol) y N-metil morfolina (3,18 ml, 29 mmol) en N,N-dimetilformamida (50 ml) a temperatura ambiente en atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre diclorometano (200 ml) y una disolución acuosa 2 N de carbonato de sodio (150 ml), y se separó la capa orgánica. La fase acuosa se extrajo con diclorometano (2 veces 200 ml) y los extractos orgánicos combinados se lavaron con una disolución acuosa saturada de cloruro de sodio (200 ml). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio anhidro y el disolvente se retiró a vacío. Se trituró el residuo con éter dietílico (50 ml) dando éster terc-butílico ácido anti-(4-{[2-(benzo[1,3]dioxol-5-iloxi)piridin-3-carbonil]amino}ciclohexil)carbámico (6,5 g) como un sólido blanco.

$^1$H NMR (400MHz, DMSO-$d^6$): $\delta$ = 8,06-8,12 (1H, m), 8,02-8,05 (1H, d), 7,94-7,98 (1H, d), 7,10-7,15 (1H, m), 6,82-6,87 (1H, d), 6,76-6,80 (1H, d), 6,50-6,70 (2H, m), 6,00 (2H, s), 3,50-370 (1H, m), 3,05-3,20 (1H, m), 1,70-1,90 (4H, m), 1,32 (9H, s), 1,10-1,30 (4H, m) ppm.

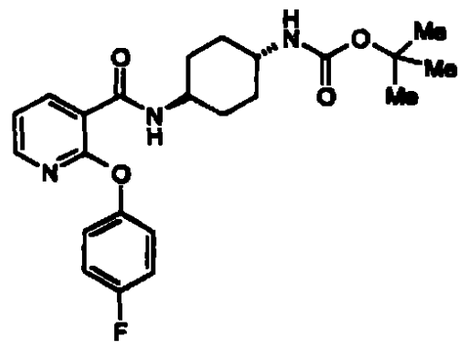
LRMS (electropulverización): m/z $[M-H]^+$ 454

**Preparación 2 : Hidrocloruro de anti-N-(4-amino-ciclohexil)-2-(benzo[1,3]dioxol-5-iloxi)-nicotinamida**



Se disolvió éster terc-butílico del ácido anti-(4-{[2-{benzo[1,3]dioxol-5-iloxi)piridin-3-carbonil]amino}-ciclohexil)-carbámico (5,2 g, 11,4 mmol) (véase Preparación 1) en diclorometano (20 ml) y se adicionó HCl 4M en dioxano (20 ml). Se agitó la mezcla de reacción durante 2 horas. Se retiró el disolvente a vacío y el residuo se destiló azeotrópicamente con tolueno para dar hidrocloruro de anti-N-(4-aminociclohexil)-2-(benzo[1,3]dioxol-5-iloxi)-nicotinamida (5,02 g) como un aceite incoloro.

**Preparación 3 : Éster terc-butílico del ácido anti-(4-{[2-(4-fluorofenoxi)piridin-3-carbonil]amino}-ciclohexil]carbámico**



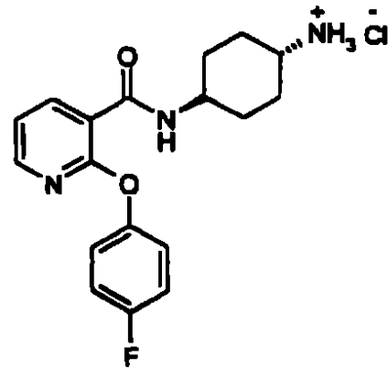
Se agitaron ácido 2-(4-fluoro-fenoxi)-nicotínico (10,88 g, 0,046 moles) (véase solicitud de patente de referencia WO 98/45268), 1-hidroxibenzotriazol (9,32 g, 0,069 moles) e hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (11,46 g, 0,06 moles) en N,N-dimetil-

formamida (150ml) a temperatura ambiente y se adicionó éster terc-butílico del ácido anti-(4-amino-ciclohexil)-carbámico (10 g, 0,046 moles) (véase Preparación 40) seguido por adición de N-metil morfolina (7,59 ml, 0,069 moles). La mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 18 horas. La mezcla de reacción se repartió entre acetato de etilo (400 ml) y agua (400 ml), y se separó la capa orgánica, se lavó con una disolución acuosa saturada de cloruro de sodio (300 ml), se secó sobre sulfato de sodio anhidro y se retiró el disolvente a vacío. Se trituró el residuo con éter dietílico (50 ml) dando el éster terc-butílico del ácido anti-(4-{[2-(4-fluorofenoxi)piridin-3-carbonil]amino}ciclohexil)carbámico (14,52 g) como un sólido blanco.

H NMR (400MHz, DMSO-$d^6$/$D_2O$): $\delta$ = 8,08-8,12 (1H, d), 7,94-7,98 (1H, d), 7,09-7,20 (5H, m), 3,58-3,63 (1H, m), 3,13-3,20 (1H, m), 1,79-1,83 (2H, m), 1,69-1,78 (2H, m), 1,30 (9H, s), 1,18-1,30 (4H, m) ppm.

LRMS (electropulverización): m/z $[M-H]^+$ 428

**Preparación 4 : Hidrocloruro de anti-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)-nicotinamida**




Se disolvió éster terc-butílico del ácido anti-(4-{[2-(4-fluorofenoxi)-piridin-3-carbonil]amino}ciclohexil)carbámico (14,81 g, 0,039 moles) (véase Preparación

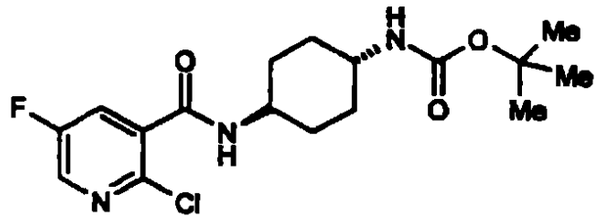
3) en metanol 10 ml) y se adicionó HCl 4M en dioxano (200 ml). Se agitó la mezcla de reacción en atmósfera de nitrógeno a temperatura ambiente durante 4 horas.

Se retiró el disolvente a vacío y el precipitado blanco resultante se trituró con éter (50 ml) dando hidrocloruro de anti-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)nicotinamida (14,00 g) como un sólido blanco.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8,20-8,26 (1H, d), 8,16-8,18 (1H, s), 8,04-8,15 (3H, s ancho), 7,98-8,02 (1H, d), 7,17-7,26 (4H, m), 3,42-3,57 (1H, m), 2,88-3,01 (1H, m), 1,88-2,03 (4H, m), 1,23-1,50 (4H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 330

**Preparación 5 : Éster terc-butílico del ácido anti-{4-[(2-cloro-5-fluoropiridin-3-carbonil)amino]-ciclohexil}-carbámico**



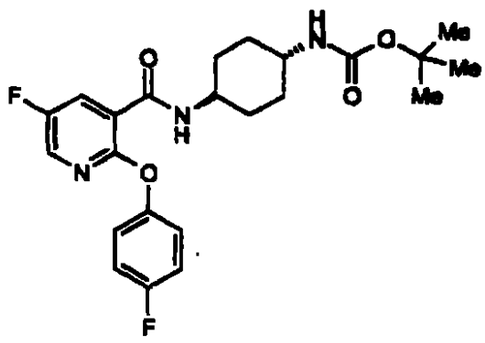

Se agitaron ácido 2-cloro-5-fluoro nicotínico (3,95 g, 0,022 moles) (véase Preparación 41), 1-hidroxibenzotriazol (4,56 g, 0,034 moles) y hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (5,61 g, 0,029 moles) en N,N-dimetilformamida (50 ml) a temperatura ambiente durante 30 minutos. Se adicionó n-metil morfolina (4,95 ml, 0,045 moles) seguido por el éster terc-butílico del ácido anti-(4-amino-ciclohexil)-carbámico (4,82 g, 0,022 moles) (véase Preparación 43) y la mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 18 horas. Se repartió la mezcla entre acetato de etilo (100 ml) y agua (100 ml), se separó la fase orgánica, se lavó con una disolución acuosa saturada de

cloruro de sodio (100 ml), se secó sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío. El residuo se trituró con éter dietílico (3 veces 10 ml) dando éster terc-butílico del ácido anti-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]ciclohexil}carbámico (7,56 g) como un sólido blanco.

H NMR (300MHz, $CDCl_3$): δ = 8,32-8,35 (1H, d), 7,82-7,88 (1H, m), 6,32-6,41 (1H, d), 4,38-4,51 (1H, m), 3,87-4,02 (1H, m), 2,03-2,21 (4H, m), 1,45 (9H, 5), 1,26-1,41 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 389.

**Preparación 6: Éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}ciclohexil]carbámico**



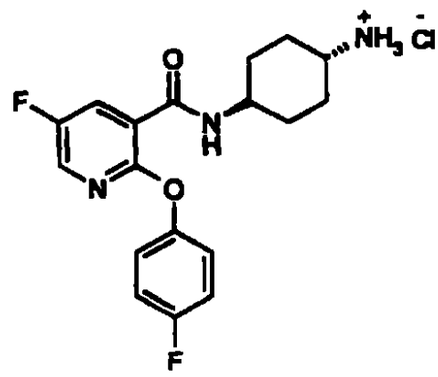

Se agitaron éster terc-butílico del ácido anti-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]-ciclohexil)-carbámico (7,64 g, 0,02 moles) (véase Preparación 5), 4-fluorofenol (2,30 g, 0,02 moles) y carbonato de cesio (13,35 g, 0,04 moles) en N,N-dimetilformamida (50 ml) a 60°C en atmósfera de nitrógeno durante 18 horas. La mezcla se repartió entre acetato de etilo (100 ml) y agua (100 ml), se separó la capa orgánica, se lavó con una disolución acuosa saturada de cloruro de sodio (100 ml), se secó sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. Se purificó el disolvente por cromatografía instantánea en columna de gel de sílice eluyendo

con un gradiente de disolventes de diclorometano al 100 % cambiando a diclorometano : metanol 98:2, en volumen, dando el éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}-ciclohexil)carbámico (4,93 g) como un sólido blanco.

H NMR (300MHz, $CDCl_3$): δ = 8,31-8,37 (1H, m), 8,02-8,05 (1H, d), 7,65-7,72 (1H, d), 7,10-7,20 (4H, m), 4,38-4,48 (1H, m), 3,88-4,02 (1H, m), 2,01-2,20 (4H, m), 1,43 (9H, s), 1,23-1,40 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+NH_4]^+$ 465

**Preparación 7 : Hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluorofenoxi)-nicotinamida**



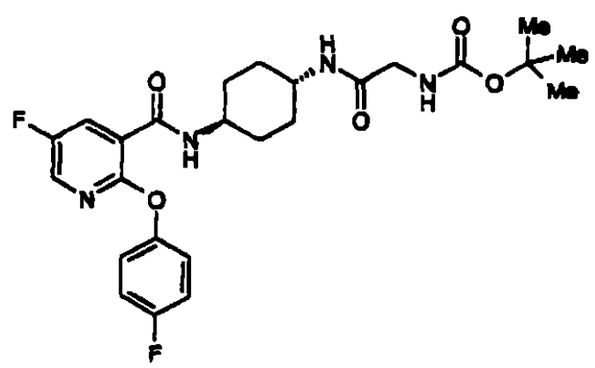

Se disolvió éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}-ciclohexil)-carbámico (4,93 g, 0,011 moles) (véase Preparación 6) en diclorometano (50 ml) y se burbujeó gas cloruro de hidrógeno a la solución a 0°C hasta que se saturó la solución (30 minutos). La mezcla de reacción se agitó en una atmósfera de nitrógeno a temperatura ambiente durante otras 2 horas y se retiró el disolvente a vacío. Se trituró el precipitado blanco resultante con éter (3 veces 10 ml) dando hidrocloruro de anti-N(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (3,64 g) como un sólido blanco.

H NMR (300MHz, DMSO-$d^6$): δ = 8,32-8,38 (1H, d), 8,18-8,22

(1H, m), 7,92-8,08 (4H, m), 7,16-7,28 (4H, m), 3,60-3,77 (1H, m), 2,95-3,07 (1H, m), 1,83-2,03 (4H, m), 1,23-1,52 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 348

**Preparación 8 : Éster terc-butílico del ácido anti-[(4-{[5-fluoro-2-(4-fluorofenoxi)piridin-3-carbonil]amino}-ciclohexilcarbamoil)metil]carbámico**



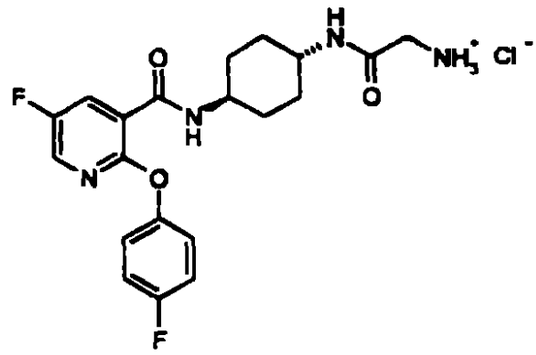
Se agitaron hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (1,13 g, 2,94 mmol) (véase Preparación 7), 1-hidroxibenzotriazol (597 mg, 4,42 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (734 mg, 3,83 mmol), N-metil morfolina (0,65 ml, 5,89 moles) y ácido terc-butoxicarbonilamino-acético (516 mg, 2,94 mmol) en N,N-dimetilformamida (10 ml) a temperatura ambiente durante 18 horas. La mezcla de reacción se repartió entre acetato de etilo (50 ml) y agua (50 ml), se separó la capa orgánica, se lavó con una disolución acuosa de cloruro de sodio (50 ml), se secó sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío dando el éster terc-butílico del ácido anti-[(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-ciclohexilcarbamoil)metil]carbámico (1,48 g) como un sólido blanco.

$^1H$ NMR (300MHz, $CDCl_3$): $\delta$ = 8,30-8,40 (1H, m), 8,00-8,04 (1H, d), 7,67-7,77 (1H, d), 7,08-7,21 (4H, m), 6,00-6,11

(1H, m), 5,09-5,21 (1H, s ancho), 3,92-4,06 (1H, m), 3,75-3,84 (3H, m), 2,00-2,25 (4H, m), 1,28-1,60 (13H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 505, $[M+H-Boc]^+$ 405.

**Preparación 9 : Hidrocloruro de anti-N[4-(2-amino-acetil-amino)ciclohexil]-5-fluoro-2-(4-fluorofenoxi)nicotinamida**



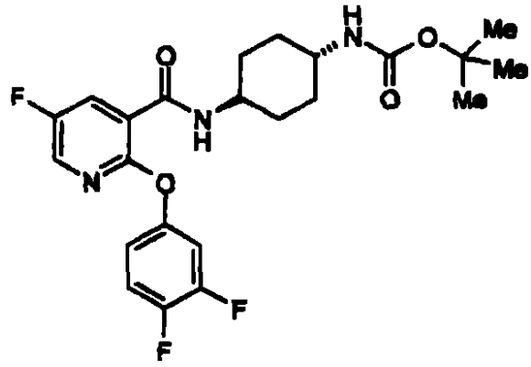
éster terc-butílico del ácido anti-[(4-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]amino}ciclohexil-carbamoil)-metil]-carbámico (1,47 g, 2,91 mmol) (véase Preparación 8) se disolvió en diclorometano (20 ml) y se borboteó en la solución cloruro de hidrógeno gas a 0°C hasta que se saturó la solución (30 minutos). Se agitó la reacción en atmósfera de nitrógeno a temperatura ambiente durante otras 18 horas, y se separó el disolvente a vacío. Se trituró el precipitado blanco resultante con éter (3 veces 10 ml) dando hidrocloruro de anti-N-[4-(2-amino-acetilamino)ciclohexil]-5-fluoro-2-(4-fluorofenoxi)-nicotinamida (1,24 g) como un sólido blanco.

$^1H$ NMR (300MHz, DMSO-$d^6$): $\delta$ = 8,34-8,43 (2H, m), 8,19-8,21 (1H, d), 8,10-8,18 (3H, s ancho), 7,92-7,99 (1H, dd), 7,18-7,32 (4H, m), 3,66-3,82 (1H, m), 3,42-3,60 (3H, m, parcialmente enmascarada por el disolvente), 1,78-1,99 (4H, m), 1,22-1,50 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 405.

**Preparación 10 : Éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(3,4-difluorofenoxi)-piridina-3-carbonil]-**

**amino}-ciclohexil]-carbámico**

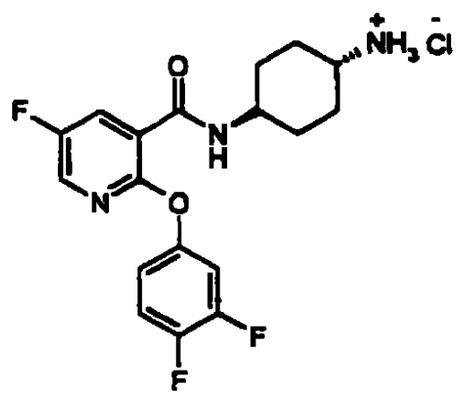


Se agitaron éster terc-butílico del ácido anti-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]ciclohexil}-carbámico (675 mg, 1,81 mmol) (véase Preparación 5), 3,4-difluorofenol (236 mg, 1,81 mmol) y carbonato de cesio (1,18 g, 3,63 mmol) en N,N-dimetilformamida (10 ml) a 60°C en atmósfera de nitrógeno durante 18 horas. La mezcla se repartió entre acetato de etilo (20 ml) y agua (20 ml), se separó la capa orgánica, se lavó con una disolución acuosa saturada de cloruro de sodio (20 ml), se secó sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío. El residuo se trituró con éter dietílico (3 veces 5 ml) dando éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(3,4-difluorofenoxi)-piridin-3-carbonil]-amino}ciclohexil)-carbámico (490 mg) como un sólido blanco.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8,31-8,38 (1H, m), 8,03-8,06 (1H, d), 7,68-7,77 (1H, d), 7,17-7,28 (1H, m, parcialmente enmascarada por el disolvente), 7,00-7,08 (1H, m), 6,86-6,93 (1H, m), 4,34-4,45 (1H, m), 3,86-4,04 (1H, m), 2,01-2,20 (4H, m), 1,45 (9H, s), 1,24-1,40 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+NH_4]^+$ 483

**Preparación 11 : Hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(3,4-difluoro-fenoxi)-nicotinamida**

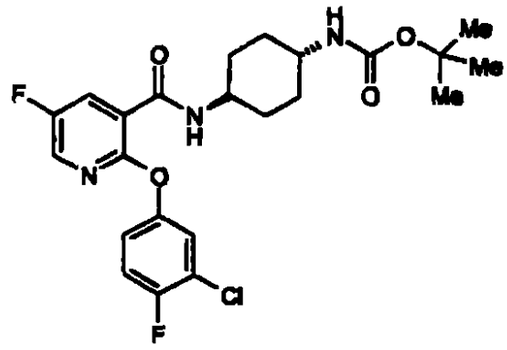


Se disolvió éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(3,4-difluorofenoxi)piridin-3-carbonil]amino}ciclohexil)carbámico (480 mg, 1,03 mmol) (véase Preparación 10) en diclorometano (10 ml) y se burbujeó gas cloruro de hidrógeno en la solución a 0°C hasta saturación de la solución (30 minutos). La mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 18 horas y a continuación se retiró el disolvente a vacío. Se trituró el precipitado blanco resultante con éter (3 veces 5 ml) dando el hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(3,4-difluoro-fenoxi)-nicotinamida (360 g) como un sólido blanco.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8,36-8,41 (1H, d), 8,21-8,26 (1H, d), 7,93-8,11 (4H, m), 7,35-7,60 (2H, m), 7,01-7,13 (1H, m), 3,60-3,83 (1H, m), 2,88-3,12 (1H, m), 1,85-2,10 (4H, m), 1,25-1,58 (4H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 366

**Preparación 12 : Éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(3-cloro-4-fluorofenoxi)piridin-3-carbonil]-amino}ciclohexil)carbámico**

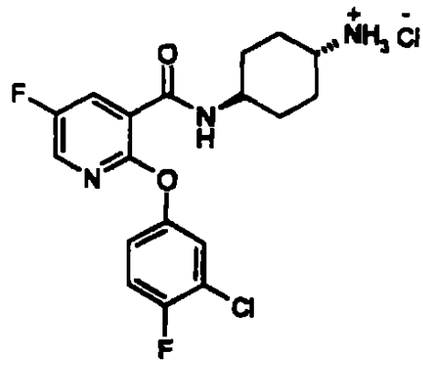


Se agitaron éster terc-butílico del ácido anti-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]-ciclohexil}-carbámico (675 mg, 1,81 mmol) (véase Preparación 5), 3-cloro-4-fluorofenol (266 mg, 1,81 mmol) y carbonato de cesio (1,18 g, 3,63 mmol) en N,N-dimetilformamida (10 ml) a 60°C en una atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre acetato de etilo (20 ml) y agua (20 ml), y se separó la capa orgánica, se lavó con una disolución acuosa saturada de cloruro de sodio (20 ml), se secó sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. Se trituró el residuo con éter dietílico (3 veces 5 ml) dando el éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(3-cloro-4-fluorofenoxi)-piridin-3-carbonil]amino}ciclohexil)-carbámico (540 mg) como un sólido blanco.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8,31-8,38 (1H, m), 8,03-8,06 (1H, d), 7,50-7,58 (1H, d), 7,18-7,30 (1H, m, parcialmente enmascarada por el disolvente), 7,02-7,10 (1H, m), 4,36-4,45 (1H, m), 3,80-4,05 (1H, m), 2,01-2,20 (4H, m), 1,44 (9H, s), 1,28-1,41 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+NH_4]^+$ 499, 501.

**Preparación 13 : Hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(3-cloro-4-fluoro-fenoxi)nicotinamida**

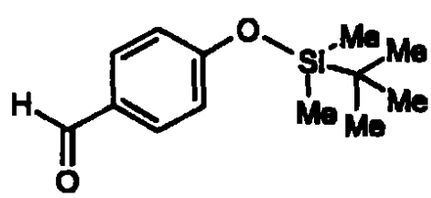


Se disolvió el éster terc-butílico del ácido anti-(4-{[5-fluoro-2-(3-cloro-4-fluorofenoxi)piridin-3-carbonil]amino}ciclohexil)carbámico (530 mg, 1,10 mmol) (véase Preparación 12) en diclorometano (10 ml) y se burbujeó gas cloruro de hidrógeno en la solución a 0°C hasta que se saturó la solución (30 minutos). Se agitó la mezcla de reacción en atmósfera de nitrógeno a temperatura ambiente durante 18 horas, y se retiró el disolvente a vacío. El precipitado blanco resultante se trituró con éter (3 veces 5 ml) dando el hidrocloruro de anti-N-(4-aminociclohexil)-5-fluoro-2-(3-cloro-4-fluorofenoxi)-nicotinamida (390 g) como un sólido blanco.

$^1$H NMR (300MHz, DMSO-d$^6$): δ = 8,32-8,40 (1H, d), 8,22-8,26 (1H, d), 7,93-8,11 (3H, s ancho), 7,90-8,02 (1H, m), 7,40-7,52 (2H, m), 7,16-7,24 (1H, m), 3,60-3,81 (1H, m), 2,90-3,08 (1H, m), 1,85-2,00 (4H, m), 1,23-1,60 (4H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 382.

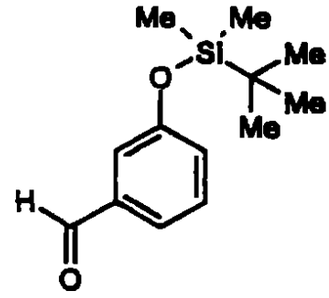
**Preparación 14 : 4-(terc-Butil-dimetil-silaniloxi)-benzaldehído**



Se adicionó 4-hidroxibenzaldehído (5,14 g, 42,1 mmol) a una suspensión de cloruro de terc-butil-dimetil-sililo (6,7 g, 44,4 mmol) e imidazol (3,03 g, 44,5 mmol) en diclorometano (100 ml) en atmósfera de nitrógeno a temperatura ambiente. Se agitó la mezcla de reacción a temperatura ambiente durante 18 horas, y se lavó secuencialmente con ácido clorhídrico 1 M (2 veces 50 ml) seguido por una disolución acuosa saturada de hidrógeno carbonato de sodio (50 ml). La fase orgánica se separó, se secó sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío. El aceite amarillo residual se pasó a través de un lecho de gel de sílice eluyendo con diclorometano : pentano 1:1, en volumen, dando 4-(terc-butil-dimetil-silaniloxi)-benzaldehído (7,5 g) como un aceite amarillo dorado.

H NMR (400MHz, $CDCl_3$): δ= 9,88 (1H, s), 7,74-7,81 (2H, d), 6,87-6,95 (2H, d), 1,00 (9H, s), 0,25 (6H, s) ppm.

**Preparación 15: 3-(terc-Butil-dimetil-silaniloxi)-benzaldehído**

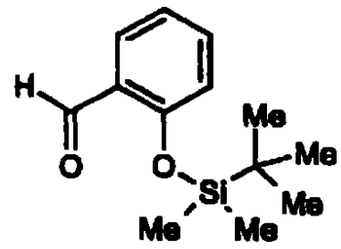



Se adicionó 3-hidroxibenzaldehído (5,14 g, 42,1 mmol) a una suspensión de cloruro de terc-butil-dimetil-sililo (6,7 g, 44,4 mmol) e imidazol (3,03 g, 44,5 mmol) en diclorometano (100 ml) en atmósfera de nitrógeno a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 18 horas, y se lavó la mezcla secuencialmente con ácido clorhídrico 1 M (2 veces 50

ml) seguido por una disolución acuosa saturada de hidrógeno carbonato de sodio (50 ml). Se separó la fase orgánica, se secó sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío. El aceite amarillo residual se pasó a través de un lecho de gel de sílice eluyendo con diclorometano : pentano 1:1, en volumen, dando 3-(terc-butil-dimetil-silaniloxi)-benzaldehído (9,2 g) como un aceite amarillo dorado.

$^1$H NMR (400MHz, $CDCl_3$): δ = 9,98 (1H, s), 7,42-7,46 (1H, m), 7,35-7,41 (1H, t), 7,28-7,34 (1H, m), 7,05-7,11 (1H, m), 0,98 (9H, s), 0,22 (6H, s) ppm.

**Preparación 16: 2-(terc-Butil-dimetil-silaniloxi)-benzaldehído**

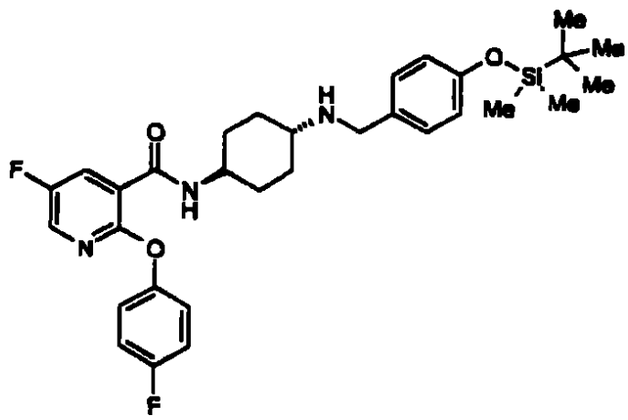



Se adicionó 2-hidroxibenzaldehído (5,14 g, 42,1 mmol) a una suspensión de cloruro de terc-butil-dimetil-sililo (6,7 g, 44,4 mmol) e imidazol (3,03 g, 44,5 mmol) en diclorometano (100 ml) en atmósfera de nitrógeno a temperatura ambiente. Se agitó la mezcla de reacción a temperatura ambiente durante 18 horas, y se lavó secuencialmente con ácido clorhídrico 1 M (2 veces 50 ml) seguido por una disolución acuosa saturada de hidrógeno carbonato de sodio (50 ml). Se separó la fase orgánica, se secó sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío. El aceite amarillo residual se pasó a través de un lecho de gel de sílice eluyendo con diclorometano : pentano 1:1, en volumen, 2-(terc-butil-dimetil-silaniloxi)benzaldehído (8,6 g) como un aceite amarillo

dorado.

H NMR (400MHz, CDCl$_3$): $\delta$ = 10,48 (1H, s), 7,78-7,83 (1H, d), 7,42-7,47 (1H, t), 6,96-7,04 (1H, t), 6,86-6,91 (1H, d), 1,01 (9H, s), 0,29 (6H, s) ppm.

**Preparación 17 : anti-N-{4-[4-(terc-Butil-dimetil-silaniloxi)bencilamino]ciclohexil}-5-fluoro-2-(4-fluorofenoxi)-nicotinamida**



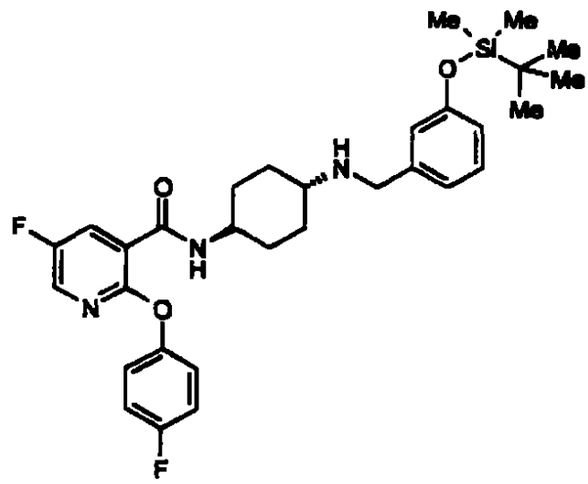
Se disolvió hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (500 mg, 2,15 mmol) (véase preparación 7) en triclorometano (15 ml) y se adicionó diisopropiletilamina (0,44 ml, 2,54 mmol). La mezcla de reacción se agitó durante 1 hora y entonces se adicionó secuencialmente 4-(terc-butil-dimetil-silaniloxi)-benzaldehído (750 mg, 3,173 mmol) (véase Preparación 14), triacetoxiborohidruro de sodio (673 mg, 3,173 mmol) y ácido acético (0,3 ml, 5,08 mmol). La mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 18 horas. La mezcla de reacción se lavó con una disolución acuosa saturada de hidrógeno carbonato de sodio(15 ml) y la fase orgánica se secó sobre sulfato de magnesio anhidro. El disolvente se retiró a vacío y el residuo se purificó por cromatografía instantánea en columna sobre gel de sílice, eluyendo con un gradiente de disolventes de diclorometano : metanol

100:2, cambiando a 100:4, en volumen, dando anti-N{4-[4-(terc-butil-dimetil-silaniloxi)-bencilamino]-ciclohexil}-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (270 mg) como un sólido blanquecino.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,28-8,34 (1H, m), 7,97-7,99 (1H, d), 7,61-7,65 (1H, d), 7,16-7,19 (2H, d), 7,03-7,15 (4H, m), 6,72-6,78 (2H, d), 3,90-4,03 (1H, m), 3,71 (2H, s), 2,46-2,57 (1H, m), 2,07-2,18 (2H, d), 1,97-2,06 (2H, d), 1,17-1,29 (4H, m), 0,95 (9H, s), 0,17 (6H, s) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 568.

**Preparación 18 : anti-N-{4-[3-(terc-Butil-dimetil-silaniloxi)-bencilamino]-ciclohexil}-5-fluoro-2-(4-fluorofenoxi)nicotinamida**



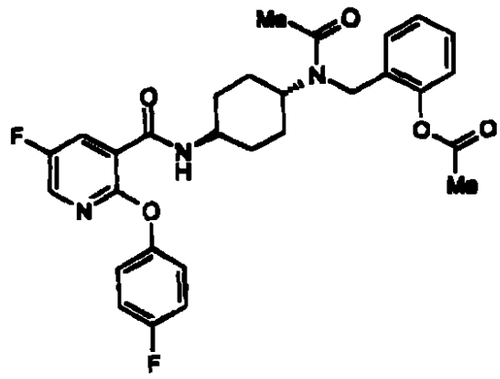

Se disolvió hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (500 mg, 2,14 mmol) (véase Preparación 7) en diclorometano (10 ml) y se adicionó diisopropil etilamina (0,56 ml, 3,21 mmol). Se agitó la mezcla de reacción a temperatura ambiente durante 1 hora y se adicionó secuencialmente 3-(terc-butil-dimetil-silaniloxi)benzaldehído (766 mg, 3,21 mmol) (véase Preparación 15), triacetoxiborohidruro de sodio (681 mg, 3,21 mmol) y ácido acético (0,19 ml, 3,21

mmol). Se agitó la mezcla de reacción en atmósfera de nitrógeno a temperatura ambiente durante 18 horas adicionales. Se lavó la mezcla de reacción con una disolución acuosa saturada de hidrógeno carbonato de sodio (15 ml), se separó la fase orgánica y se secó sobre sulfato de magnesio anhidro. Se retiró el disolvente a vacío y el residuo se purificó por cromatografía instantánea en columna de gel de sílice, eluyendo con diclorometano : metanol 100:2, en volumen, dando anti-N-{4-[3-(terc-butildimetil-silaniloxi)bencilamino]-ciclohexil}-5-fluoro-2-(4-fluorofenoxi)nicotinamida (937 mg) como un sólido blanquecino.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,32-8,36 (1H, m), 8,00-8,03 (1H, d), 7,65-7,70 (1H, d), 7,10-7,20 (5H, m), 6,86-6,94 (1H, d), 6,81 (1H, s), 6,68-6,74 (1H, d), 3,94-4,02 (1H, m), 3,78 (2H, s), 2,47-2,55 (1H, m), 2,07-2,15 (2H, m), 1,96-2,05 (2H, m), 1,20-1,42 (4H, m), 0,98 (9H, s), 0,19 (6H, s) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 568.

**Preparación 19 : Éster anti-2-{[acetil-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}ciclohexil)-amino]metil}fenílico del ácido acético**




Se disolvieron anti-5-fluoro-2-(4-fluoro-fenoxi)-N-[4-(2-hidroxi-bencilamino)ciclohexil]nicotinamida (350 mg, 0,772 mmol) (véase preparación 26) y diisopropil eti-

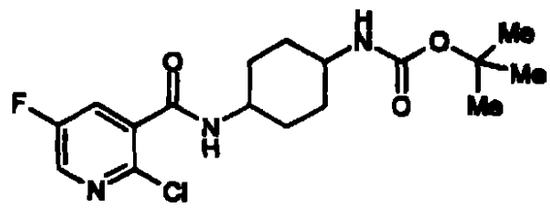
lamina (0,38 ml, 2,16 mmol) en diclorometano (10 ml) y se adicionó cloruro de acetilo (0,14 ml, 1,85 mmol). La mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 18 horas. La mezcla de reacción se lavó secuencialmente con una disolución acuosa saturada de hidrógeno carbonato de sodio (10 ml), una disolución acuosa al 10% de ácido cítrico (10 ml) y agua (10 ml) antes de secar la fase orgánica sobre sulfato de magnesio anhidro proporcionando éster anti-2-{[acetil-(4-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-ciclohexil)amino]metil}fenílico del ácido acético (277 mg) como una espuma crema.

$^1$H NMR (400MHz $CDCl_3$): δ = 8,27-8,42 (1H, m), 7,99-8,14 (1H, m), 7,58-7,75 (1H, m), 7,00-742 (7H, m), 4,43-4,67 (1H, m), 4,37 (2H, s), 3,81-3,98 (1H, m), 2,00-2,50 (10H, m), 1,74-1,86 (2H, m), 1,24-1,60 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 538, $[M+Na]^+$ 560

LRMS (electropulverización) $[M-H-OAc]^+$ 568.

**Preparación 20 : Éster terc-butílico del ácido {4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]ciclohexil}carbámico**

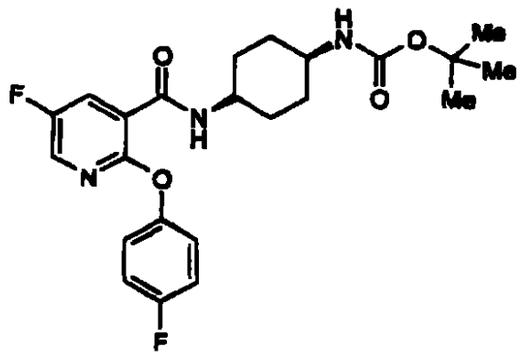



Se disolvió ácido 2-cloro-5-fluoronicotínico (3,00 g, 0,017 moles) (véase Preparación 41), en diclorometano (100 ml) y se adicionó N,N-dimetilformamida (1 gota), seguido por cloruro de oxalilo (3,0 ml, 0,034 moles). La mezcla de reacción se mantuvo a temperatura ambiente durante 4 horas, después de dicho tiempo se retiró el disolvente a vacío. Se suspendió el residuo en diclorometa-

no (100 ml) y se adicionó trietilamina (5 ml) seguido por adición de éster terc-butílico del ácido (4-amino-ciclohexil)carbámico (5,40 g, 0,026 moles) (Preparación 42). La mezcla de reacción se mantuvo en atmósfera de nitrógeno a temperatura ambiente durante 18 horas adicionales. La mezcla de reacción se lavó con agua (100 ml) y la fase orgánica se secó sobre sulfato de magnesio anhidro. Se retiró el disolvente a vacío, y se trituró el residuo con acetato de etilo/pentano (1:1, en volumen, 10 ml) dando éster terc-butílico del ácido {4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]-ciclohexil}carbámico (2,5 g, 80:20 sin:anti) como un sólido blanco.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8,32-8,38 (1H, d), 7,95-8,00 (0,8H, m), 7,81-7,88 (0,2H, d), 6,58-6,75 (0,8H, m), 6,29-6,37 (0,2H, m), 4,38-4,62 (1H, m), 4,12-4,25 (0,8H, m), 3,95-4,03 (0,2H, m), 3,58-3,73 (C,8H, m), 3,38-3,56 (0,2H, m), 2,03-2,2 (0,8H, m), 1,66-1,95 (6,4H, m), 3,87-4,02 (1H, m), 1,58 (9H, s), 1,23-1,44 (0,8H, m, parcialmente enmascarada por el disolvente) ppm.

**Preparación 21 : Éster terc-butílico del ácido sin-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}-ciclohexil)carbámico**



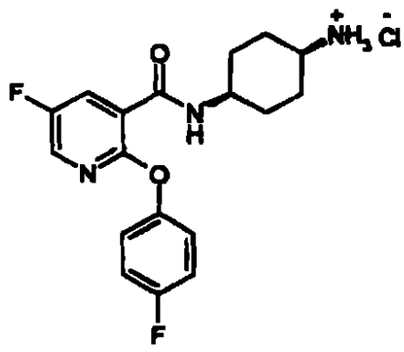

Se agitaron éster terc-butílico del ácido {4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]ciclohexil}carbámico (2,4 g, 6,46 mmol) (mezcla sin/anti 80:20) (véase

Preparación 20), 4-fluorofenol (800 mg, 7,11 mmol) y carbonato de cesio (4,2 g, 12,02 mmol) en N,N-dimetilformamida (40 ml) a 50°C en atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre acetato de etilo (100 ml) y agua (100 ml), y se separó la capa orgánica, se lavó con una disolución acuosa saturada de cloruro de sodio (100 ml), se secó sobre sulfato de magnesio anhidro y se eliminó el disolvente a vacío. El residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de diclorometano al 100 % cambiando a diclorometano : metanol 98:2, en volumen, proporcionando el éster terc-butílico del ácido sin-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}ciclohexil)carbámico (2,4 g) como un sólido blanco.

$^1$H NMR (300MHz, $CDCl_3$): δ = 8,32-8,39 (1H, m), 8,01-8,04 (1H, d), 7,90-7,99 (1H, d), 7,10-7,22 (4H, m), 4,25-4,47 (1H, m), 4,15-4,23 (1H, m), 3,56-3,68 (1H, m), 1,63-1,91 (6H, m), 1,38-1,60 (11H, m, parcialmente enmascarada por el disolvente) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 448

**Preparación 22 : Hidrocloruro de sin-N-[4-aminociclohexil)-5-fluoro-2-(4-fluorofenoxi)-nicotinamida**



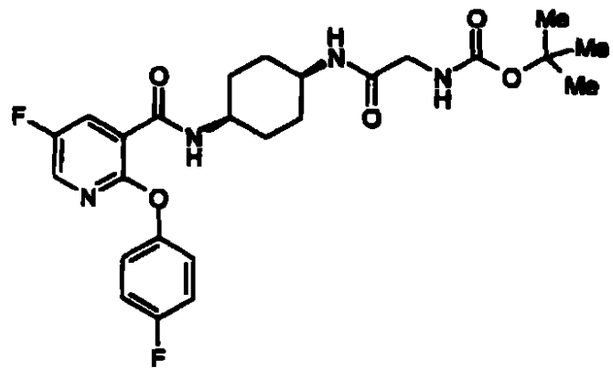
éster terc-butílico del ácido sin-(4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]amino}ciclohexil)-

carbámico(2,4 g, 5,4 mmol) (véase Preparación 21) se disolvió en HCl 4 M en dioxano (100 ml) y se agitó en atmósfera de nitrógeno a temperatura ambiente durante 4 horas. Se retiró el disolvente a vacío y el precipitado blanco resultante se trituró con diclorometano (20 ml), acetato de etilo (20 ml) y éter dietílico (20 ml) dando hidrocloruro de sin-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (1,7 g) como un sólido blanco.

H NMR (400MHz, CD$_3$OD): δ = 8,01-8,10 (2H, m), 7,08-7,23 (4H, m), 4,10-4,18 (1H, m), 3,18-3,33 (1H, m, parcialmente enmascarada por el disolvente), 1,78-2,00 (6H, m), 1,61-1,77 (2H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 348.

**Preparación 23 : Éster terc-butílico del ácido sin-[(4-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]amino}-ciclohexilcarbamoil)metil]carbámico**



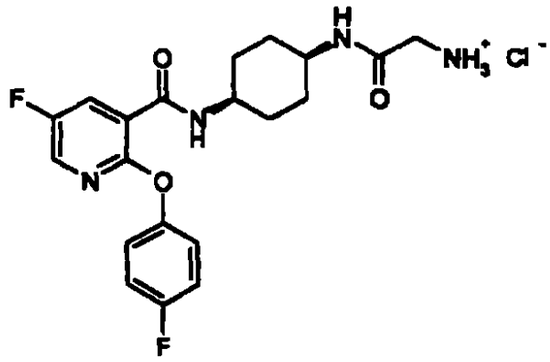

Se agitaron hidrocloruro de sin-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (200 mg, 0,521 mmol) (véase Preparación 22), 1-hidroxibenzotriazol (106 mg, 0,782 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (130 mg, 0,677 mmol), N-metil morfolina (0,12 ml, 1,04 mmol) y ácido terc-butoxicarbonilamino-acético (100 mg, 0,573 mmol) en N,N-dimetilformamida (5 ml) a temperatura ambiente durante 18 horas. La mezcla de reacción se repartió entre ace-

tato de etilo (10 ml) y agua (10 ml) y se separó la capa orgánica, se lavó con una disolución acuosa saturada de cloruro de sodio (10 ml), se secó sobre sulfato de magnesio anhidro y se separó el disolvente a vacío. El residuo se trituró con éter dietílico (5 ml) proporcionando el éster terc-butílico del ácido sin-[(4-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]amino}ciclohexilcarbamoil)metil]carbámico (182 mg) como un sólido blanco.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,32-8,38 (1H, dd), 8,02-8,04 (1H, d), 7,89-7,97 (1H, d), 7,10-7,19 (4H, m), 6,08-6,23 (1H, s ancho), 5,03-5,17 (1H, s ancho), 4,13-4,21 (1H, m), 3,89-3,98 (1H, m), 3,64-3,71 (2H, d), 1,74-1,91 (4H, m), 1,62-1,73 (2H, m), 1,47-1,60 (2H, m), 1,36 (9H, s) ppm.

LRMS (electropulverización): m/z $[M+Na]^+$ 527.

**Preparación 24: Hidrocloruro de sin-N-[4-(2-amino-acetil-amino)-ciclohexil]-5-fluoro-2-(4-fluoro-fenoxi)nicotin-amida**

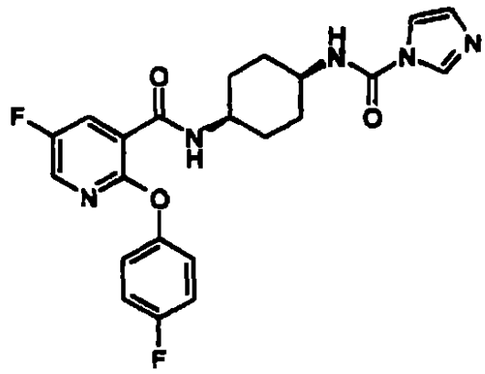


Se disolvió éster terc-butílico del ácido sin-[(4-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]amino)-ciclohexil]carbamoil)metil]carbámico (1,47 g, 2,91 mmol) (véase Preparación 23) en diclorometano (20 ml) y se borboteó gas cloruro de hidrógeno en la solución a 0°C hasta que se saturó la solución (15 minutos). Se agitó la mezcla de reacción en atmósfera de nitrógeno a temperatura

ambiente durante 45 minutos adicionales, y se retiró el disolvente a vacío. Se trituró el precipitado blanco resultante con éter (3 veces 10 ml) dando el hidrocloruro de sin-N-[4-(2-amino-acetilamino)-ciclohexil]-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (2,07 g) como un sólido blanco.

LRMS (termopulverización): m/z $[M+H]^+$ 405.

**Preparación 25 : sin-5-Fluoro-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)amino]ciclohexil}nicotinamida**



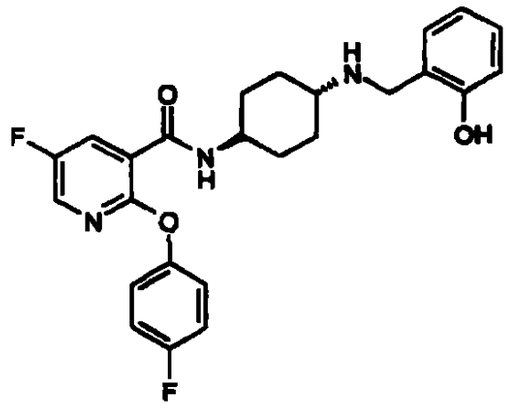
Una disolución de sin-N-(4-aminociclohexil)-5-fluoro-2-(4-fluorofenoxi)nicotinamida (220 mg, 0,52 mmol) (véase Preparación 22) en diclorometano (5 ml) se adicionó gota a gota a una suspensión de carbonildiimidazol (253 mg, 1,563 mmol) y trietilamina (0,08 ml, 0,521 mmol) en diclorometano (5 ml) durante un período de 35 minutos. La mezcla de reacción se lavó secuencialmente con agua (10 ml) seguido por una disolución acuosa saturada de cloruro de sodio (10 ml). Se separó la fase orgánica y se secó sobre sulfato de magnesio anhidro. El disolvente se retiró a vacío, y el residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de diclorometano al 100 % cambiando a diclorometano : metanol 99:1 y luego 98:2, en volumen, dando sin-5-fluoro-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)amino]ciclohexil}nicotinamida (147

mg) como una espuma blanca.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,32-8,39 (1H, m), 7,95-8,06 (3H, m), 7,19 (1H, s), 7,08-7,17 (4H, m), 7,05 (1H, s), 4,18-4,26 (1H, m), 3,92-4,02 (1H, m), 1,78-2,02 (6H, m), 1,57-1,77 (2H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 442, $[M+Na]^+$ 464

**Preparación 26 : anti-5-Fluoro-2-(4-flúor-fenoxi)-N-[4-(2-hidroxi-bencilamino)-ciclohexil]nicotinamida**



Se disolvieron 2-(terc-butil-dimetil-silaniloxi)-benzaldehído (769 mg, 3,21 mmol) (véase Preparación 16) e hidrocloruro de anti-N-(4-amino-ciclohexil)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida (900 mg, 2,14 mmol) (véase Preparación 7) en diclorometano (10 ml) y se adicionó diisopropiletilamina (0,56 ml, 3,21 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos y se adicionó ácido acético (0,19 ml, 3,21 mmol) seguido por la adición de triacetoxiborohidruro de sodio (0,681 g, 3,21 mmol). La mezcla de reacción se mantuvo a temperatura ambiente durante 18 horas. La mezcla se detuvo con agua (10 ml), se separó la fase orgánica y se secó sobre sulfato de magnesio anhidro. Se retiró el disolvente a vacío y el residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con diclorometano : metanol 100:2, en volumen, proporcionando

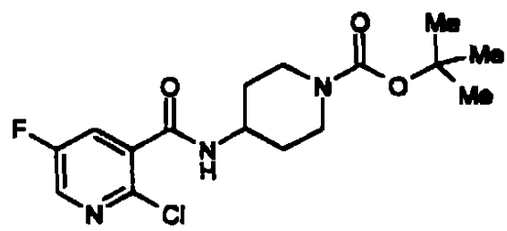
anti-5-fluoro-2-(4-flúor-fenoxi)-N-[4-(2-hidroxi-bencilamino)-ciclohexil]nicotinamida (800 mg) como un sólido blanco (sal acetato).

H NMR (400 MHz, $CDCl_3$): δ = 8,32-8,38 (1H, m), 8,01-8,04 (1H, d), 7,64-7,72 (1H, d), 7,05-7,21 (5H, m), 6,95-6,99 (1H, d), 6,81-6,84 (1H, d), 6,73-6,80 (1H, t), 3,92-4,04 (3H, m), 2,50-2,62 (1H, m), 2,02-2,20 (7H, s + m), 1,20-1,40 (4H, m) ppm.

LRMS (electropulverización): m/z $[M+H]^+$ 454

Encontrado C, 60,35; H, 5,48; N, 7,87. $C_{25}H_{25}F_2N_3O_3$. 1 moles ácido acético, 1,28 moles $H_2O$ requiere C, 80,44; H, 5,93; N, 7,83%

**Preparación 27 : Éster terc-butílico del ácido 4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]-piperidin-1-carboxílico**




Se disolvió ácido 2-cloro-5-fluoro nicotínico (5,00 g, 28,48 mmol) (véase Preparación 41), en diclorometano (200 ml) y se adicionó N,N-dimetilformamida (1 gota), seguido por adición de cloruro de oxalilo (7,45 ml, 85,44 mmol). La mezcla de reacción se mantuvo a temperatura ambiente durante 18 horas, después se retiró el disolvente a vacío. El residuo se suspendió en diclorometano (150 ml) y se adicionó trietilamina (11,91 ml, 85,44 mmol) seguido por adición del éster terc-butílico del ácido 4-amino-piperidin-1-carboxílico (6,85 g, 34,18 mmol). La mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 64 horas antes de lavarse secuencialmente con agua (2 veces 100 ml), una disolución

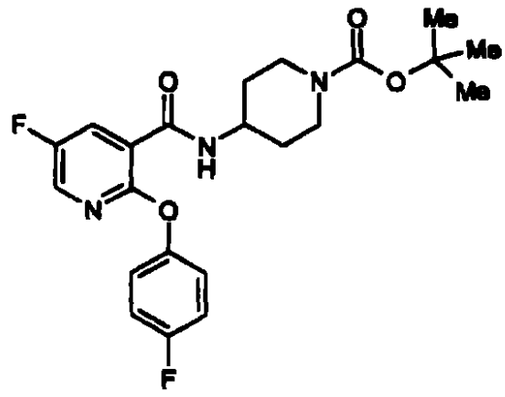
acuosa saturada de cloruro de sodio (100 ml) y una disolución al 10% de ácido cítrico en agua (50 ml). La fase orgánica se separó, se secó sobre sulfato de magnesio anhidro y el disolvente se retiró a vacío dando el éster terc-butílico del ácido 4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]-piperidin-1-carboxílico (8,7 g) como un sólido blanco.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,28-8,30 (1H, d), 7,78-7,83 (1H, m), 6,46-6,52 (1H, m), 4,04-4,13 (1H, m), 3,96-4,03 (1H, m), 2,83-2,98 (2H, t), 1,97-2,03 (2H, (1), 1,38-1,50 (11H, m) ppm.

LRMS (termopulverización): m/z $[M+Na]^+$ 380

LRMS (electropulverización): m/z $[M-H]^+$ 356.

**Preparación 28 : Éster terc-butílico del ácido 4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]-amino}piperidin-1-carboxílico**



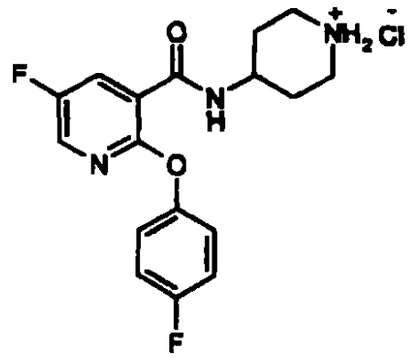

Se agitaron éster terc-butílico del ácido 4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]-piperidin-1-carboxílico (4,0 g, 11,18 mmol) (véase Preparación 27), 4-fluorofenol (1,378 g, 12,3 mmol) y carbonato de cesio (7,29 g, 33,54 mmol) en N,N-dimetilformamida (40 ml) a 55°C en atmósfera de nitrógeno durante 18 horas. Se repartió la mezcla de reacción entre acetato de etilo (50 ml) y agua (30 ml) y se separó la capa orgánica. Se lavó la capa orgánica con

una disolución acuosa saturada de cloruro de sodio (40 ml), se secó sobre sulfato de sodio anhidro y se retiró el disolvente a vacío. El residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con diclorometano. Se trituró finalmente el producto con éter dietílico (25 ml) proporcionando el éster terc-butílico del ácido 4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]-amino}piperidin-1-carboxílico (2,59 g) como un sólido blanco.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,30-8,33 (1H, m), 7,78-8,00 (1H, d), 7,73-7,80 (1H, d), 7,02-7,13 (4H, m), 4,07-4,20 (1H, m), 3,90-4,04 (1H, m), 2,87-3,03 (2H, d), 1,37-1,45 (11H, m) ppm.

LRMS (termopulverización): m/z $[M+Na]^+$ 456, $[M-H]^+$ 432.

**Preparación 29 : Hidrocloruro de 5-fluoro-2-(4-fluorofenoxi)-N-piperidin-4-il-nicotinamida**



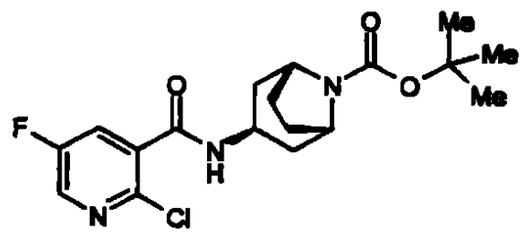
Se disolvió éster terc-butílico del ácido 4-{[5-fluoro-2-(4-fluorofenoxi)-piridin-3-carbonil]-amino}piperidin-1-carboxílico (2,58 g, 5,95 mmol) (véase preparación 28) en diclorometano (15 ml) y se borboteó gas cloruro de hidrógeno a la solución a 0°C durante 10 minutos. La mezcla de reacción se mantuvo en atmósfera de nitrógeno a temperatura ambiente durante 45 minutos adicionales y se retiró el disolvente a vacío. El precipitado blanco resultante se trituró con éter dietílico (2 veces 10 ml)

dando el hidrocloruro de 5-fluoro-2-(4-fluorofeno-xi)-N-piperidin-4-il-nicotinamida (2,14 g) como un sólido blanco.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,04-8,07 (1H, d), 7,96-8,01 (1H, m), 7,10-7,21 (4H, m), 4,13-4,22 (1H, m), 3,39-3,44 (2H, d), 3,11-3,20 (2H, t), 2,18-2,26 (2H, d), 1,77-1,90 (2H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 334.

**Preparación 30: Éster terc-butílico del ácido endo-3-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-8-aza-biciclo-[3.2.1]octano-8-carboxílico**



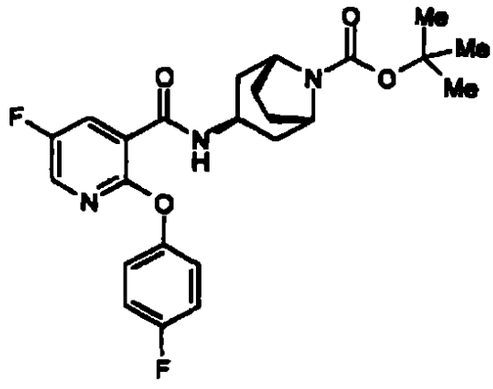

Se disolvió ácido 2-cloro-5-fluoro nicotínico (1,75 g, 10 mmol) (véase Preparación 44) en diclorometano (250 ml) y se adicionó N,N-dimetilformamida (0,4 ml) seguido por adición de cloruro de oxalilo (4,4 ml, 50 mmol). La mezcla de reacción se mantuvo a temperatura ambiente durante 18 horas después de este tiempo se retiró el disolvente a vacío. El residuo se destiló azeotrópicamente con tolueno, luego se suspendió en diclorometano (200 ml) y se adicionó el éster terc-butílico del ácido 3-amino-8-aza biciclo[3.2.1]octano-8-carboxílico (2,26 g, 10 mmol) (véase solicitud de patente de referencia WO 00/38680) seguido por adición de trietilamina (2,82 ml, 20 mmol). La mezcla de reacción se mantuvo en atmósfera de nitrógeno a temperatura ambiente durante 3 horas antes de que se lavase con una disolución acuosa saturada de cloruro de sodio (3 veces 100 ml) y se separó la capa orgánica. Se retiró el disolvente a vacío y el residuo se purificó por

cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de diclorometano: metanol 100:0 cambiando a 90:10, en volumen, dando el éster terc-butílico del ácido endo-3-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-8-aza-biciclo-[3.2.1]octano-8-carboxílico (1,12 g) como una espuma blanca.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,31-8,34 (1H, d), 7,97-8,02 (1H, dd), 7,18-7,23 (1H, m, parcialmente enmascarada por el disolvente), 4,34-4,39 (1H, m), 4,15-4,32 (2H, s ancho), 2,19-2,38 (2H, s ancho), 2,07-2,13 (2H, m), 1,82-1,90 (2H, m), 1,71-1,79 (2H, d), 1,45 (9H, s) ppm.

LRMS (electropulverización): m/z $[M+Na]^+$ 406, $[M-H]^+$ 382.

**Preparación 31 : Éster terc-butílico del ácido endo-3-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]-amino}-8-aza-biciclo[3.2.1]octano-8-carboxílico**



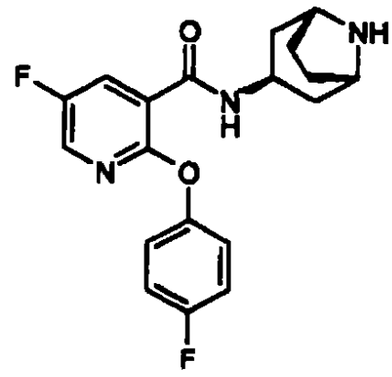

Se agitaron éster terc-butílico del ácido endo-3-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-8-aza-biciclo-[3.2.1]octano-8-carboxílico (119 mg, 0,31 mmol) (véase Preparación 30), 4-fluorofenol (39 mg, 0,34 mmol) y carbonato de cesio (202 mg, 0,62 mmol) en N,N-dimetilformamida (2 ml) a 60°C en atmósfera de nitrógeno durante 18 horas. La mezcla de reacción se repartió entre acetato de etilo (10 ml) y agua (10 ml), y se separó la

capa orgánica. Se lavó la capa orgánica con una disolución acuosa saturada de cloruro de sodio (3 veces 10 ml) y se concentró a vacío para dar un residuo que se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de acetato de etilo: pentano 10:90 cambiando a 50:50, en volumen. El producto se trituró finalmente con pentano (5 ml) dando el éster terc-butílico del ácido endo-3-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-8-aza-biciclo[3.2.1]octano-8-carboxílico (100 mg) como un sólido blanco.

H NMR (400MHz, $CDCl_3$): δ 8,51-8,58 (1H, d), 8,32-8,36 (1H, dd), 7,98-8,00 (1H, d), 7,01-7,15 (4H, m), 4,37-4,43 (1H, m), 4,11-4,30 (2H, s ancho), 2,14-2,36 (2H, s ancho), 1,91-1,98 (2H, m), 1,70-1,84 (4H, m), 1,43 (9H, s) ppm.

LRMS (electropulverización): m/z $[M+Na]^+$ 482, $[M-H]^+$ 458.

**Preparación 32 : endo-N-(8-Aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluorofenoxi)nicotinamida**



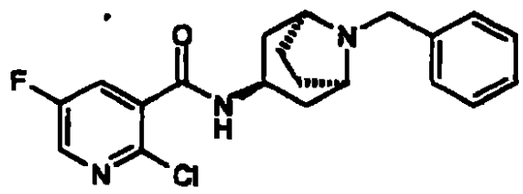

Se disolvió éster terc-butílico del ácido endo-3-{[5-fluoro-2-(4-fluorofenoxi)piridin-3-carbonil]amino}-8-aza-biciclo[3.2.1]octano-8-carboxílico (1,92 g, 4,2 mmol) (véase Preparación 31) en cloruro de acetilo 2,2 M en metanol (20 ml) y la reacción se agitó a temperatura am-

biente en atmósfera de nitrógeno durante 1 hora. Se calentó la mezcla de reacción a 50°C durante 3 horas antes de separar el disolvente a vacío. Se repartió el residuo entre diclorometano (50 ml) y agua (50 ml), el pH de la fase acuosa se ajustó a pH>8 por adición de hidrógeno carbonato de sodio y se separó la capa orgánica. La fase acuosa se extrajo adicionalmente con acetato de etilo (50 ml) seguido por metanol al 10 % en diclorometano (5 veces 50 ml). Los extractos orgánicos combinados se concentraron a presión reducida. El residuo se destiló azeotrópicamente con tolueno dando endo-N-(8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluorofenoxi)-nicotinamida (1,40 g) como un sólido blanco.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8,34-8,39 (1H, d), 8,16-8,18 (1H, d), 7,97-8,01 (1H, dd), 7,18-7,23 (4H, d), 3,99-4,06 (1H, m), 3,33-3,40 (2H, s ancho, parcialmente enmascarada por el disolvente), 1,85-1,99 (4H, m), 1,64-1,72 (2H, d), 1,49-1,57 (2H, m) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 360.

**Preparación 33 : exo-N-(8-Bencil-8-aza-biciclo[3.2.1]oct-3-il-2-cloro-5-fluoro-nicotinamida**

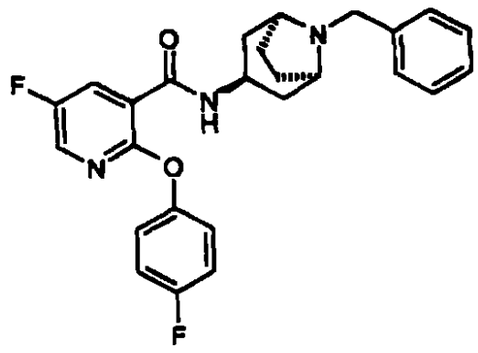



Se disolvió ácido 2-cloro-5-fluoro nicotínico (8,78 g, 50 mmol) (véase Preparación 41), en diclorometano (1 l) y se adicionó N,N-dimetilformamida (0,4 ml), seguido por adición de cloruro de oxalilo (22,3 ml, 250 mmol). La mezcla de reacción se mantuvo a temperatura ambiente durante 18 horas después de este tiempo se retiró el disolvente a vacío. El residuo se destiló azeotrópicamente con tolueno, se suspendió en diclorometano (300 ml) y se adi-

cionó exo-8-bencil-8-aza-biciclo[3.2.1]oct-3-ilamina (solicitud de patente de referencia WO 00/38680) (10,82 g, 50 mmol) seguido por adición de trietilamina (14 ml, 100 mmol) en triclorometano (100 ml). Se mantuvo la mezcla de reacción en atmósfera de nitrógeno a temperatura ambiente durante 5 horas y se lavó con una disolución acuosa saturada de cloruro de sodio (3 veces 300 ml). La fase orgánica se separó, se concentró a vacío y el residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de diclorometano: metanol 100:0 cambiando a 90:10, en volumen, dando exo-N-(8-Bencil-8-aza-biciclo-[3.2.1]-oct-3-il-2-cloro-5-fluoro-nicotinamida (17 g) como un sólido blanco. $^1$H NMR (400MHz, $CDCl_3$): δ 8,30-8,32 (1H, d), 7,81-7,85 (1H, dd), 7,20-7,38 (5H, m, parcialmente enmascarado por el disolvente), 6,28-6,31 (1H, d), 4,30-4,42 (1H, m), 3,55 (2H, s), 3,22-3,30 (2H, s ancho), 2,02-2,13 (2H, m), 1,91-1,99 (2H, m), 1,72-1,80 (2H, cuarteto), 1,60-1,70 (2H, t) ppm.

LRMS (electropulverización): m/z $[M+H]^+$ 374, $[M-H]^+$ 372.

**Preparación 34: exo-N-(8-Bencil-8-aza-biciclo[3.2.1]oct-3-il-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida**



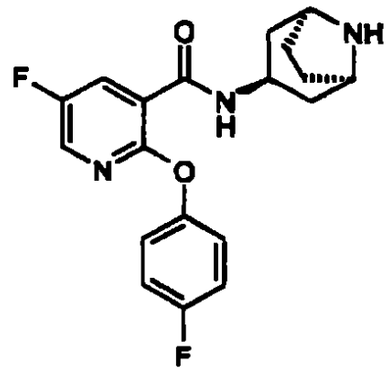
Se agitaron exo-N-(8-Bencil-8-aza-biciclo-[3.2.1]-oct-3-il-2-cloro-5-fluoro-nicotinamida (7,9 g, 21 mmol) (véase Preparación 33), 4-fluorofenol (2,6 g, 23 mmol) y

carbonato de cesio (13,8 g, 42 mmol) en N,N-dimetilformamida (200 ml) a 70°C en atmósfera de nitrógeno durante 20 horas. La mezcla de reacción se repartió entre acetato de etilo (300 ml) y agua (300 ml) y se separó la capa orgánica. La fase orgánica se lavó con una disolución acuosa saturada de cloruro de sodio (3 veces 200 ml), se concentró a vacío y el residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con un gradiente de disolventes de acetato de etilo : pentano 20:80 cambiando a 100:0, en volumen. Se trituró el producto con pentano (30 ml) dando exo-N-(8-Bencil-8-aza-biciclo[3.2.1]oct-3-il-5-fluoro-2(4-fluoro-fenoxi)-nicotinamida (6,3 g) como un sólido blanco.

$^1$H NMR (400MHz, $CDCl_3$): δ = 8,26-8,30 (1H, dd), 7,96-7,98 (1H, d), 7,58-7,64 (1H, d), 7,17-7,33 (5H, m), 7,04-7,16 (4H, m), 4,30-4,42 (1H, m), 3,48 (2H, s), 3,20-3,25 (2H, s ancho), 2,03-2,11 (2H, m), 1,88-1,96 (2H, m), 1,72-1,80 (2H, cuarteto), 1,55-1,62 (2H, m, parcialmente enmascarada por el disolvente) ppm.

LRMS (electropulverización): m/z $[M+H]^+$ 450, $[M-H]^+$ 448.

**Preparación 35 : exo-N-(8-Aza-biciclo[3.2.1]oct-3-il]-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida**



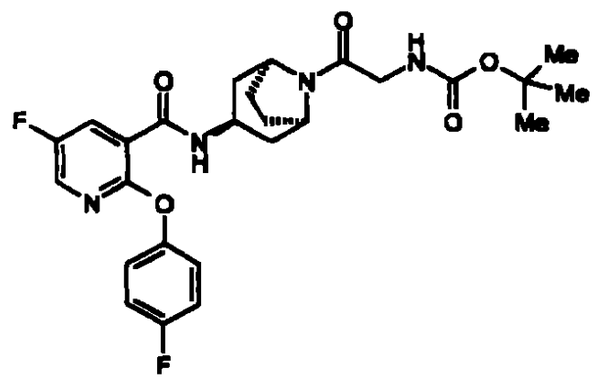

Se adicionó paladio al 10% sobre carbono (0,5 g) y formiato amónico (7,5 g, 115 mmol) a una solución de exo-

N-(8-bencil-8-aza-biciclo[3.2.1]oct-3-il-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (5,15 g, 11,5 mmol) (véase Preparación 34) en etanol (35 ml) en atmósfera de nitrógeno y la mezcla de reacción se calentó a reflujo durante 25 minutos. Se enfrió la mezcla de reacción, se filtro a través de una columna corta de arbocel (lavada con etanol) y el filtrado se concentró a presión reducida. El residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con diclorometano: metanol : amoniaco 90:10:1, en volumen, dando exo-N-(8-Aza-biciclo[3.2.1]oct-3-il]-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (3,4 g) como una espuma blanca.

H NMR (400MHz, $CDCl_3$): δ = 8,26-8,31 (1H, dd), 7,97-7,99 (1H, d), 7,56-7,70 (1H, d), 7,00-7,14 (4H, m), 4,33-4,43 (1H, m), 3,52-3,60 (2H, s ancho), 1,97-2,06 (2H, m), 1,73-1,88 (4H, m), 1,41-1,50 (2H, t) ppm.

LRMS (termopulverización): m/z $[M+H]^+$ 360

**Preparación 36 : Éster terc-butílico del ácido exo-[2-(3-{[5-fluoro-2-(4-fluorofenoxi)piridin-3-carbonil]amino)-8-azo-biciclo[3.2.1]oct-8-il)-2-oxo-etil]-carbámico**



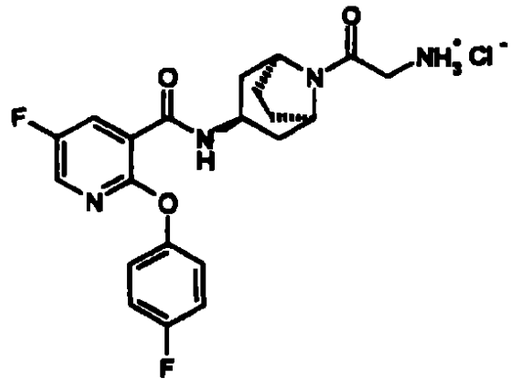
Se agitaron n-terc-butoxicarbonil-glicina (284 mg, 1,6 mmol), 1-hidroxibenzotriazol (257 mg, 1,9 mmol) y hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (375 mg, 1,9 mmol) en diclorometano (10 ml) a temperatura

ambiente y se adicionó exo-N-(8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluorofenoxi)nicotinamida (570 mg, 1,6 mmol) (véase Preparación 35) seguido por la adición de N-metil morfolina (0,21 ml, 1,9 mmol). La mezcla de reacción se agitó en atmósfera de nitrógeno a temperatura ambiente durante 4 horas antes de lavarse con agua (10 ml). La fase orgánica se separó, se concentró a vacío y el residuo se purificó por cromatografía instantánea en columna de gel de sílice eluyendo con diclorometano : metanol 100:0 cambiando a 98:2, en volumen, dando el éster terc-butílico del ácido exo-[2-(3-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino)-8-azo-biciclo[3.2.1]oct-8-il)-2-oxo-etil]-carbámico (760 mg) como un aceite.

$^1$H NMR (400MHz, $CDCl_3$): δ= 8,28-8,34 (1H, m), 8,0-8,02 (1H, m), 7,59-7,65 (1H, d), 7,05-7,16 (4H, m), 5,37-5,43 (1H, s ancho), 4,72-4,78 (1H, s ancho), 4,57-4,70 (1H, m), 4,15-4,20 (1H, s ancho), 3,89-3,94 (2H, s ancho), 2,16-2,23 (1H, m), 1,94-2,15 (2H, m), 1,82-1,92 (1H, m), 1,58-1,68 (1H, t), 1,40-1,56 (10H, m), 0,90-0,96 (2H, d) ppm.

LRMS (electropulverización): m/z $[M+Na]^+$ 539, $[M-H]^-$ 515.

**Preparación 37 : Hidrocloruro de exo-N-[8-(2-amino-acetil)-8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluoro-fenoxi)nicotinamida**

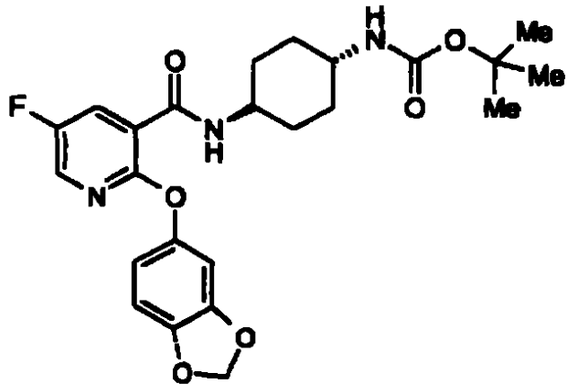


Se disolvió éster terc-butílico del ácido exo-[2-(3-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino)-8-azo-biciclo[3.2.1]oct-8-il)-2-oxo-etil]-carbámico (760 g, 1,5 mmol) (véase Preparación 36) en cloruro de acetilo 2 M en metanol (10 ml). La mezcla de reacción se agitó a 50° en atmósfera de nitrógeno durante 3 horas entonces el disolvente se retiró a vacío. El residuo se destiló azeotrópicamente con metanol (5 ml) y se secó a vacío dando Hidrocloruro de exo-N-[8-(2-amino-acetil)-8-aza-biciclo[3.2.1]oct-3-il)-5-fluoro-2-(4-fluoro-fenoxi)-nicotinamida (600 mg) como un sólido blanco.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8,29-8,33 (1H, d), 8,13-8,23 (3H, m), 7,92-7,96 (1H, dd), 7,16-7,25 (4H, m), 4,50-4,58 (1H, s ancho), 4,28-4,41 (1H, m), 4,21-4,27 (1H, m), 3,80-3,90 (1H, m), 3,60-3,72 (1H, m), 1,70-2,06 (6H, m), 1,49-1,64 (2H, m) ppm.

LRMS (termopulverización): m/z [M+H]$^+$ 417.

**Preparación 38 : Éster terc-butílico del ácido anti-(4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]-amino}ciclohexil)-carbámico**



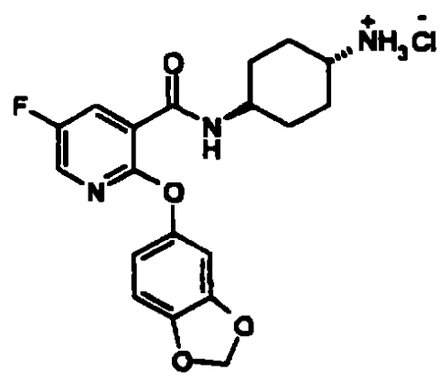

Se agitaron ácido 2-(4-benzo[1,3]dioxol-5-iloxi)-5-fluoro-nicotínico (5,0 g, 18,04 mmol) (véase solicitud de patente de referencia WO 98/45268), 1-hidroxibenzotriazol (3,66 g, 27,06 mmol), hidrocloruro de 1-(3-dimetilamino-

propil)-3-etilcarbodiimida (4,50 g, 23,45 mmol) en N,N-dimetilformamida (40 ml) a temperatura ambiente en atmósfera de nitrógeno durante 45 minutos. Se adicionó éster terc-butílico del ácido anti-(4-amino-ciclohexil)-carbámico (3,87 g, 18,04 mmol) (véase Preparación 40) seguido por adición de N-metil morfolina (4 ml, 36,08 mmol) y la mezcla de reacción se agitó durante 16 horas adicionales. Se retiró el disolvente a vacío, el residuo se disolvió en acetato de etilo y la solución se lavó secuencialmente con agua y una disolución acuosa saturada de cloruro de sodio. Se separó la capa orgánica, se secó sobre sulfato de sodio anhidro y se retiró el disolvente a vacío. El residuo se trituró con éter dietílico y se secó a vacío para dar el éster terc-butílico del ácido anti-(4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]-amino}ciclohexil)carbámico (6,695 g) como un sólido blanco.

H NMR (400MHz, DMSO-$d^6$): $\delta$ = 8,15 (1H, m), 7,88 (1H, m), 6,85 (1H, d), 6,78 (1H, d), 6,64 (1H, d), 6,58 (2H, m), 5,99 (2H, s), 3,62 (1H, m), 3,15 (1H, m), 1,70-1,90 (4H, m), 1,32 (9H, s), 1,10-1,30 (4H, m) ppm.

LRMS (termopulverización): m/z $[M+Na]^+$ 496

**Preparación 39 : Hidrocloruro de anti-N-(4-amino-ciclohexil)-2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-nicotinamida**

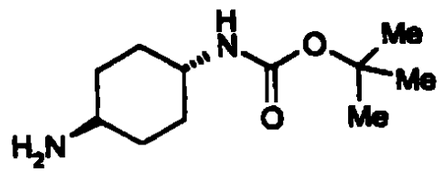


Se trató éster terc-butílico del ácido anti-(4-{[2-

(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]-amino}ciclohexil)carbámico (6,7 g, 14,15 mmol) (véase Preparación 38) con HCl 4M en dioxano (40 ml) y la mezcla de reacción se agitó durante 90 minutos. El disolvente se redujo a vacío y precipitó un sólido. El precipitado se suspendió en éter dietílico, se filtró y se secó a vacío para dar hidrocloruro de anti-N-(4-amino-ciclohexil)-2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-nicotinamida (6,13 g) como un sólido blanco.

$^1$H NMR (400MHz, DMSO-d$^6$): δ = 8,24 (1H, d), 8,20 (1H, d), 7,86-7,99 (4H, m), 6,86 (1H, d), 6,80(1H, d), 6,58 (1H, m), 5,99 (2H, s), 3,60-3,70 (1H, m), 2,90-2,95 (1H, m), 1,85-1,98 (4H, m), 1,25-1,45 (4H, m) ppm.

**Preparación 40 : Éster terc-butílico del ácido anti-(4-amino-ciclohexil)-carbámico**



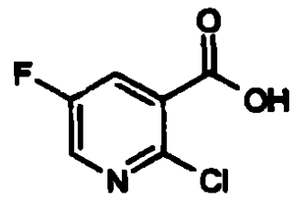

Se disolvió anti 1,4-diamino ciclohexano (18,27 g, 0,16 moles) en diclorometano (80 ml) y la solución se enfrió a 0°C en atmósfera de nitrógeno. Se mantuvo la mezcla de reacción a 0°C y se adicionó una disolución de dicarbonato de di-terc-butilo (6,98 g, 0,032 moles) en diclorometano (70 ml) gota a gota durante un período de 5 horas. La mezcla de reacción se agitó a temperatura ambiente durante 16 horas adicionales y se lavó con agua (200 ml). Se separó la capa orgánica, se extrajo con una disolución acuosa al 10% de ácido cítrico (200 ml) y se descargó la fase orgánica. El pH de la fase acuosa se incremento a pH>8 por adición de 0,88 de amoniaco y se extrajo con diclorometano (3 veces 150 ml). Se combinaron los extractos, se secaron sobre sulfato de magnesio an-

hidro y se retiró el disolvente a vacío para dar el éster terc-butílico del ácido anti-(4-amino-ciclohexil)-carbámico (4,83 g) como un sólido.

H NMR (400MHz, $CDCl_3$): δ = 4,35 (s ancho, 1 H), 4,55 (s ancho, 1H), 3,40 (s ancho, 1H), 2,60-2,65 (m, 1H), 1,80-2,00 (m, 4H), 1,10-1,50 (m, 14H) ppm.

LRMS (electropulverización): m/z $[M+H]^+$ 215.

**Preparación 41: Ácido 2-cloro-5-fluoronicotínico**

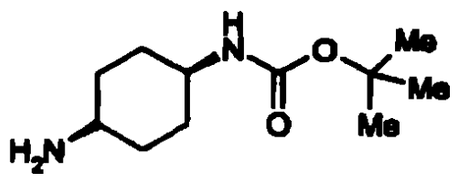



Se disolvió 2-cloro-5-fluoro-nicotinoato de etilo (50,4 g, 0,247 moles) (véase referencia J. Med. Chem., 1993, 36 (18), 2676-88) en tetrahidrofurano (350 ml) y se adicionó una disolución acuosa 2 M de hidróxido de litio (247 ml, 0,495 moles). Se agitó la mezcla de reacción a temperatura ambiente durante 3 días. El pH de la solución se redujo a pH1 por adición de ácido clorhídrico 6 N y se extrajo con diclorometano (3 veces). Los extractos combinados se secaron sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío para dar un sólido que se trituró con éter dietílico y se secó a vacío para dar ácido 2-cloro-5-fluoronicotínico (40,56 g) como un sólido blanco.

$^1H$ NMR (400MHz, DMSO-$d^6$): δ = 8,20 (1H, s), 8,62 (1H, s) ppm.

LRMS (electropulverización): m/z $[M+H]^+$ 174.

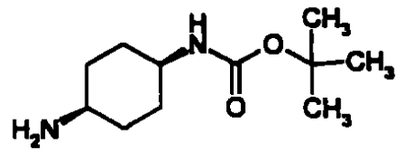
**Preparación 42a : sin:anti 80:20 Éster terc-butílico del ácido (4-amino-ciclohexil)-carbámico**



Se disolvió sin:anti 80:20 1,4-diamino ciclohexano (20 g, 0,175 moles) en diclorometano (160 ml) y se enfrió la solución a 0°C en atmósfera de nitrógeno. La mezcla de reacción se mantuvo a 0°C y se adicionó gota a gota una disolución de dicarbamato de di-t-butilo (7,65 g, 0,035 moles) en diclorometano (40 ml) sobre un período de 5 horas. Se agitó la mezcla de reacción a temperatura ambiente durante 16 horas adicionales y se lavó con agua (200 ml). Se separó la capa orgánica, se extrajo con una disolución acuosa al 10% de ácido cítrico (200 ml) y se descargó la fase orgánica. El pH de la fase acuosa se incremento a pH>8 por adición de 0,88 de amoniaco y se extrajo con diclorometano (2 veces 150 ml). Se combinaron los extractos orgánicos, se secaron sobre sulfato de magnesio anhidro y se retiró el disolvente a vacío. Se trituró el residuo con pentano para dar sin:anti 80:20 éster terc-butílico del ácido (4-amino-ciclohexil)-carbámico (5,143 g) como un sólido.

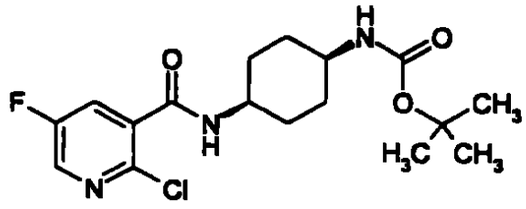
$^1$H NMR (400MHz, $CDCl_3$): $\delta$ = 4,60 (s ancho, 0,8H), 4,36 (s ancho, 0,2H), 3,63 (s ancho, 0,8H), 3,39 (s ancho, 0,2H), 3,80-3,86 (m, 0,8H), 2,60-2,65 (m, 0,2H), 1,96-2,00 (m, 0,2H), 1,80-1,86 (m, 0,2H), 1,10-2,75 (m, ~17H) ppm.
LRMS (electropulverización) m/z $[M+H]^+$ 215.

**Preparación 42b: Éster terc-butílico del ácido sin-(4-amino-ciclohexil)-carbámico**



Se mezcló paladio al 5% sobre carbón vegetal (5 g) con tolueno (10 ml) y se añadió a éster terc-butílico del ácido (4-azido-ciclohexil)-carbámico (170 g, 0,71 mol, véase WO 99/54284) en metanol (400 ml). La mezcla se hidrógeno (80 atmósferas) a temperatura ambiente durante 18 horas y después se filtró. El disolvente se evaporó a vacío y el residuo se trituró con acetato de etilo (50 ml) y después con hexano (200 ml). El sólido obtenido se aisló por filtración, se disolvió en acetato de etilo (600 ml) y se filtró a través de Celite®. El filtrado se concentró a vacío para dar un lodo que se diluyó con hexano (300 ml). El sólido obtenido se aisló por filtración y se lavó con acetato de etilo en hexano (20:80). Las aguas madres se combinaron y evaporaron a vacío, el residuo se purificó por cromatografía sobre gel de sílice utilizando acetato de etilo y después metanol como eluyente. El material obtenido se cristalizó en acetato de etilo y hexano y se combinó con la primera cosecha para dar éster terc-butílico del ácido sin-(4-amino-ciclohexil)-carbámico como un sólido blanco (76 g).
p.f. 88-90°C,

**Preparación 43: Éster terc-butílico del ácido sin-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-ciclohexil}-carbámico**

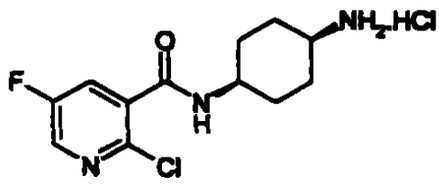


Se añadieron ácido 2-cloro-5-fluoronicotínico (1 g, 5,7 mmol, véase la Preparación 41), hidrocloruro de 1-(3-dimetilaminopropil-3-etilcarbodiimida (1,2 g, 6,27 mmol) y e hidrato de 1-hidroxibenzotriazol (0,847 g, 6,27 mmol) a éster terc-butílico del ácido (4-amino-ciclohexil)-carbámico (1,28 g, 5,98 mmol, véase la Preparación 42b) en N,N-dimetilformamida (20 ml) conteniendo trietilamina (2,38 ml, 17 mmol). La mezcla se agitó durante 18 horas y después se repartió entre acetato de etilo y agua. La solución orgánica se lavó con agua y después con solución saturada de cloruro de sodio, se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando ciclohexano en acetato de etilo (40:60) para dar éster terc-butílico del ácido sin-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-ciclohexil}-carbámico (1,01 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,33 (1H, d), 7,80 (1H, m), 6,67 (1H, s), 4,54 (1H, m), 4,16 (1H, m), 3,64 (1H, s), 1,86 (6H, m), 1,76 (2H, m), 1,27 (9H, s).

LCMS (electropulverización): m/z $[M+Na]^+$ 394, 396

**Preparación 44: Hidrocloruro de sin-N-(4-amino-ciclohexil)-2-cloro-5-fluoro-nicotinamida**

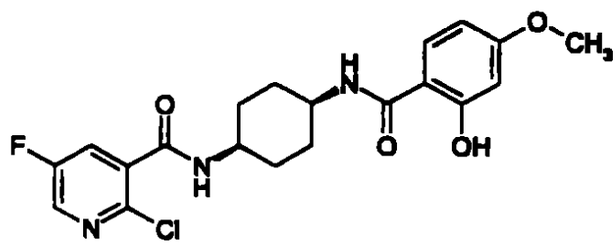


Se añadió cloruro de hidrógeno (4M en 1,4-dioxano, 20 ml) a éster terc-butílico del ácido sin-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-ciclohexil}-carbámico (1,01 g, 2,72 mmol, véase la Preparación 43) en 1,4-dioxano (10 ml) y se agitó durante 1 hora. El disolvente se evaporó a vacío y el residuo se trituró con éter dietílico. El material resultante se secó a vacío para dar hidrocloruro de sin-N-(4-amino-ciclohexil)-2-cloro-5-fluoro-nicotinamida como un sólido blanquecino (1,11 g).

H NMR (400MHz, $CD_3OD$): δ 8,41 (1H, d), 7,79 (1H, m), 4,07 (1H, m), 3,25 (1H, m), 1,88 (8H, m).

LCMS (electropulverización): m/z $[M+H]^+$ 372, 274

**Preparación 45: Sin-2-Cloro-5-fluoro-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-nicotinamida**



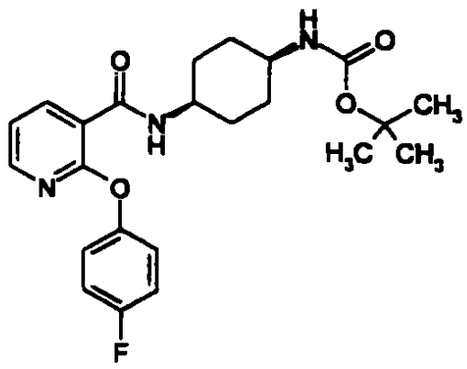

Se añadió hidrocloruro de 1-(3-dimetilaminopropil-3-etilcarbodiimida (3,27 g, 17 mmol) a hidrocloruro de sin-N-(4-amino-ciclohexil)-2-cloro-5-fluoro-nicotinamida (3,5 g, 11,3 mmol, véase la Preparación 44), hidrato de 1-hidroxibenzotriazol (1,69 g, 12,5 mmol) y ácido 2-hidroxi-4-metoxibenzoico (1,91 g, 11,31 mmol) en N,N-dimetilformamida (50 ml) conteniendo trietilamina (8 ml, 57 mmol). La mezcla se agitó 18 horas y después se evaporó a vacío. El residuo se repartió entre acetato de etilo y agua y la fase orgánica se secó y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sí-

lice utilizando acetato de etilo en pentano (30:70) y cambiando después el eluyente de la columna a hidróxido de amonio y metanol en diclorometano (1:10:90). El material obtenido se trituró con metanol en diclorometano (5:95) para dar sin-2-cloro-5-fluoro-N-[4-(2-hidroxi-4-metoxi-benzoilamino)-ciclohexil]-nicotinamida como un sólido blanco (940 mg).

$^1$H NMR (400MHz, DMSO-$d_6$): δ 12,78 (1H, s), 8,53 (2H, s), 8,23 (1H, d), 7,94 (1H, m), 7,84 (1H, d), 6,43 (1H, d), 6,38 (1H, s), 3,88 (2H, m), 3,74 (3H, s), 1,73 (8H, m).

LCMS (electropulverización): m/z [M+H]$^+$ 444, 446

**Preparación 46: Éster terc-butílico del ácido sin-(4-{[2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-ciclohexil)-carbámico**



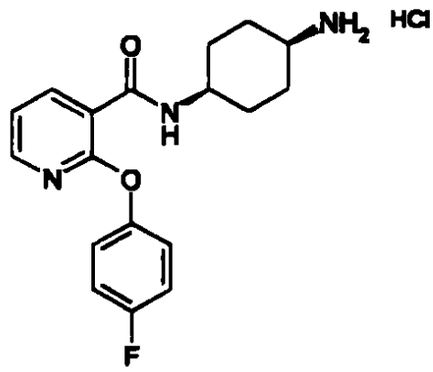
Se añadió hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (2,24 g, 5,89 mmol) a ácido 2-(4-fluoro-fenoxi)-nicotínico (0,916 g, 3,93 mmol), base de Hünig (1,37 ml, 7,86 mmol) y a éster terc-butílico del ácido sin-(4-amino-ciclohexil)-carbámico (1,01 g, 4,71 mmol, véase la Preparación 42-B) en N,N-dimetilformamida (26,2 ml) y se agitó durante 18 horas. La mezcla de reacción se repartió entre agua (100 ml) y una mezcla de éter dietílico (200 ml) y acetato de etilo (50 ml). La capa acuosa se separó y se extrajo con aceta-

to de etilo (50 ml) y las capas orgánicas combinadas se lavaron con una solución saturada de cloruro de sodio, se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando acetato de etilo en ciclohexano como eluyente (gradiente de 25:73 a 50:50) para dar éster terc-butílico del ácido sin-(4-{[2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-carbámico como un sólido blanco (1,07 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,60 (1H, d), 8,20 (1H, d), 1,91 (1H, d), 1,17 (5H, m), 4,40 (1H, m), 4,19 (1H, s), 3,61 (1H, s), 1,77 (8H, m), 1,42 (9H, s).

LCMS (electropulverización): m/z $[M+Na]^+$ 452

**Preparación 47: Hidrocloruro de sin-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)-nicotinamida**

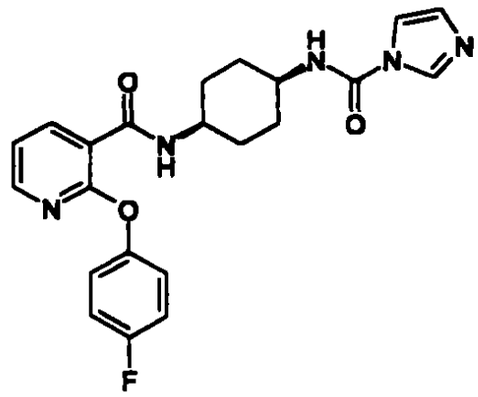



Se suspendió éster terc-butílico del ácido sin-(4-{[2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexil)-carbámico (989 mg, 2,3 mmol, véase la Preparación 46) en una solución de cloruro de hidrógeno en 1,4 dioxano (4M, 20 ml) y se agitó durante 3,5 horas a temperatura ambiente, después de lo cual se evaporó el disolvente a vacío para dar hidrocloruro de sin-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)-nicotinamida como un sólido blanco (1,04 g).

$^1$H NMR (400MHz, CD$_3$OD): δ 8,29 (1H, d), 8,19 (1H, d), 7,22 (5H, m), 4,19 (1H, m), 3,28 (1H, m), 2,94 (6H, m), 1,73 (2H, m).

LCMS (electropulverización): m/z [M+H]$^+$ 330

**Preparación 48: Sin-2-(4-Fluoro-fenoxi)-N-{4-(imidazol-1-carbonil)-amino]-ciclohexil}-nicotinamida**

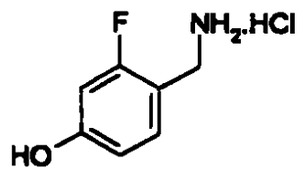


Una solución de hidrocloruro de sin-N-(4-amino-ciclohexil)-2-(4-fluoro-fenoxi)-nicotinamida (300 mg, 0,82 mmol) (véase la Preparación 47) y trietilamina (110 µl, 0,82 mmol) en diclorometano (10 ml) se añadió a lo largo de 1 hora a una solución de 1,1'-carbonildiimidazol (399 mg, 2,46 mmol) en diclorometano (5 ml) en atmósfera de nitrógeno. La mezcla se agitó durante 18 horas y después se diluyó con agua (10 ml). La solución orgánica se lavó con solución saturada de cloruro de sodio (10 ml), se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano (5:95) para dar sin-2-(4-fluoro-fenoxi)-N-{4-[(imidazol-1-carbonil)-amino]-ciclohexil}-nicotinamida como una espuma blanca (269 mg).

$^1$H NMR (400MHz, CDCl$_3$): δ 8,61 (1H, d), 8,39 (1H, m), 8,21 (1H, d), 7,99 (1H, d), 7,13 (7H, m), 5,78 (1H, m), 4,23

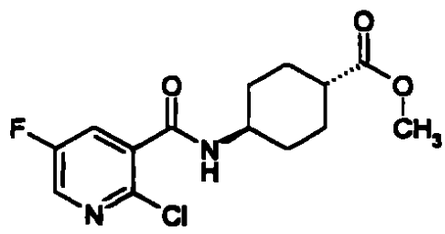
(1H, m), 4,00 (1H, m), 1,88 (8H, m).
LCMS (electropulverización): m/z $[M+H]^+$ 426

**Preparación 49: Hidrocloruro de 4-aminometil-3-fluorofenol**




Una mezcla de 2-fluoro-4-hidroxi-benzonitrilo (6 g, 43,8 mmol), hidróxido de paladio (600 mg), etanol (60 ml) y ácido clorhídrico 2N (6 ml) se hidrógeno (4,12 bar) durante 18 horas. La mezcla se filtró a través de Arbocel® y la torta del filtro se lavó con metanol y los filtrados se evaporaron a vacío. El residuo se trituró con éter dietílico para dar hidrocloruro de 4-aminometil-3-fluorofenol (4,71 g).
$^1H$ NMR (400MHz, DMSO-$d_6$): δ 10,26 (1H, d), 8,30 (1H, s), 7,39 (1H, m), 6,63 (2H, m), 3,94 (2H, d).

**Preparación 50: Éster metílico del ácido anti-4-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-ciclohexanocarboxílico**



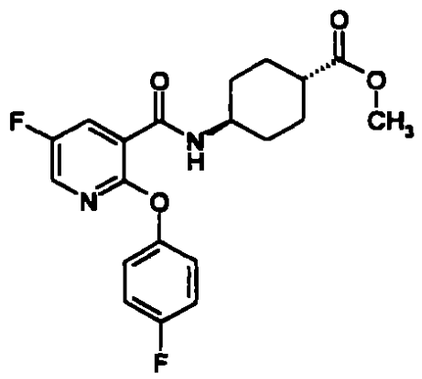

Ácido 2-cloro-5-fluoronicotínico (3 g, 17 mmol, véase la Preparación 41), hidrocloruro de 1-(3-dimetilaminopropil-3-etilcarbodiimida (4,26 g, 22 mmol) e

hidrato de 1-hidroxibenzotriazol (3,46 g, 26 mmol) se agitaron en N,N-dimetilformamida (20 ml) durante 30 minutos. Se añadieron hidrocloruro de éster metílico del ácido anti-4-amino-ciclohexanocarboxílico (3,31 g, 17 mmol, véase la referencia J. Med. Chem. 1977, 20(2), 279) y 4-metilmorfolina (3,76 ml, 34 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se repartió entre agua y acetato de etilo y la solución orgánica se lavó con una solución saturada de cloruro de sodio, se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente de 0:100 a 3:97) y el material aislado se secó a vacío para dar éster metílico del ácido anti-4-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-ciclohexanocarboxílico como un sólido (4,23 g).

H NMR (300MHz, $CDCl_3$): δ 8,32 (1H, d), 7,83 (1H, m), 6,44 (1H, d), 3,96 (1H, m), 3,69 (3H, s), 2,16 (5H, m), 1,63 (2H, m), 1,33 (2H, m).

LCMS (electropulverización): m/z $[M-H]^-$ 313

**Preparación 51: Éster metílico del ácido anti-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexanocarboxílico**



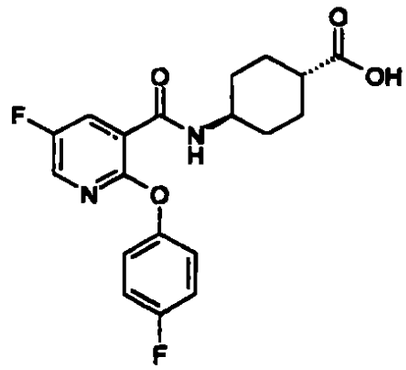
Se añadió éster metílico del ácido anti-4-[(2-cloro-

5-fluoro-piridin-3-carbonil)amino]-ciclohexanocarboxílico (4,22 g, 13 mmol, véase la Preparación 50) a una mezcla de 4-fluorofenol (1,5 g, 13 mmol) y carbonato de cesio (8,71 g, 27 mmol) en N,N-dimetilformamida (30 ml) y se agitó en atmósfera de nitrógeno a 60°C durante 18 horas. La mezcla se repartió entre agua y acetato de etilo y la solución orgánica se lavó con una solución saturada de cloruro de sodio, se secó sobre sulfato de magnesio y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando metanol en diclorometano como eluyente (gradiente de 0:100 a 2:98) y el material aislado se secó a vacío para dar éster metílico del ácido anti-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexano-carboxílico como un sólido (3,71 g).

$^1$H NMR (300MHz, $CDCl_3$): δ 8,36 (1H, m), 8,02 (1H, d), 7,72 (1H, d), 7,14 (4H, m), 4,00 (1H, m), 3,70 (3H, s), 2,22 (3H, m), 1,67 (2H, m), 1,30 (2H, m).

LCMS (termopulverización): m/z $[M]^+$ 390

**Preparación 52: Ácido anti-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]-amino}-ciclohexanocarboxílico**



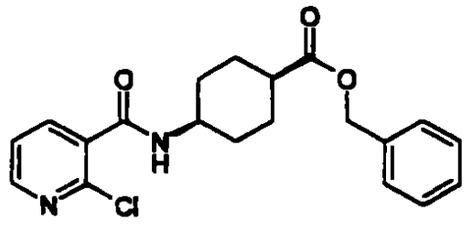
Se disolvió éster metílico del ácido anti-{[5-fluoro-2-(4-fluoro-fenoxi)piridin-3-carbonil]amino}-ciclohexano-carboxílico (3,7 g, 9,48 mmol, véase Preparación 52) en una mezcla de tetrahidrofurano (40 ml) y una disolu-

ción de hidróxido de litio 1M (19 ml, 19 mmol) y se agitó en atmósfera de nitrógeno durante 18 horas. Se adicionó ácido clorhídrico 2N (10 ml) y la mezcla se extrajo con diclorometano (3 veces). Se lavaron las soluciones orgánicas combinadas con una disolución saturada de cloruro de sodio, se secó sobre sulfato de magnesio anhidro y se evaporó a vacío. El residuo se trituró con éter dietílico y el sólido obtenido se secó a vacío para dar ácido anti-{[5-fluoro-2-(4-fluoro-fenoxi)-piridin-3-carbonil]amino}-ciclohexanocarboxílico (2,45 g).

$^1$H NMR (300MHz, $CDCl_3$): δ 12,0 (1H, s), 8,29 (1H, d), 8,20 (1H, d), 7,95 (1H, d), 7,21 (4H, m), 3,70 (1H, m), 2,17 (1H, m), 1,91 (4H, m), 1,34 (4H, m).

LCMS (termopulverización): m/z $[M]^+$ 376

**Preparación 53 : Éster bencílico del ácido sin-4-[(2-cloro-piridin-3-carbonil)amino]ciclohexanocarboxílico**



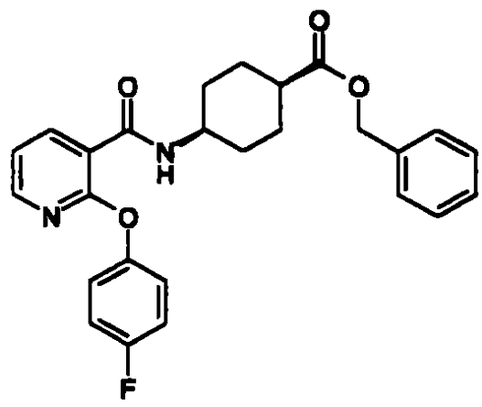
Se suspendió ácido 2-cloronicotínico (2 g, 12,69 mmol) en diclorometano (320 ml) en atmósfera de nitrógeno, se adicionó cloruro de oxalilo (3,32 ml, 38 mmol) y entonces se adicionó una gota de N,N-dimetilformamida y la mezcla se agitó durante 3 horas. Se evaporó el disolvente a vacío y el residuo se disolvió en diclorometano (110 ml). Se adicionó una solución del tosilato del éster bencílico del ácido sin-4-amino-ciclohexanocarboxílico (6,18 g, 15,23 mmol, véase preparación 62) y trietilamina (5,31 ml, 38 mmol) en diclorometano (50 ml) y la mezcla se agitó en atmósfera de nitrógeno durante 18 horas. La

mezcla de reacción se lavó con agua (2 veces 100 ml), con disolución saturada de cloruro de sodio (100 ml), se secó sobre sulfato de magnesio y se evaporó a vacío. Se disolvió el residuo en diclorometano (50 ml), se lavó con disolución de ácido cítrico (50 ml), con disolución saturada de cloruro de sodio se secó y se evaporó a vacío para dar éster bencílico del ácido sin-4-[(2-cloro-piridin-3-carbonil)amino]ciclohexanocarboxílico como un sólido naranja (4,80 g).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,43 (1H, m), 8,06 (1H, m), 7,31 (6H, m), 6,44 (1H, m), 5,11 (2H, s), 4,16 (1H, m), 2,37 (1H, m), 1,94 (2H, m), 1,73 (6H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 395, 397

**Preparación 54 : Éster bencílico del ácido sin-4-{[(2-(4-fluoro-fenoxi)-piridin-3-carbonil)amino]ciclohexanocarboxílico**



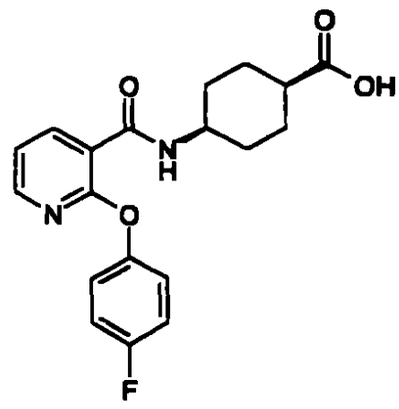
Se adicionó éster bencílico del ácido sin-4-[(2-cloro-piridin-3-carbonil)amino]ciclohexanocarboxílico (2 g, 5,36 mmol, véase Preparación 53) a una mezcla de 4-fluorofenol (661 mg, 5,90 mmol) y carbonato de cesio (3,495 g, 10,72 mmol) en N,N-dimetilformamida (20 ml) y se agitó en atmósfera de nitrógeno a 55°C durante 18 horas. Se repartió la mezcla entre agua (20 ml) y acetato

de etilo (30 ml) se lavó la solución orgánica con una disolución saturada de cloruro de sodio (20 ml), se secó sobre sulfato de magnesio y se evaporó a vacío. Se purificó el residuo por cromatografía sobre gel de sílice empleando metanol en diclorometano como eluyente (gradiente de 0:100 a 1:99) para dar éster bencílico del ácido sin-4-{[(2-(4-fluoro-fenoxi)-piridin-3-carbonil)amino]ciclohexanocarboxílico como un sólido blanco (1,078 g).

H NMR (400MHz, $CDCl_3$): δ 8,78 (1H, d), 8,17 (1H, d), 7,91 (1H, d), 7,28 (5H, m), 7,10 (5H, m), 5,04 (2H, s), 4,20 (1H, m), 2,52 (1H, m), 1,80 (8H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 449

**Preparación 55 : Ácido sin-4-{[(2-(4-fluoro-fenoxi)-piridin-3-carbonil)amino]ciclohexanocarboxílico**



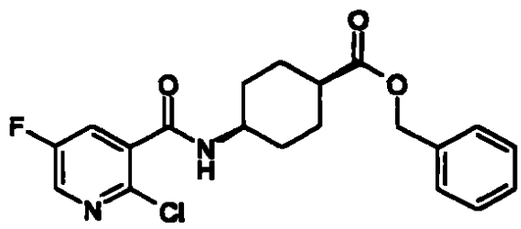
Se adicionó paladio al 10% sobre carbono (250 mg) a éster bencílico del ácido sin-4-{[(2-(4-fluoro-fenoxi)-piridin-3-carbonil)amino]ciclohexanocarboxílico (1,07 g, 5,36 mmol, véase Preparación 54) en metanol (25 ml). La mezcla se hidrógeno a 60 psi (4,14 bar) durante 30 minutos y a continuación se filtro a través de Arbocel®. Se lavó la torta del filtro con metanol y los filtrados combinados se evaporaron a vacío. El residuo se purificó por cromatografía sobre gel de sílice empleando metanol en

diclorometano (gradiente 0:100 a 1:99) para dar ácido sin-4-{[(2-(4-fluoro-fenoxi)-piridin-3-carbonil)amino]ciclohexanocarboxílico como un polvo blanco (363 mg).

$^1$H NMR (400MHz, $CD_3OD$): δ 8,39 (1H, d), 8,24 (1H, d), 8,17 (1H, d), 7,16 (5H, m), 4,10 (1H, m), 2,48 (1H, m), 1,89 (2H, m), 1,77 (6H, m)

LCMS (termopulverización): m/z $[M]^+$ 359

**Preparación 56 : Éster bencílico del ácido sin-4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]ciclohexanocarboxílico**



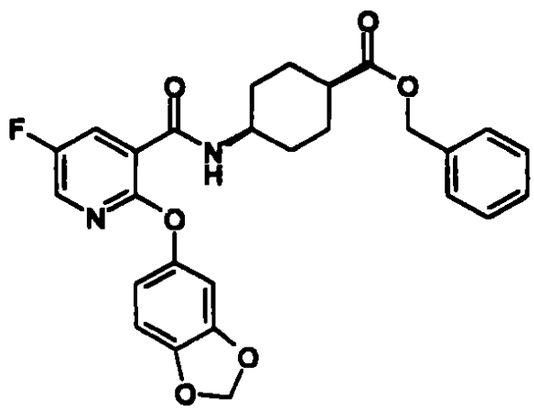
Se suspendió ácido 2-cloro-5-fluoronicotínico (1 g, 5,7 mmol, véase preparación 41) en diclorometano (80 ml) en atmósfera de nitrógeno Se adicionó cloruro de oxalilo (1,49 ml, 17,1 mmol) y a continuación una gota de N,N-dimetilformamida y la mezcla se agitó durante 1,25 horas. Se evaporó el disolvente a vacío y se disolvió el residuo en diclorometano (60 ml). Se adicionó una suspensión del tosilato del éster bencílico del ácido 4-amino-ciclohexanocarboxílico (2,77 g, 6,84 mmol, véase preparación 62) y trietilamina (2,38 ml, 17,1 mmol) en diclorometano (20 ml) y la mezcla se agitó en atmósfera de nitrógeno durante 18 horas. Se lavó la mezcla con agua (2 veces 75 ml) una disolución saturada de cloruro de sodio (100 ml), se secó sobre sulfato de magnesio anhidro y se evaporó a vacío. El residuo se purificó por cromatografía sobre gel de sílice empleando metanol en diclorometano como eluyente (gradiente de 0:100 a 1:99) para dar éster

bencílico del ácido sin-4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]ciclohexanocarboxílico como un sólido naranja (2,18 g).

$^1$H NMR (400MHz, $CD_3OD$): δ 8,30 (1H, d), 7,87 (1H, m), 7,33 (5H, m), 6,64 (1H, s), 5,12 (2H, s), 4,14 (1H, m), 2,55 (1H, m), 1,93 (2H, m), 1,79 (4H, m), 1,68 (2H, m).

LCMS (termopulverización): m/z $[M+NH_4]^+$ 408

**Preparación 57 : Éster bencílico del ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]-amino}ciclohexanocarboxílico**



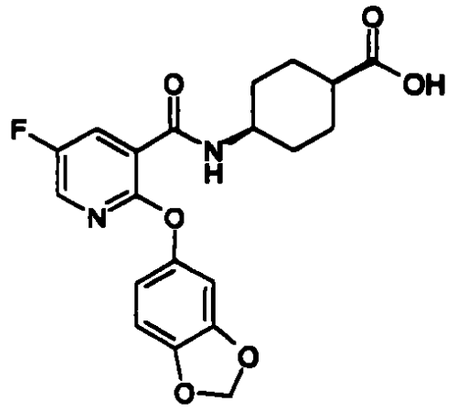
Se adicionaron carbonato de cesio (3,38 g, 10,38 mmol) y 3,4-metilendioxifenol (78 mg, 5,71) a una solución del éster bencílico del ácido sin-4-[(2-cloro-5-fluoro-piridin-3-carbonil)amino]ciclohexanocarboxílico (2,03 g, 5,19 mmol, véase Preparación 56) en N,N-dimetilformamida (20 ml) y la mezcla se agitó en atmósfera de nitrógeno durante 18 horas a 55°C. Se repartió la mezcla entre agua (30 ml) y acetato de etilo (30 ml), se lavó la solución orgánica con una disolución saturada de cloruro de sodio (30 ml), se secó sobre sulfato de magnesio anhidro y se evaporó a vacío. El residuo se purificó se purificó por cromatografía sobre gel de sílice usando dicl rometano como eluyente para dar éster bencílico del

ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]amino}ciclohexanocarboxílico como un sólido naranja (2,07 g)

$^1$H NMR (400MHz, $CDCl_3$): δ 8,34 (1H, m), 8,06 (1H, m), 8,00 (1H, m), 7,31 (5H, m), 6,80 (1H, d), 6,65 (1H, m), 6,59 (1H, m), 6,00 (2H, s), 5,09 (2H, s), 4,19 (1H, m), 2,34 (1H, m), 1,80 (8H, m).

LCMS (electropulverización): m/z $[M+Na]^+$ 515

**Preparación 58 : Ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]amino}ciclohexanocarboxílico**



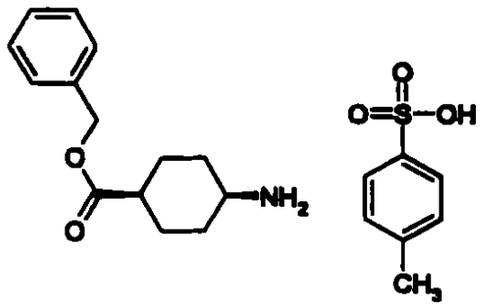
Se adicionó paladio sobre carbono al 10% (50 mg) a éster bencílico del ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]amino}ciclohexanocarboxílico (200 mg, 0,406 mmol, véase Preparación 57) en metanol (5 ml). La mezcla se hidrógeno a 60 psi (4,14 bar) durante 2 horas y a continuación se filtro a través de Arbocel®. Se lavó la torta del filtro con metanol y los filtrados combinados se evaporaron a vacío. El residuo se purificó por cromatografía sobre gel de sílice empleando metanol en diclorometano (2:98) para dar ácido sin-4-{[2-(benzo[1,3]dioxol-5-iloxi)-5-fluoro-piridin-3-carbonil]amino}ciclohexanocarboxílico como un sólido

blanco (50 mg).

$^1$H NMR (400MHz, $CDCl_3$): δ 8,30 (1H, m), 8,01 (2H, m), 6,79 (1H, d), 6,66 (1H, d), 6,57 (1H, m), 5,97 (2H, s), 4,18 (1H, m), 2,53 (1H, m), 1,79 (8H, m).

LCMS (electropulverización): m/z [M+Na]$^+$ 425

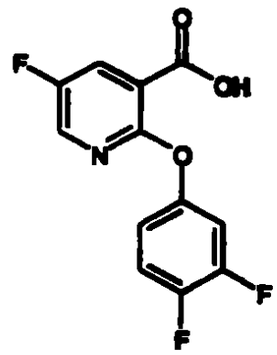
**Preparación 59 : Tosilato del éster bencílico del ácido sin-4-amino-ciclohexanocarboxílico**



Se disolvió ácido 4-amino-ciclohexanocarboxílico (10 g, 69,9 mmol) en ácido clorhídrico 1N (70 ml, 70 mmol) y la mezcla se evaporó a vacío. El residuo se secó por destilación azeotrópica con tolueno ( 2 veces 50 ml). Se adicionaron alcohol bencílico (36 ml, 0,25 mmol), tolueno (220 ml) y ácido p-toluenosulfónico hidrato (15,9 g, 83,6 mmol) y la mezcla se calentó a reflujo durante 24 horas usando una trampa de Dean Starke. Se enfrió a temperatura ambiente la mezcla de reacción y se añadió éter dietílico (100 ml). se aisló el sólido formado por filtración y se lavó con éter dietílico y se secó a vacío a 40°C para dar el compuesto del título (27,3 g).

LCMS (electropulverización): m/z [M+Na]$^+$ 283

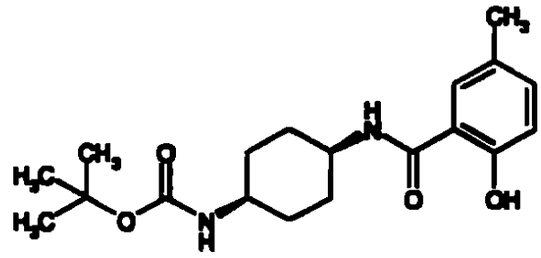
**Preparación 60: Ácido 2-(3,4-Difluoro-fenoxi)-5-fluoro-nicotínico**



Se secó sobre sulfato de magnesio una solución de 3,4-difluorofenol (29,25 g, 225 mmol) en dioxano (300 ml), después se filtró. Se añadieron 2-cloro-5-fluoronicotinoato de etilo (J. Med. Chem., 1993, 36(18), 2676-88) (30,6 g, 150 mmol) y carbonato de cesio recién secado (73,2 g, 225 mmol) y la reacción se agitó a reflujo durante 18 horas. La mezcla enfriada se concentró a vacío, el residuo se repartió entre agua (1500 ml) y éter (1500 ml), y las capas se separaron. La fase acuosa se extrajo adicionalmente con éter y las soluciones orgánicas combinadas se lavaron con solución saturada de bicarbonato de sodio, agua, después salmuera, se secó sobre sulfato de magnesio y se evaporó a vacío para dar un aceite marrón (48,4 g). Se agitó enérgicamente una mezcla de este éster intermedio y una solución de hidróxido de litio 1N (450 ml), en tetrahidrofurano (450 ml), a temperatura ambiente durante 18 horas. El tetrahidrofurano se separó a vacío y la solución acuosa residual se aciduló a pH 5 utilizando ácido clorhídrico 2N (aproximadamente 150 ml). La solución se lavó con éter (2 veces) y después se aciduló por adición de más ácido clorhídrico 2N (150 ml). El precipitado resultante se filtró y se secó para proporcionar el compuesto del título como un sólido blanco (25,92 g).

$^1$H NMR (400 MHz, $CD_3OD$): δ 6,94 (1H, m), 7,10 (1H, m), 7,25 (1H, dd), 8,14 (2H, m).

**Preparación 61: Éster terc-butílico del ácido sin-[4-(2-hidroxi-5-metil-benzoilamino)-ciclohexil]-carbámico**

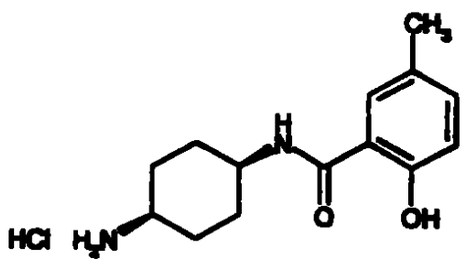


Se añadieron base de Hünig (8,72 g, 67,5 mmol) seguido por hidrato de 1-hidroxibenzotriazol (6,99 g, 51,75 mmol) a una solución de la amina procedente de la preparación 42B (9,64 g, 45 mmol) en diclorometano (110 ml), y la suspensión se agitó durante 5 minutos. Después se añadieron en porciones hidrocloruro de 1-(3-dimetilamino-propil)-3-etilcarbodiimida (11,22 g, 58,5 mmol) seguido por ácido 5-metil-salicílico (6,33 g, 41,6 mmol), y la reacción se agitó a temperatura ambiente durante 48 horas. La mezcla se diluyó con diclorometano (200 ml), y se lavó con agua (250 ml). La capa acuosa se aciduló a pH 3 utilizando ácido clorhídrico 2M y se volvió a repartir con la capa orgánica. Esta fase orgánica se separó, se lavó con agua, se secó sobre sulfato de magnesio y se evaporó a vacío. El aceite naranja residual se trituró con acetato de etilo y después con éter, el sólido resultante se filtró, se lavó con éter y se secó a vacío para proporcionar el compuesto del título como un sólido cristalino blanco, (9,95 g).

$^1$H NMR (400 MHz, $CD_3OD$): δ 1,38 (9H, s), 1,55 (4H, m), 2,22 (3H, s), 3,40 (1H, m), 3,82 (1H, m), 6,66 (1H, m), 6,75 (1H, s), 7,15 (1H, d), 7,69 (1H, s), 8,38 (1H, d), 12,08 (1H, s).

LCMS (electropulverización): m/z $[M+Na]^+$ 371

**Preparación 62: Hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-5-metil-benzamida**

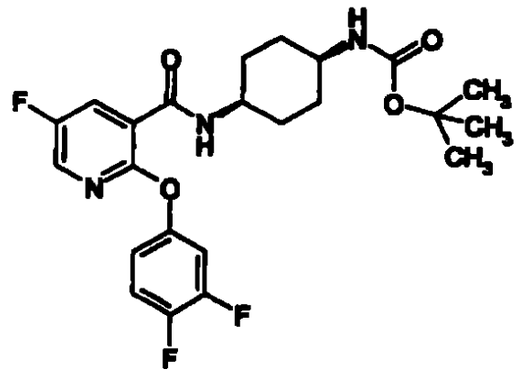


Una solución de la amina protegida procedente de la preparación 61 (9,8 g, 28,1 mmol) en diclorometano seco (600 ml) se enfrió a 4°C, y se purgó con nitrógeno. Esta solución se saturó con gas cloruro de hidrógeno, y después se agitó durante 3 horas más. La mezcla se concentró a vacío, y el residuo se destiló azeotrópicamente con diclorometano. El producto se trituró con éter, y el sólido resultante se filtró, y se secó para proporcionar el compuesto del título (7,6 g).

$^1$H NMR (400 MHz, DMSO$d_6$): δ 1,55-1,92 (8H, m), 2,10 (3H, s), 3,10 (1H, m), 3,90 (1H, m), 6,80 (1H, d), 7,15 (1H, d), 7,73 (1H, s), 8,00 (3H, s), 8,35 (1H, s), 11,35 (1H, s).

LCMS (electropulverización): m/z $[M+H]^+$ 249

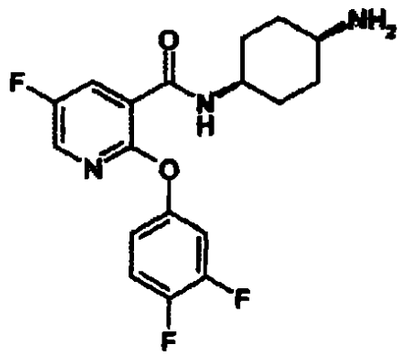
**Preparación 63: Éster terc-butílico del ácido sin-(4-{[2-(3,4-difluoro-fenoxi)-5-fluoro-piridin-3-carbonil]-amino}-ciclohexil)-carbámico**



Se mezcló el éster terc-butílico del ácido sin-{4-[(2-cloro-5-fluoro-piridin-3-carbonil)-amino]-ciclohexil}-carbámico (500 mg, 1,35 mmol, véase Preparación 43) con 3,4-difluorofenol (280 mg, 2 mmol) y carbonato de cesio (2,2 g, 6,7 mmol) en N-metilpirrolidinona (10 ml) y se calentó a 80°C durante 16 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y el disolvente se concentró a vacío. El residuo se disolvió en una disolución de hidróxido de sodio 1N y la disolución se extrajo con acetato de etilo (4 veces, 25 ml). Las disoluciones orgánicas combinadas se lavaron con una disolución de ácido cítrico al 10% (2 veces, 20 ml) y salmuera (20 ml), después se secó sobre sulfato de magnesio y se concentró a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando acetato de etilo en pentano como eluyente (50:50) para dar el éster terc-butílico del ácido sin-(4-{[2-(3,4-difluoro-fenoxi)-5-fluoro-piridin-3-carbonil]-amino}-ciclohexil)-carbámico como un sólido blanco (340 mg).

LCMS (electropulverización): m/z $[M+H]^+$ 466

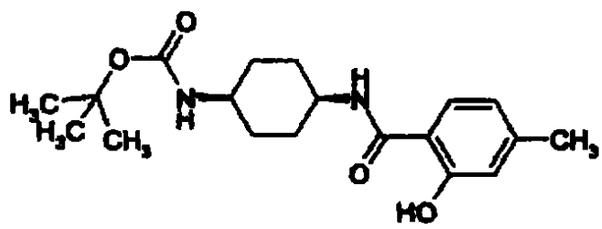
**Preparación 64: Sin-N-(4-Amino-ciclohexil)-2-(3,4-difluoro-fenoxi)-5-fluoro-nicotinamida**



Se disolvió el éster terc-butílico del ácido sin-(4-{[2-(3,4-difluoro-fenoxi)-5-fluoro-piridin-3-carbonil]-amino}-ciclohexil)-carbámico (11,25 g, 24,2 mmol, véase Preparación 63) en diclorometano (200 ml) a 0°C. Se burbujeó gas cloruro de hidrógeno dentro de la disolución con agitación durante 45 minutos y la mezcla se agitó a 0°C durante 20 minutos más. La mezcla de reacción se concentró a vacío y el residuo se disolvió en una disolución de hidróxido de sodio 1N. La disolución acuosa se extrajo con diclorometano. Las fases se separaron y la disolución orgánica se secó sobre sulfato de magnesio y se concentró a vacío para dar sin-N-(4-Amino-ciclohexil)-2-(3,4-difluoro-fenoxi)-5-fluoro-nicotinamida (7,36 g).

LCMS (electropulverización): m/z $[M+H]^+$ 366

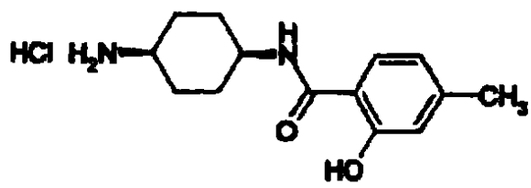
**Preparación 65: Éster terc-butílico del ácido sin-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-carbámico**



Se adicionó ácido 4-metilsalicílico (3,5 g, 23 mmol) a una mezcla del éster terc-butílico del ácido sin-(4-amino-ciclohexil)-carbámico (5,35 g, 25 mmol, véase Preparación 42-b) hidrato de 1-hidroxibenzotriazol (3,88 g, 28,8 mmol), hidrocloruro de 1,(3-dimetilaminopropil-3-etilcarbodiimida (6,23 g, 32,5 mmol) y diisopropiletilamina (4,84 g, 37,5 mmol) en diclorometano (65 ml). La mezcla se agitó a temperatura ambiente durante 72 horas y se diluyó con diclorometano (100 ml). Se añadió agua (150 ml) y la capa acuosa se aciduló a pH 3 por adición de ácido clorhídrico 2M. Las fases se separaron y la fase orgánica se lavó con agua (2 veces, 100 ml) y se secó sobre sulfato de magnesio. La disolución orgánica se concentró a vacío y el residuo se trituró con acetato de etilo caliente para dar el éster terc-butílico del ácido sin-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-carbámico (5,2 g).

LCMS (electropulverización): m/z [M+Na]⁺ 371

**Preparación 66: Hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-4-metil-benzamida**

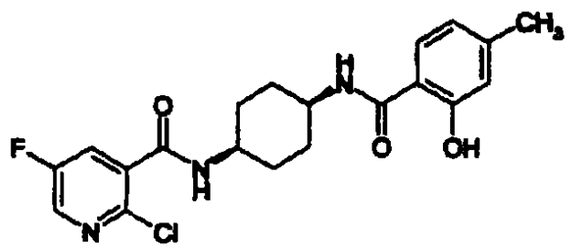



Se suspendió el éster terc-butílico del ácido sin-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-carbámico (5,1 g, 14,6 mmol, véase Preparación 65) en diclorometano (400 ml) y se enfrió a 0°C. La mezcla se purgó bajo nitrógeno y se burbujeó gas cloruro de hidrógeno dentro de la mezcla durante 10 minutos para dar una disolución saturada. La mezcla de reacción se agitó a 4°C durante 3 horas y después se concentró a vacío. El residuo se co-

evaporó con diclorometano (2 veces) y se trituró con éster dietílico. El producto obtenido se aisló por filtración y se lavó con éter dietílico para dar el hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-4-metil-benzamida como un sólido blanco (4,21 g).

LCMS (electropulverización): m/z $[M+H]^+$ 249

**Preparación 67: Sin-2-Cloro-5-fluoro-N-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-nicotinamida**

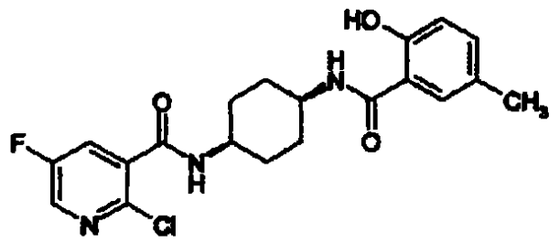



Se añadió hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1,68 g, 5,85 mmol) a hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-4-metil-benzamida (2 g, 7,02 mmol) (véase Preparación 66), ácido 2-cloro-5-fluoronicotínico (1,03 g, 5,85 mmol, véase Preparación 41), hidrato de 1-hidroxibenzotriazol (0,95 g, 7,02 mmol) y diisopropiletilamina (4,6 ml, 26,3 mmol) en diclorometano (50 ml) y la mezcla se agitó a temperatura ambiente bajo atmósfera de nitrógeno durante 16 horas. Se añadió más hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,56 g, 2,9 mmol) y la mezcla se agitó durante 2 horas más. La mezcla de reacción se repartió entre ácido clorhídrico 1N y diclorometano. Las fases se separaron y la capa acuosa se extrajo con diclorometano (2 veces). Las soluciones orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron a vacío. El producto obtenido se recristalizó de acetato de isopropilo para dar la sin-2-Cloro-5-fluoro-N-[4-(2-hidroxi-4-metil-benzoilamino)-ciclohexil]-nicotinamida como un sólido blanco

(1,3 g).

LCMS (electropulverización): m/z $[M+H]^+$ 406

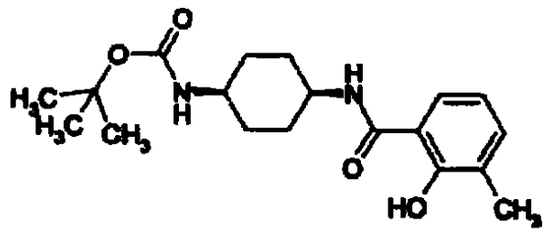
**Preparación 68: Sin-2-Cloro-5-fluoro-N-[4-(2-hidroxi-5-metil-benzoilamino)-ciclohexil]-nicotinamida**



Se añadió hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (245 mg g, 3,9 mmol) a una mezcla de hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-5-metil-benzamida (1 g, 3,5 mmol, véase Preparación 62), hidrato de 1-hidroxibenzotriazol (492 mg, 3,7 mmol) y ácido 2-cloro-5-fluoronicotínico (0,65 g, 3,7 mmol, véase Preparación 41), y trietilamina (0,96 ml, 8,75 mmol) en N,N-dimetilformamida (20 ml) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se concentró a vacío y el residuo se repartió entre acetato de etilo y agua. Las capas se separaron y la capa orgánica se secó sobre sulfato de magnesio y se concentró a vacío para dar sin-2-cloro-5-fluoro-N-[4-(2-hidroxi-5-metil-benzoilamino)-ciclohexil]-nicotinamida (1 g).

LCMS (electropulverización): m/z $[M+H]^+$ 406

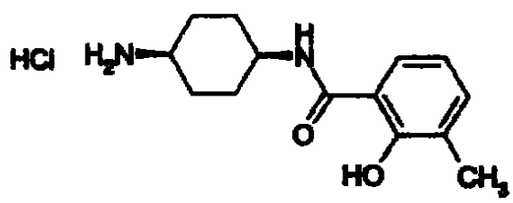
**Preparación 69: Éster terc-butílico del ácido sin-[4-(2-hidroxi-3-metil-benzoilamino)-ciclohexil]-carbámico**



Se añadió ácido 3-metilsalicílico (2,74 g, 18 mmol) a una mezcla del éster terc-butílico del ácido sin-(4-amino-ciclohexil)-carbámico (4,28 g, 20 mmol, véase Preparación 42-b), hidrato de 1-hidroxibenzotriazol (3,19, 24 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (4,97 g, 26 mmol) y diisopropiletilamina (3,87 g, 30 mmol) en diclorometano (45 ml). La mezcla se agitó a temperatura ambiente durante 40 horas y se repartió entre diclorometano y agua (75 ml). La capa acuosa se extrajo con diclorometano y las fases orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron a vació. El producto obtenido se aisló por filtración para dar el éster terc-butílico del ácido sin-[4-(2-hidroxi-3-metil-benzoilamino)-ciclohexil]-carbámico (1,14 g).

LCMS (electropulverización): m/z $[M+H]^+$ 349

**Preparación 70: Hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-3-metil-benzamida**

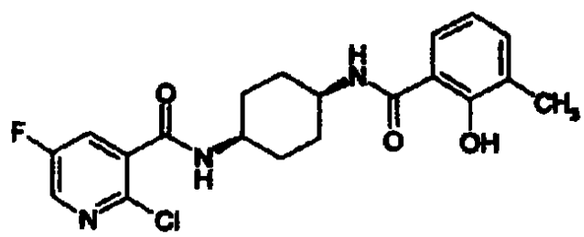


El éster terc-butílico del ácido sin-[4-(2-hidroxi-3-metil-benzoilamino)-ciclohexil]-carbámico (1,14 g, 3,3

mmol, véase Preparación 69) se suspendió en diclorometano (17 ml) y se enfrió a 0°C. Se burbujeó gas cloruro de hidrógeno a la mezcla durante 20 minutos y la mezcla se calentó hasta la temperatura ambiente y se agitó durante 16 horas. Se burbujeó cloruro de hidrógeno a la mezcla durante 15 minutos más y la mezcla se agitó a temperatura ambiente durante 15 minutos. Se añadió metanol a la mezcla de reacción y el disolvente se concentró a vacío para dar el hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-3-metil-benzamida (0,96 g).

LCMS (electropulverización): m/z $[M+H]^+$ 249

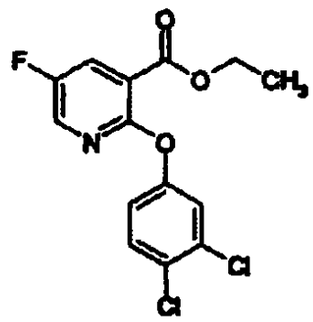
**Preparación 71: Sin-2-Cloro-5-fluoro-N-[4-(2-hidroxi-3-metil-benzoilamino)-ciclohexil]-nicotinamida**



Se añadió hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,81 g, 4,24 mmol) a una mezcla de hidrocloruro de sin-N-(4-amino-ciclohexil)-2-hidroxi-3-metil-benzamida (0,96 g, 3,4 mmol, véase Preparación 70), hidrato de 1-hidroxibenzotriazol (459 mg, 3,4 mmol), ácido 2-cloro-5-fluoronicotínico (497 mg, 2,8 mmol, véase Preparación 41), y diisopropilamina (2,2 ml, 12,7 mmol) en diclorometano (20 ml) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se concentró a vacío y el residuo se repartió entre diclorometano y agua. Las capas se separaron y la capa orgánica se lavó con una disolución de ácido cítrico al 10%, se secó sobre sulfato de magnesio y se concentró a vacío para dar la sin-2-cloro-5-fluoro-N-[4-(2-hidroxi-3-metil-

benzoilamino)-ciclohexil]-nicotinamida (0,71 g).
LCMS (electropulverización): m/z $[M+H]^+$ 406

**Preparación 72: Éster etílico del ácido 2-(3,4-dicloro-fenoxi)-5-fluoro-nicotínico**

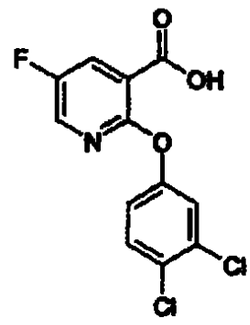


Se disolvieron 2-cloro-5-fluoronicotinato de etilo (5,09 g, 25 mmol, véase referencia J. Med. Chem., 1993, 36(18) 267-88) y 3,4-diclorofenol (6,11 g, 37,5 mmol) en 1,4 dioxano y la disolución se purgó con argón. Se añadió carbonato de cesio anhidro (12,21 g, 37,5 mmol) y la mezcla se calentó a reflujo durante 17 horas. La mezcla de reacción se repartió entre agua (300 ml) y acetato de etilo (300 ml). La capa acuosa se aciduló a pH 3 por adición de ácido clorhídrico 2M y las fases se separaron. La capa acuosa se extrajo con acetato de etilo (2 veces 100 ml) y las soluciones orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron a vacío para dar un aceite rojo. El producto aislado se redisolvió en acetato de etilo y se lavó con una disolución de carbonato de potasio al 5% (2 veces, 200 ml), una disolución de hidróxido de sodio 0,5M (2 veces, 200 ml) y una disolución de hidrógeno carbonato de sodio saturado (100 ml). La fase orgánica se secó sobre sulfato de magnesio y se concentró a vacío. El residuo se purificó por cromatografía sobre gel de sílice utilizando acetato de etilo en pentano como eluyente (4:96) para dar el éster etílico

del ácido 2-(3,4-dicloro-fenoxi)-5-fluoro-nicotínico como un aceite incoloro que cristalizó al dejarlo estar (4,95 g).

LCMS (electropulverización): m/z [M+Na]⁺ 352

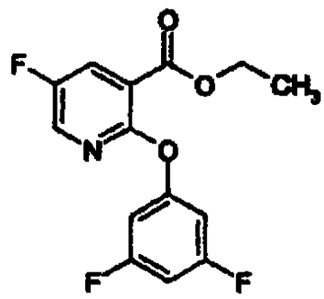
**Preparación 73: Ácido 2-(3,4-dicloro-fenoxi)-5-fluoro-nicotínico**



Se disolvió el éster etílico del ácido 2-(3,4-dicloro-fenoxi)-5-fluoro-nicotínico (4,9 g, 14,8 mmol, véase Preparación 72) en tetrahidrofurano (50 ml). Se añadieron agua (27 ml) e hidróxido de litio (1,56 g, 37,1 mmol) y la mezcla se agitó enérgicamente durante 7 horas. La mezcla de reacción se aciduló a pH5 por adición de ácido clorhídrico 2M y la mezcla se repartió entre acetato de etilo (200 ml) y agua (200 ml). La capa acuosa se aciduló a pH 3 por adición de ácido clorhídrico 2 M y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 veces, 50 ml) y las soluciones orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron a vacío para dar el ácido 2-(3,4-dicloro-fenoxi)-5-fluoro-nicotínico como un sólido blanco (4,4 g).

LCMS (electropulverización): m/z [M+Na]⁺ 348

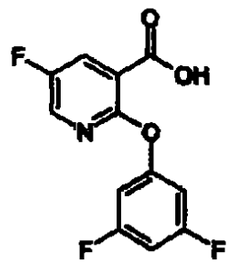
**Preparación 74: Éster etílico del ácido 2-(3,5-difluoro-fenoxi)-5-fluoro-nicotínico**



El compuesto del título se preparó a partir de 2-cloro-5-fluoronicotinato de etilo y 3,5-difluorofenol con un 23% de rendimiento siguiendo el procedimiento descrito en la Preparación 72.

LCMS (electropulverización): m/z $[M+Na]^+$ 371

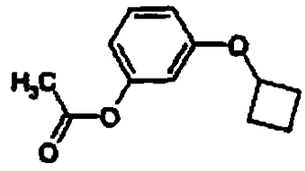
**Preparación 75: Ácido 2-(3,5-Difluoro-fenoxi)-5-fluoro-nicotínico**



El éster etílico del ácido 2-(3,4-dicloro-fenoxi)-5-fluoro-nicotínico (0,68 g, 2,25 mmol, véase Preparación 74) se disolvió en tetrahidrofurano (8 ml). Se añadieron agua (4,5 ml) e hidróxido de litio (239 mg, 5,7 mmol) y la mezcla se agitó enérgicamente durante 7 horas. La mezcla de reacción se aciduló a pH 5 por adición de ácido clorhídrico 2M y la mezcla se repartió entre acetato de etilo (50 ml) y agua (50 ml). La capa acuosa se aciduló hasta pH 3 por adición de ácido clorhídrico 2M y las fa-

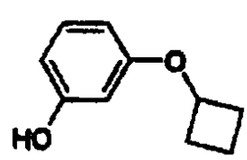
ses se separaron. La fase acuosa se extrajo con acetato de etilo (2 veces, 25 ml) y las soluciones orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron a vacío para dar el ácido 2-(3,5-difluoro-fenoxi)-5-fluoro-nicotínico como un sólido blanco (0,57 g).
LCMS (electropulverización): m/z $[M+H]^+$ 268

**Preparación 76: Éster 3-ciclobutoxi-fenílico del ácido acético**



Se mezcló el éster 3-hidroxi-fenílico del ácido acético (1 ml, 9 mmol) con ciclobutanol (0,58 g, 8 mmol), trifenilfosfina (2,1 g, 8 mmol) y azodicarboxilato de diisopropilo (1,57 ml, 8 mmol) en tetrahidrofurano (20 ml) a 0°C bajo una atmósfera de nitrógeno. La mezcla se calentó a temperatura ambiente y se agitó durante 16 horas. La mezcla de reacción se concentró a vacío, el residuo se purificó por cromatografía sobre gel de sílice utilizando acetato de etilo en pentano como eluyente (gradiente desde 0:100 hasta 15:85) para dar el éster 3-ciclobutoxi-fenílico del ácido acético (340 mg).
LCMS (electropulverización): m/z $[M+H]^+$ 207

**Preparación 77: 3-Ciclobutoxi-fenol**



Se disolvió el éster 3-ciclobutoxi-fenílico del áci-

do acético (340 mg, 1,65 mmol) en metanol (6 ml) y se añadió una disolución 1M de hidróxido de sodio (2 ml, 2 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 24 horas y después se aciduló con ácido clorhídrico 2M. La mezcla de reacción se extrajo con acetato de etilo y la disolución orgánica se secó sobre sulfato de magnesio y se concentró a vacío para dar 3-ciclobutoxi-fenol (300 mg).

LCMS (electropulverización): m/z $[M+H]^+$ 165

**Actividad *in vitro* de los derivados de nicotinamida**

La actividad inhibidora de PDE4 de los derivados de nicotinamida de fórmula (1) se determinó por la capacidad de los compuestos para inhibir la hidrólisis de cAMP a AMP por PDE4 (ver también referencia 1). Se incubó con PDE4, cAMP marcado con tritio. Después de la incubación, el AMP radiomarcado producido es capaz de unirse a perlas SPA de silicato de itrio. Estas perlas de SPA producen posteriormente luz que puede cuantificarse mediante recuento de centelleo. La adición de un inhibidor de PDE4 previene la formación de AMP a partir de cAMP y la cuentas disminuyen. La $IC_{50}$ de un inhibidor de PDE4 puede definirse como la concentración de un compuesto que conduce a una reducción del 50% en cuentas en comparación con los pocillos de control de PDE4 solamente (sin inhibidor).

Las propiedades anti-inflamatorias de los derivados de nicotinamida de la fórmula (1) se demuestran por su capacidad para inhibir la liberación de TNFα a partir de células mononucleares de sangre periférica humana (véase también referencia 2). Se recoge sangre venosa procedente de voluntarios sanos y las células mononucleares se purifican por centrifugación a través de lechos Histopaque (Ficoll). Se estimula la producción del TNFα procedente de estas células por adición de lipopolisacárido. Tras 18 horas de incubación en presencia de LPS, se separa el sobrenadante celular y se determina la concentración de

TNFα en el sobrenadante por ELISA. La adición de inhibidores de PDE4 reduce la cantidad de TNFα producido. Se determina una $IC_{5}$ que es igual a la concentración del compuesto que proporciona el 50% de inhibición de la producción de TNFα cuando se compara con los pocillos de control estimulados por LPS.

Todos los ejemplos fueron probados en el ensayo descrito anteriormente y se encontró que tenían una $IC_{5}$ (escrutinio de TNFα) inferior a 300 nM. Y para la mayoría de los compuestos ensayados, se encontró que tenían una $IC_{5}$ (escrutinio de TNFα) de incluso menos de 100 nM.

Con el fin de ilustrar, la siguiente tabla indica la IC. exacta (escrutinio de TNFα) de algunos ejemplos representativos de la presente invención:

| Ejemplo N° | $IC_{50}$ (nM) | Ejemplo N° | $IC_{50}$ (nM) |
|---|---|---|---|
| 6 | 23,50 | 8 | 22 |
| 14 | 13 | 16 | 0,28 |
| 17 | 8,50 | 20 | 113 |
| 22 | 156 | 23 | 7,80 |
| 25 | 8,50 | 26 | 5,40 |
| 27 | 39,50 | 28 | 217 |
| 30 | 2,60 | 41 | 4,90 |
| 44 | 91 | 47 | 0,28 |
| 48 | 1,66 | 51 | 2,09 |
| 54 | 2,80 | 56 | 1,90 |
| 57 | 13 | 58 | 3,50 |
| 66 | 18,30 | 69 | 49 |
| 72 | 1,10 | 76 | 49 |

| | | | |
|---|---|---|---|
| 79 | 25,50 | 80 | 7,40 |
| 81 | 30 | 85 | 28 |
| 88 | 114 | 91 | 37 |
| 92 | 185 | 93 | 5 |
| 95 | 3,20 | 97 | 30 |
| 100 | 56 | 106 | 3,60 |
| 110 | 14 | 116 | 25 |
| 123 | 21 | 129 | 30 |
| 135 | 74 | 137 | 16 |
| 152 | 0,20 | 12 | 1 |
| 155 | 0,09 | 156 | 0,14 |
| 157 | 2 | 159 | 4,60 |
| 172 | 4,30 | 173 | 2,10 |
| 174 | 0,014 | 178 | 0,15 |
| 183 | 0,07 | 186 | 0,20 |
| 187 | 0,006 | 190 | 0,06 |
| 193 | 9 | 194 | 0,07 |
| 195 | 0,40 | 197 | 1,80 |
| 199 | 0,70 | 200 | 0,05 |
| 201 | 0,30 | 203 | 7 |
| 204 | 0,30 | 205 | 0,55 |
| 208 | 0,09 | 210 | 13 |
| 213 | 0,20 | 217 | 0,30 |

**Referencias**

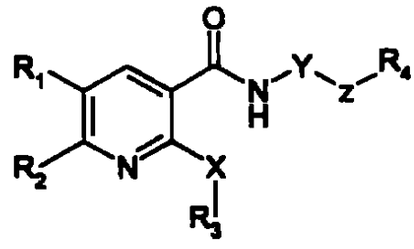
1. Thompson JW, Teraski WL, Epstein PM, Strada SJ., "Assay of nucleotidephosphodiesterase and resolution of

multiple molecular forms of the isoenzime", *Advances in cyclic nucleotides research*, editado por Brooker G, Greengard P, Robinson GA. Raven Press, New York 1979, 10, p. 69-92.

2. Yoshimura T, Kurita C, Nagao T, Usami E, Nakao T, Watanabe S, Kobayashi J, Yamazaki F, Tanaka H, Nagai H., "Effects of cAMP-phosphodiesterase isozyme inhibitor on cytokine production by lipopolysaccharide-stimulated human peripheral blood mononuclear cells", *Gen. Pharmacol.*, 1997, 29(4), p.63

**REIVINDICACIONES**

1. Un compuesto de fórmula (1):



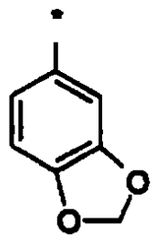
(1)

en la cual

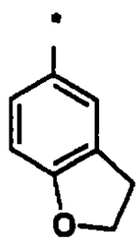
- ❖ $R_1$ y $R_2$ son cada uno un miembro independientemente seleccionado entre el grupo formado por átomo de hidrógeno, halo, ciano, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$),
- ❖ X es -O-, -S- o -NH-,
- ❖ $R_3$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_6$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes cada uno seleccionado independientemente entre el grupo formado por halo, ciano, trifluorometilo, trifluoroetilo, trifluorometoxi, trifluoroetoxi, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), tioalquilo($C_1$-$C_4$), -C(=O)$NH_2$, -C(=O)NH-(alquilo($C_1$-$C_4$)), hidroxi, -O-C(=O)alquilo($C_1$-$C_4$), -C(=O)-O-alquilo($C_1$-$C_4$) e hidroxialquilo($C_1$-$C_4$), cicloalquilo($C_3$-$C_6$) y cicloalquiloxi($C_3$-$C_6$), o

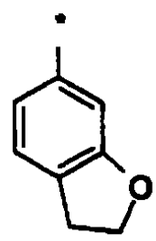
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1) a (1.4):



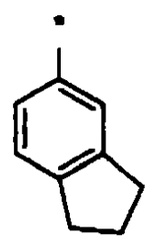
(1.1)



(1.2)



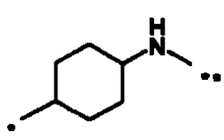
(1.3)



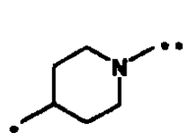
(1.4)

en la que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1) a (1.4) a la porción restante de fórmula (1),

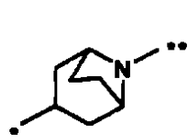
❖ Y es un miembro seleccionado entre el grupo formado por las fórmulas parciales (1.5) a (1.8):



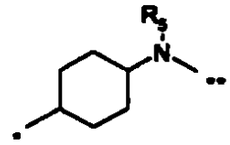
(1.5)



(1.6)



(1.7)

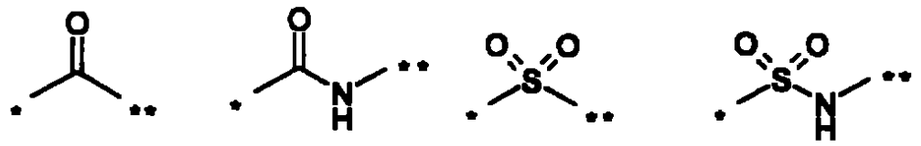


(1.8)

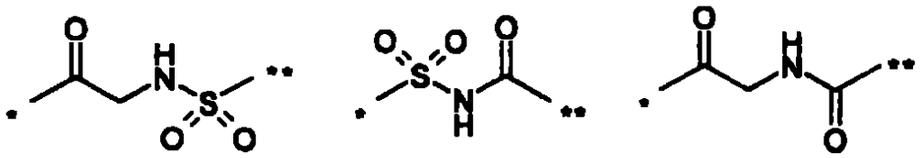
en la que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones Z restantes de fórmula (1),

y en que $R_5$ es un miembro seleccionado entre los grupos formados por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido independientemente con 1 a 3 sustituyentes cada uno seleccionado entre el grupo formado por halo, ciano, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxi, hidroxialquilo($C_1$-$C_4$), ácido carboxílico (-COOH), -C(=O)-O-alquilo($C_1$-$C_4$), haloalquilo($C_1$-$C_4$) y $-C(O)NH_2$,

❖ Z es un miembro seleccionado entre el grupo formado por las fórmulas parciales (1.9) a (1.15):



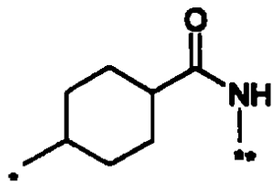
(1.9) (1.10) (1.11) (1.12)



(1.13) (1.14) (1.15)

en la que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.9) a (1.15) a las porciones Y restantes de fórmula (1) y "***" indica el punto de unión de cada fórmula parcial (1.9) a (1.15) a las porciones $R_4$ restantes de fórmula (1),

❖ o alternativamente Y-Z juntos representa un grupo de fórmula (1.16):



(1.16)

en la que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de fórmula (1) y "***" indica el punto de unión de la fórmula parcial (1.16) a las porciones $-R_4$ restantes de fórmula (1),

❖ y $R_4$ es un miembro seleccionado entre el grupo formado por:

(a) fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes

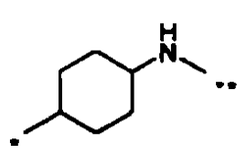
cada uno seleccionado independientemente entre el grupo formado por ácido carboxílico (-COOH), -C(=O)-O-alquilo-($C_1$-$C_4$), alquil($C_1$-$C_4$)-COOH, alquil($C_1$-$C_4$)-C(O)-O-alquilo-($C_1$-$C_4$), halo, ciano, -C(=O)$NH_2$, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), haloalquilo($C_1$-$C_4$), hidroxi e hidroxialquilo($C_1$-$C_4$), o (b) alquilo($C_1$-$C_6$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grupo formado por un grupo hidroxi, ácido carboxílico, -C(=O)-Oalquilo($C_1$-$C_4$), fenilo, naftilo, heteroarilo o cicloalquilo($C_3$-$C_6$), en que dichos grupos fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$) están opcionalmente sustituidos con 1 a 3 sustituyentes cada uno seleccionado independientemente entre el grupo formado por ácido carboxílico (-COOH), C(=O)Oalquilo($C_1$-$C_4$), halo, ciano, -C(=O)$NH_2$, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), haloalquilo($C_1$-$C_4$), hidroxi e hidroxialquilo($C_1$-$C_4$),

o, si es apropiado, sus sales y/o isómeros, tautómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos farmacéuticamente aceptables del mismo,

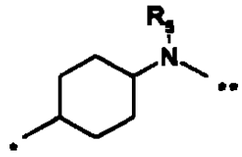
con la condición que:

1) cuando:

- $R_3$ se selecciona entre el grupo formado por átomo de hidrógeno, halo y metilo
- $R_2$ es un átomo de hidrógeno,
- X es -O-,
- $R_1$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_3$),
- Y es una fórmula parcial (1.5) o (1.8)



(1.5)



(1.8)

en la que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de fórmula (1), y en que $R_4$ es un miembro seleccionado entre los grupos formados por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_3$) o hidroxi, y

- Z es un radical -C(=O)-

entonces $R_4$ no puede ser:

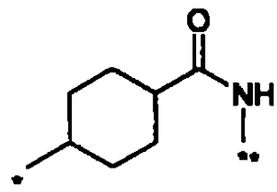
a) un cicloalquilo($C_3$-$C_8$) opcionalmente sustituido con alquilo($C_1$-$C_4$),

b) un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico están cada uno opcionalmente sustituidos con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_3$), o

c) un alquilo($C_2$-$C_4$) opcionalmente sustituido con un hidroxi, o con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_3$) o alcoxi($C_1$-$C_3$),

2) y cuando:

- $R_1$ se selecciona entre el grupo formado por un átomo de hidrógeno, halo y metilo,
- $R_2$ es un átomo de hidrógeno,
- X es -O-,
- $R_4$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_3$), y
- Y-Z representa una fórmula parcial (1.16):



(1.16)

en la que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones -$R_4$ restantes de fórmula (1),

entonces $R_4$ no puede ser:

a) un cicloalquilo($C_3$-$C_6$) o

b) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico están cada uno opcionalmente sustituidos con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_3$),

3) y cuando:

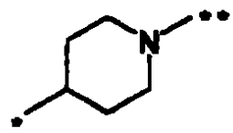
❖ $R_4$ se selecciona entre el grupo formado por átomo de hidrógeno, halo y metilo,

❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_1$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 ó 2 sustituyente(s) cada uno independientemente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_3$), y

❖ Y es una fórmula parcial (1.6):



(1.6)

en la que el símbolo "**" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "***" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de fórmula (1),

y

❖ Z es un radical -C(O)-,

entonces $R_4$ no puede ser un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S.

2. Un compuesto de acuerdo con la reivindicación 1 en el que:

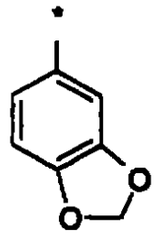
❖ $R_1$ y $R_2$ son cada uno un miembro independientemente seleccionado del grupo formado por un átomo de hidrógeno, halo, ciano, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$),

❖ X es -O-,

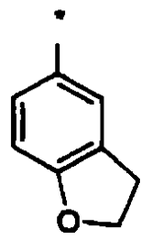
❖ $R_4$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo opcionalmente sustituido con 1 a 3 sustituyentes cada uno seleccionado independientemente del grupo formado por halo, ciano, trifluorometilo, trifluorometoxi, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$), tioalquilo($C_1$-$C_4$), -C(=O)$NH_2$, -C(=O)NH(alquilo($C_1$-$C_4$)), hidroxi, -O-C(=O)-alquilo($C_1$-$C_4$), -C(O)-O-alquilo($C_1$-$C_4$) e hidroxi alquilo($C_1$-$C_4$), cicloalquilo($C_3$-$C_8$) y cicloalquiloxi($C_3$-$C_8$), o

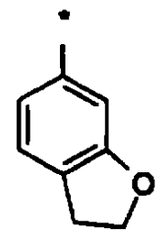
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1) a (1.4):



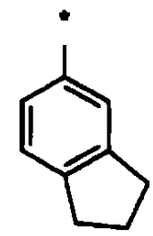
(1.1)



(1.2)



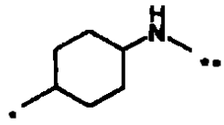
(1.3)



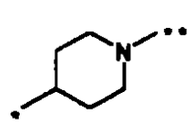
(1.4)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1) a (1.4) a la porción restante de fórmula (1),

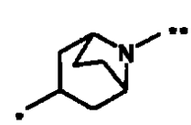
❖ Y es un miembro seleccionado del grupo formado por las fórmulas parciales (1.5) a (1.8):



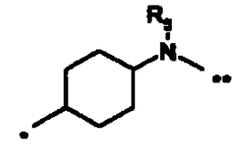
(1.5)



(1.6)



(1.7)



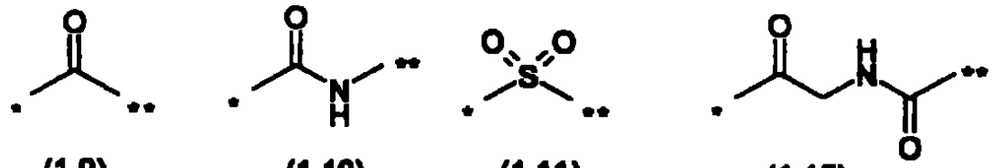
(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones Z restantes de fórmula (1),

y en que $R_r$ es un miembro seleccionado entre los grupos formados por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionado independientemente cada uno del grupo formado por halo, ciano, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxi, hidroxialquilo($C_1$-$C_4$), ácido carboxílico, -C(O)-O-alquilo($C_1$-$C_4$), haloalquilo($C_1$-$C_4$) y -C(=O)$NH_2$,

❖ Z es un miembro seleccionado del grupo formado por las

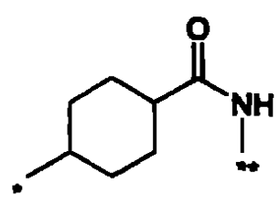
fórmulas parciales (1.9) a (1.11) y (1.15):



(1.9) (1.10) (1.11) (1.15)

en que el símbolo "*" indica los puntos de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones Y restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones $R_4$ restantes de fórmula (1),

❖ o alternativamente Y-Z juntos representan un grupo de fórmula (1.16):



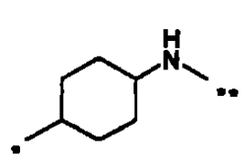
(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones $-R_4$ restantes de fórmula (1),

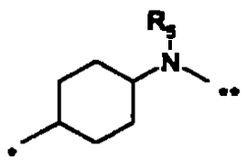
❖ y $R_4$ es un miembro seleccionado entre los grupos formados por:

fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionados independientemente cada uno del grupo formado por ácido carboxílico (-COOH), -C(=O)-O-alquilo($C_1$-$C_4$), alquil($C_1$-$C_4$)-COOH, alquil($C_1$-$C_4$)-C(=O)-O-alquilo($C_1$-$C_4$), halo, ciano, -C(=O)$NH_2$, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$),

haloalquilo($C_1$-$C_4$), hidroxi e hidroxialquilo($C_1$-$C_4$), o
(b) alquilo($C_1$-$C_4$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grupo formado por un grupo hidroxi, ácido carboxílico, -C(=O)-O-alquilo($C_1$-$C_4$), fenilo, naftilo, heteroarilo o cicloalquilo($C_3$-$C_{11}$), en que dichos grupos fenilo, naftilo heteroarilo y cicloalquilo($C_3$-$C_{11}$) está cada uno opcionalmente sustituido con 1 a 3 sustituyentes cada uno independientemente seleccionado del grupo formado por ácido carboxílico, C(C=O)Oalquilo($C_1$-$C_4$), halo, ciano, -C(=O)$NH_2$, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$), haloalquilo($C_1$-C ), hidroxi e hidroxialquilo($C_1$-$C_4$),
o, si es apropiado, sus sales farmacéuticamente aceptables y/o isómeros, tautómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos del mismo,
con la condición de que:
1) cuando:
❖ $R_1$ se selecciona del grupo formado por un átomo de hidrógeno, halo y metilo
❖ $R_2$ es un átomo de hidrógeno,
❖ X es -O-,
❖ $R_3$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y también está opcionalmente sustituido con 1 sustituyente seleccionado del grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$),
❖ Y es una fórmula parcial (1.5) o (1.8):



(1.5)



(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula par-

cial a las porciones Z restantes de fórmula (1), y en que $R_4$ es un miembro seleccionado entre el grupo formado por alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$) o hidroxi, y

❖ Z es un radical -C(=O)-

entonces $R_4$ no puede ser:

a) un cicloalquilo($C_3$-$C_8$) opcionalmente sustituido con alquilo($C_1$-$C_4$),

b) un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, estando dicho fenilo y anillo heterocíclico cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$), o

c) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S, estando el fenilo y el anillo heterocíclico cada uno opcionalmente sustituidos por hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_3$),

2) y cuando:

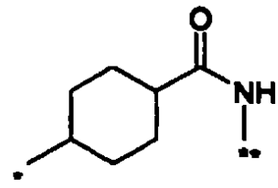
❖ $R_1$ se selecciona entre el grupo formado por un átomo de hidrógeno, halo y metilo,

❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_4$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$), y

❖ Y-Z representa una fórmula parcial (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones $R_4$ restantes de la fórmula (1),

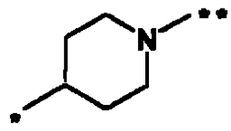
entonces $R_4$ no puede ser:

a) un cicloalquilo($C_3$-$C_6$) o

b) un alquilo($C_1$-$C_7$) opcionalmente sustituido con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S, estando el fenilo y el anillo heterocíclico cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

3) y cuando:

- ❖ $R_3$ se selecciona entre el grupo formado por un átomo de hidrógeno, halo y metilo,
- ❖ $R_5$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_1$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 ó 2 sustituyente(s) cada uno independientemente seleccionado entre el grupo formado por halo, alquilo($C_1$-$C_4$) y alcoxi($C_1$-$C_4$), y
- ❖ Y es una fórmula parcial (1.6):



(1.6)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de la fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de la fórmula (1), y

❖ Z es un radical -C(=O)-,

entonces $R_4$ no puede ser un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o por un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S.

3. Un compuesto de acuerdo con la reivindicación 1 en el que:

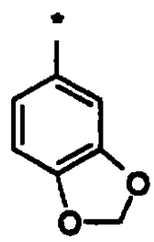
❖ $R_1$ y $R_2$ son cada uno un miembro independientemente seleccionado del grupo formado por un átomo de hidrógeno y halo,

❖ X es -O-,

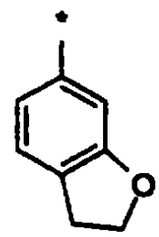
❖ $R_3$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo opcionalmente sustituido con 1 ó 2 sustituyentes seleccionado cada uno independientemente del grupo formado por halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), trifluorometilo, trifluorometoxi, cicloalquilo($C_3$-$C_6$), cicloalquiloxi($C_3$-$C_5$) y tioalquilo($C_1$-$C_4$), o

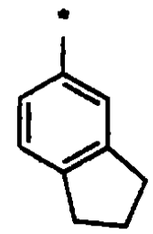
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1), (1,3) o (1.4):



(1.1)



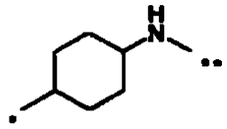
(1.3)



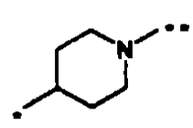
(1.4)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1), (1,3) o (1.4) a la porción restante de fórmula (1),

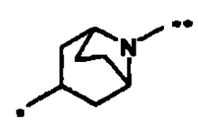
❖ Y es un miembro seleccionado del grupo formado por las fórmulas parciales (1.5) a (1.8):



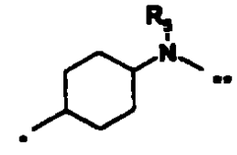
(1.5)



(1.6)



(1.7)

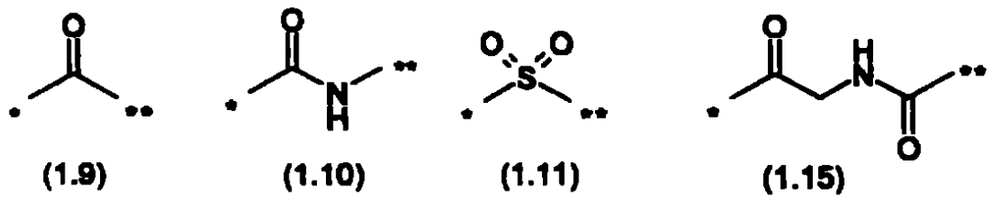


(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las porciones Z restantes de fórmula (1),

y en que $R_3$ es un grupo alquil($C_1$-$C_4$)-fenilo en que dicho fenilo está opcionalmente sustituido con 1 a 3 sustituyentes seleccionado cada uno independientemente del grupo formado por hidroxi, ácido carboxílico, C(=O)Oalquilo($C_1$-$C_4$) e hidroxialquilo($C_1$-$C_4$),

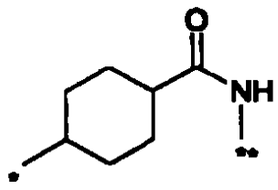
❖ Z es un miembro seleccionado entre el grupo formado por las fórmulas parciales (1.9) a (1.11) y (1.15):



(1.9) (1.10) (1.11) (1.15)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones restantes Y de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las porciones restantes $R_1$ de fórmula (1),

❖ o alternativamente Y-Z juntos representan un grupo de fórmula (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones $-R_4$ de fórmula (1),

❖ y $R_4$ es un miembro seleccionado entre los grupos formados por:

(a) fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$), cada uno opcionalmente sustituido con 1 a 3 sustituyentes seleccionado independientemente cada uno del grupo formado por un ácido carboxílico (-COOH), -C(O)-O-alquilo($C_1$-C ), alquil($C_1$-$C_4$)-COOH, alquil($C_1$-$C_4$)-C(=O)-O-alquilo($C_1$-$C_4$), halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxialquilo($C_1$-$C_4$) e hidroxi, o

(b) alquilo($C_1$-$C_8$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grupo formado por un grupo hidroxi, ácido carboxílico, -

C(=O)-O-alquilo($C_1$-$C_4$), fenilo, naftilo, heteroarilo o cicloalquilo($C_3$-$C_8$), en que dichos grupos fenilo, naftilo, heteroarilo y cicloalquilo($C_3$-$C_8$) está cada uno opcionalmente sustituidos con 1 a 3 sustituyentes seleccionado cada uno independientemente del grupo formado por ácido carboxílico (-COOH), C(=O)Oalquilo($C_1$-$C_4$), halo, alquilo($C_1$-$C_4$), alcoxi($C_1$-$C_4$), hidroxialquilo($C_1$-$C_4$) e hidroxi,

o, si es apropiado, sus sales y/o isómeros, tautómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos farmacéuticamente aceptables del mismo,

con la condición que:

1) cuando:

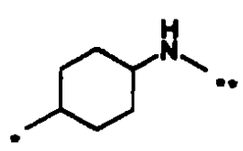
❖ $R_1$ está seleccionado del grupo formado por un átomo de hidrógeno y halo,

❖ $R_2$ es un átomo de hidrógeno,

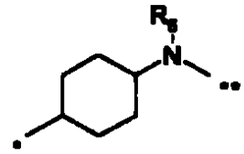
❖ X es -O-,

❖ $R_3$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado entre el grupo formado por halo y alquilo($C_1$-$C_3$),

❖ Y es una fórmula parcial (1.5) o (1.8):



(1.5)



(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones Z restantes de fórmula (1), y en que $R_3$ es un alquil($C_1$-$C_4$)-fenilo, en que dicho grupo fenilo está opcionalmente sustituido con hidroxi, y

❖ Z es un radical -C(=O)-

entonces $R_4$ no puede ser:

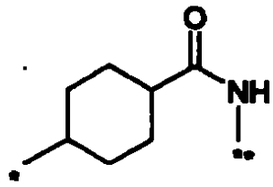
a) un cicloalquilo($C_3$-$C_8$) opcionalmente sustituido con alquilo($C_1$-$C_4$),

b) un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionado(s) independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_3$), o

c) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S, cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

2) y cuando:

- ❖ $R_2$ se selecciona del grupo formado por un átomo de hidrógeno y halo,
- ❖ $R_1$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_3$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado del grupo formado por halo y alquilo($C_1$-$C_2$), y
- ❖ Y-Z representa una fórmula parcial (1.16):




**(1.16)**

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las porciones restantes -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las porciones restantes -$R_4$ de fórmula (1),

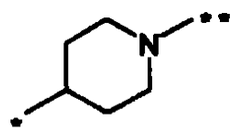
entonces $R_4$ no puede ser:

a) un cicloalquilo($C_3$-$C_8$) o

b) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un fenilo o un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) seleccionados independientemente entre N, O y S cuyo fenilo y anillo heterocíclico está cada uno opcionalmente sustituido con hidroxi, halo, alquilo($C_1$-$C_4$) o alcoxi($C_1$-$C_4$),

3) y cuando:

- ❖ $R_2$ está seleccionado del grupo formado por un átomo de hidrógeno y halo,
- ❖ $R_3$ es un átomo de hidrógeno,
- ❖ X es -O-,
- ❖ $R_1$ es un fenilo sustituido con un tioalquilo($C_1$-$C_4$) en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente(s) seleccionado entre el grupo formado por halo y alquilo($C_1$-$C_3$),
- ❖ Y es una fórmula parcial (1.6):



(1.6)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las porciones -NH- restantes de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las porciones restantes Z de fórmula (1), y

- ❖ Z es un radical -C(=O)-,

entonces $R_4$ no puede ser un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un anillo heterocíclico de 5 ó 6 miembros que incorpora 1 a 3 heteroátomo(s) independientemente seleccionados entre N, O y S.

4. Un compuesto de acuerdo con la reivindicación 1 en el que:

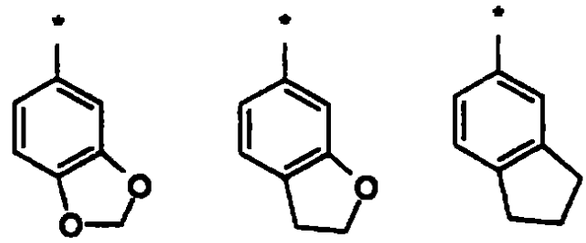
❖ $R_1$ es un átomo de hidrógeno o flúor y $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ R, es un miembro seleccionado de los grupos formados por:

(a) fenilo opcionalmente sustituido con 1 ó 2 sustituyentes seleccionados independientemente del grupo formado por flúor, cloro, bromo, metilo, etilo, metoxi, trifluorometilo, trifluorometoxi, ciclopropilo, ciclobutiloxi, y metiltio, o

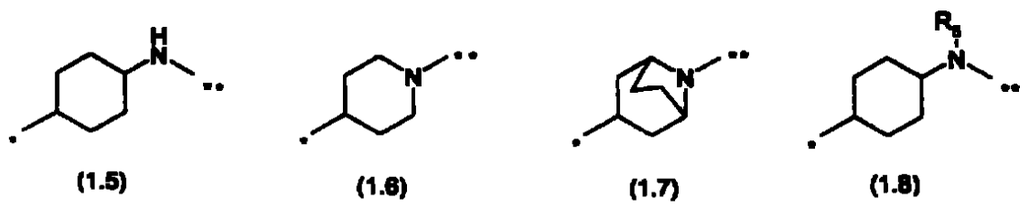
(b) los grupos bicíclicos conforme a una de las siguientes estructuras (1.1), (1,3) o (1.4):



(1.1) (1.3) (1.4)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.1), (1.3) o (1.4) a la porción restante de fórmula (1),

❖ Y es un miembro seleccionado del grupo formado por las fórmulas parciales (1.5) a (1.8):



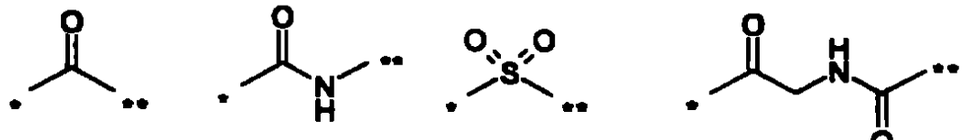
(1.5) (1.6) (1.7) (1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial (1.5) a (1.8) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de ca-

da fórmula parcial (1.5) a (1.8) a las restantes porciones Z de fórmula (1),

y en que $R_5$ es un grupo bencilo sustituido con un sustituyente hidroxi sobre el anillo

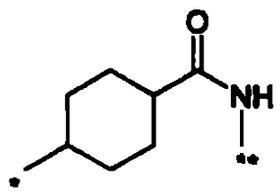
❖ Z es un miembro seleccionado del grupo formado por las fórmulas parciales (1.9) a (1.11) y (1.15):



(1.9) (1.10) (1.11) (1.15)

en que el símbolo "*" indica los puntos de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las restante porciones Y de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial (1.9) a (1.11) y (1.15) a las restantes porciones $R_4$ de fórmula (1),

❖ o alternativamente Y-Z juntos representa un grupo de fórmula (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones $-R_4$ de fórmula (1),

❖ y $R_2$ es un miembro seleccionado de los grupos formados por:

(a. fenilo opcionalmente sustituido con 1 a 3 sustitu-

yentes seleccionado independientemente cada uno del grupo formado por un ácido carboxílico, -C(=O)-O-metilo, flúor, cloro, metilo, iso-propilo, metoxi e hidroxi, o

(b) naftilo opcionalmente sustituido con un hidroxi,

(c) piridilo opcionalmente sustituido con un hidroxi o un grupo -C(=O)Ometilo,

(d) un cicloalquilo($C_3$-$C_6$) opcionalmente sustituido con un sustituyente seleccionado del grupo formado por hidroxi, -C(=O)-O-alquilo($C_1$-$C_4$) y alquil($C_1$-$C_4$)-C(=O)-O-alquilo($C_1$-$C_4$),

(e) alquilo($C_1$-$C_6$) opcionalmente sustituido con 1 ó 2 sustituyentes independientemente seleccionados entre el grupo formado por un hidroxi, ácido carboxílico, -C(=O)Ometilo, -C(=O)Oetilo, cicloalquilo($C_3$-$C_6$) y fenilo, en que dicho fenilo está opcionalmente sustituido con 1 ó 2 sustituyentes seleccionado cada uno independientemente del grupo formado por flúor, cloro, metilo, metoxi e hidroxi,

o, si es apropiado, sus sales y/o isómeros, tautómeros, solvatos, polimorfos, variaciones isotópicas y metabolitos farmacéuticamente aceptables de los mismos,

con la condición de que:

1) cuando:

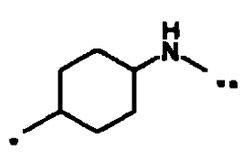
❖ $R_2$ está seleccionado del grupo formado por un átomo de hidrógeno y flúor,

❖ $R_1$ es un átomo de hidrógeno,

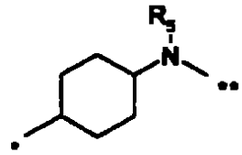
❖ X es -O-,

❖ $R_3$ es un fenilo sustituido con un -S-metilo en posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado del grupo formado por flúor, cloro, metilo y etilo,

❖ Y es una fórmula parcial (1.5) o (1.8):



(1.5)



(1.8)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de cada fórmula parcial a las restantes porciones Z de fórmula (1), y en que $R_3$ es un bencilo opcionalmente sustituido con hidroxi, y

❖ Z es un radical -C(=O)-

entonces $R_4$ no puede ser:

a un cicloalquilo($C_3$-$C_6$) sin sustituir,

b; un fenilo opcionalmente sustituido con hidroxi, flúor, cloro, metilo, iso-propilo o metoxi o alcoxi($C_1$-$C_4$),

c) un piridilo opcionalmente sustituido con un hidroxi, o

d) un alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi, o con un fenilo opcionalmente sustituido con hidroxi, flúor, cloro, metilo o metoxi,

2) y cuando:

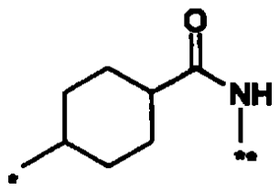
❖ $R_1$ está seleccionado del grupo formado por un átomo de hidrógeno y flúor,

❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_3$ es un fenilo sustituido con -S-metilo en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente seleccionado del grupo formado por flúor, cloro, metilo y etilo, y

❖ Y-Z representa una fórmula parcial (1.16):



(1.16)

en que el símbolo "*" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -NH- de fórmula (1) y "**" indica el punto de unión de la fórmula parcial (1.16) a las restantes porciones -$R_4$ de la fórmula (1),

entonces $R_4$ no puede ser:

a) un cicloalquilo($C_3$-$C_7$) o

b) un alquilo($C_1$-$C_7$) opcionalmente sustituido con un fenilo opcionalmente sustituido con hidroxi, flúor, cloro, metilo y metoxi,

3) y cuando:

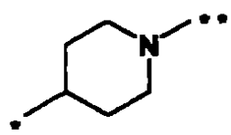
❖ $R_3$ está seleccionado del grupo formado por un átomo de hidrógeno y flúor,

❖ $R_2$ es un átomo de hidrógeno,

❖ X es -O-,

❖ $R_1$ es un fenilo sustituido con -S-metilo en la posición 3 ó 4 de dicho fenilo y está también opcionalmente sustituido con 1 sustituyente(s) seleccionado del grupo formado por flúor, cloro, metilo y etilo,

❖ Y es una fórmula parcial (1.6):

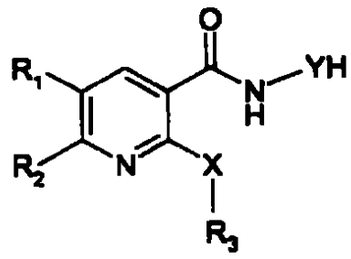


(1.6)

en que el símbolo "*" indica el punto de unión de cada fórmula parcial a las restantes porciones -NH- de fórmula (I) y "**" indica el punto de unión de cada fórmula parcial a las restantes porciones de Z de fórmula (1), y

❖ Z es un radical -C(=O)-,
entonces $R_4$ no puede ser alquilo($C_1$-$C_6$) opcionalmente sustituido con un hidroxi.

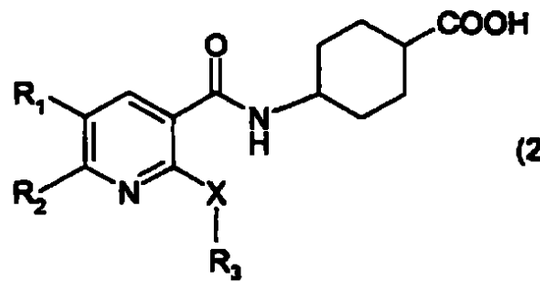
5. Un procedimiento para la preparación de un compuesto de fórmula (1, como se describe en la reivindicación 1, en la que Z representa un grupo de fórmula parcial (1.9) a (1.15), o una sal o forma derivada farmacéuticamente aceptable del mismo, caracterizado porque comprende la etapa de hacer reaccionar un compuesto de fórmula:



(2.1)

en la que $R_1$, $R_2$, X, $R_3$ e Y son como se definen el la reivindicación 1,
con el correspondiente derivado cloruro de $R_4$-sulfonilo en que Z representa un grupo de fórmula parcial (1.11), (1,12) o (1.14),
o con el correspondiente derivado ácido $R_4$-carboxílico en que Z representa un grupo de fórmula parcial (1.9), (1,13) o (1.15),
o con carbonildiimidazol en que Z representa un grupo de fórmula parcial (1.10).

6. Un procedimiento para la preparación de un compuesto de fórmula (1 como se describe en la reivindicación 1 en el que Y-Z representan juntos un grupo de fórmula parcial (1.16) o una sal o forma derivada farmacéuticamente aceptable del mismo, caracterizado porque comprende la etapa de hacer reaccionar un compuesto de fórmula:




(2.2)

en la que $R_1$, $R_2$, X y $R_4$ son como se definieron en la reivindicación 1,

con una amina que lleva un sustituyente $R_4$.

7. Una composición farmacéutica que incluye un compuesto de fórmula (1) como se define en la reivindicación 1 o una sal o forma derivada farmacéuticamente aceptable del mismo, junto con excipientes y/o aditivos farmacéuticamente inocuos acostumbrados.

8. Un compuesto de fórmula (1) como se define en la reivindicación 1 o una sal, forma derivada o composición farmacéuticamente aceptable del mismo, para uso como un medicamento.

9. Un compuesto de fórmula (1) como se define en la reivindicación 1 o una sal, forma derivada o composición farmacéuticamente aceptables del mismo, para uso en el tratamiento de enfermedades, trastornos y dolencias en los cuales están implicadas las isozimas PDE4.

10. Un compuesto de fórmula (1) como se define en la reivindicación 1 o una sal, forma derivada o composición farmacéuticamente aceptable del mismo, para uso en el tratamiento de enfermedades, trastornos y dolencias inflamatorias, respiratorias y alérgicas, y en el tratamiento de heridas.

11. Un compuesto de fórmula (1) como se define en la reivindicación 1 o una sal, forma derivada o composición farmacéuticamente aceptable del mismo, para uso en el tratamiento de enfermedades, trastornos y dolencias se-

leccionadas del grupo formado por:

- asma de cualquier tipo, etiología, o patogénesis, en particular asma que es un miembro seleccionado del grupo formado por asma atópica, asma no atópica, asma alérgica, asma bronquial atópica mediada por IgE, asma bronquial, asma esencial, asma verdadera, asma intrínseca provocada por alteraciones patofisiológicas, asma extrínseca provocada por factores ambientales, asma esencial de causa inaparente o desconocida, asma no atópica, asma bronquítica, asma enfisematosa, asma inducida por el ejercicio, asma inducida por alergenos, asma inducida por aire frío, asma ocupacional, asma infecciosa provocada por infección bacteriana, fúngica, protozoaria o vírica, asma no alérgica, asma incipiente y síndrome del niño jadeante,
- broncoconstricción crónica o aguda, bronquitis crónica, obstrucción de las vías respiratorias pequeñas, y enfisema,
- enfermedades obstructivas o inflamatorias de las vías respiratorias de cualquier tipo, etiología o patogénesis, en particular una enfermedad obstructiva o inflamatoria de las vías respiratorias que es un miembro seleccionado del grupo formado por neumonía eosinófila crónica, enfermedad pulmonar obstructiva crónica (COPD), COPD que incluye bronquitis crónica, enfisema pulmonar o disnea asociadas con la misma, CODP que está caracterizada por la obstrucción progresiva irreversible de las vías respiratorias, el síndrome de insuficiencia respiratoria del adulto (ARDS) y exacerbación de la hiperreactividad de las vías respiratorias consecuente a la terapia con otros fármacos,
- neumoconiosis de cualquier tipo, etiología o patogénesis, en particular neumoconiosis que es un miembro seleccionado del grupo formado por aluminosis o enfermedades de trabajadores de la bauxita, antracosis o asma

de los mineros, asbestosis o asma de los ajustadores de vapor, calicosis o enfermedad de los obreros del pedernal, ptilosis provocada por la inhalación del polvo procedente de las plumas de avestruz, siderosis provocada por la inhalación de partículas de hierro, silicosis o enfermedad de los molineros, bisinosis o asma del polvo del algodón y neumoconiosis del talco;

- bronquitis de cualquier tipo, etiología o patogénesis, en particular bronquitis que es un miembro seleccionado del grupo formado por bronquitis aguda, bronquitis laringotraqueal aguda, bronquitis araquídica, bronquitis catarral, bronquitis seudomembranosa, bronquitis seca, bronquitis asmática infecciosa, bronquitis productiva, bronquitis estafilococica o bronquitis estreptococica y bronquitis vesicular,
- bronquiectasia de cualquier tipo, etiología o patogénesis, en particular bronquiectasia que es un miembro seleccionado del grupo formado por bronquiectasia cilíndrica, bronquiectasia saculiforme, bronquiectasia fusiforme, bronquiectasia capilar, bronquiectasia quística, bronquiectasia seca y bronquiectasia folicular,
- rinitis alérgica estacional o rinitis alérgica perenne o sinusitis de cualquier tipo, etiología o patogénesis, en particular sinusitis que es un miembro seleccionado del grupo formado por sinusitis purulenta o no purulenta, sinusitis aguda o crónica y sinusitis etmoidal, frontal, maxilar o esfenoidal,
- artritis reumatoide de cualquier tipo, etiología o patogénesis, en particular artritis reumatoide que es un miembro seleccionado del grupo formado 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, en particular un trastorno relacionado con eosinófilos que es un miembro seleccionado del grupo formado por eosinofilia, eosinofilia de infiltración pulmonar, síndrome de Loffler, neumonía eosinofílica crónica, eosinofilia pulmonar tropical, aspergilosis bronconeumónica, aspergiloma, granulomas conteniendo eosinófilos, vasculitis granulomatosa alérgica o síndrome de Churg-Strauss, poliarteritis nodosa (PAN) y vasculitis necrotizante sistémica.
- dermatitis atópica, dermatitis alérgica, dermatitis de contacto, o eczema atópico o alérgico,
- urticaria de cualquier tipo, etiología o patogénesis, en particular urticaria que es un miembro seleccionado del grupo formado por urticaria mediada por el sistema inmune, urticaria mediada por el complemento, urticaria inducida por material urticariogénico, urticaria inducida por agentes físicos, urticaria inducida por estrés, urticaria idiopática, urticaria aguda, urticaria crónica, angioedema, urticaria colinérgica, urticaria por frío en la forma dominante autosómica o en la forma adquirida, urticaria de contacto, urticaria gigante y urticaria papular,
- conjuntivitis de cualquier tipo, etiología o patogénesis, en particular conjuntivitis, que es un miembro seleccionado del grupo formado por conjuntivitis actínica, conjuntivitis catarral aguda, conjuntivitis contagiosa aguda, conjuntivitis alérgica, conjuntivitis atópica, conjuntivitis catarral crónica, conjuntivitis purulenta y conjuntivitis primaveral,
- uveítis de cualquier tipo, etiología o patogénesis, en particular uveítes que es un miembro seleccionado del grupo formado por inflamación de toda o parte de la uvea, uveítis anterior, iritis, ciclitis, iridociclitis, uveítis granulomatosa, uveítis no granulomatosa,

uveítis facoantigénica, uveítis posterior, coroiditis; y corioretinitis,

- psoriasis;
- esclerosis múltiple de cualquier tipo, etiología o patogénesis, en particular esclerosis múltiple que es un miembro seleccionado del grupo formado por esclerosis múltiple progresiva primaria y esclerosis múltiple que remite con recidivas,
- enfermedades autoinmunes/inflamatorias de cualquier tipo, etiología o patogénesis, en particular una enfermedad auntoinmune/inflamatoria que es un miembro seleccionado del grupo formado por trastornos hematológicos autoinmunes, anemia hemolítica, anemia aplásica, anemia pura de glóbulos rojos, púrpura trombocitopénica idiopática, lupus eritematoso sistémico, policondritis, esclerodermа, granulomatosis de Wegner, dermatomiositis, hepatitis activa crónica, miastenia gravis, síndrome de Stevens-Johnson, síndrome de malabsorción intestinal idiopático, enfermedades inflamatorias del intestino autoinmunes, colitis ulcerativas, oftalmopatía endocrina, enfermedad de Grave, sarcoidosis, alveolitis, neumonitis de hipersensibilidad crónica, cirrosis biliar primaria, diabetes juvenil o diabetes melitus tipo I, queratoconjuntivitis sicca, queratoconjuntivitis epidémica, fibrosis pulmonar intersticial difusa o fibrosis pulmonar intersticial, fibrosis pulmonar idiopática, fibrosis quística, glomerulonefritis con y sin síndrome nefrótico, glomerulonefritis aguda, síndrome nefrótico idiopático, nefropatía de cambio mínimo, enfermedades inflamatorias/hiperproliferativas de la piel, pénfigo familiar benigno, pénfigo eritematoso, pénfigo foliáceo y pénfigo vulgar,
- prevención del rechazo de injertos alogénicos posteriores al transplante de órganos,
- enfermedad inflamatoria del intestino (IBD) de cual-

quier tipo, etiología o patogénesis, en particular enfermedad inflamatoria del intestino que es un miembro seleccionado del grupo formado por colitis colágena, colitis poliposa, colitis transmural, colitis ulcerativa y enfermedad de Crohn (CD),

- choque séptico de cualquier tipo, etiología o patogénesis, en particular choque séptico que es un miembro seleccionado del grupo formado por insuficiencia renal, insuficiencia renal aguda, caquexia, caquexia malárica, caquexia hipofisial, caquexia urémica, caquexia cardíaca, caquexia suprarrenal o enfermedad de Adison, caquexia cancerosa y caquexia como consecuencia de infección por el virus de inmunodeficiencia humana (HIV),
- daño hepático,
- hipertensión pulmonar de cualquier tipo, etiología o patogénesis incluyendo hipertensión pulmonar primaria/hipertensión esencial, hipertensión pulmonar secundaria a la insuficiencia cardíaca congestiva, hipertensión pulmonar secundaria a la enfermedad pulmonar obstructiva crónica, hipertensión venosa pulmonar, hipertensión arterial 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, en particular un trastorno del sistema nervioso central que es un miembro seleccionado del grupo formado por depresión, enfermedad de Alzheimer, enfermedad de Parkinson, empeoramiento de la memoria y el aprendizaje, disquinesia tardía, dependencia de fármacos, demencia arterioesclerótica y demencias que acompañan la corea de Huntington, enfermedad de Wilson, parálisis agitans, y atrofias talámicas,
- infección, especialmente infección por virus en que di-

chos virus aumentan la producción de TNF-α en su hospedador, o en que dichos virus son sensibles a la regulación en ascenso del TNF-α en su huésped de modo que su replicación u otras actividades vitales estén adversamente impactadas, incluyendo un virus que es un miembro seleccionado del grupo formado por HIV-1, HIV-2, y HIV-3, citomegalovirus (CMV), influenza, adenovirus y virus Herpes incluyendo Herpes zoster y Herpes simplex,

- infecciones por levaduras y hongos en que dichas levaduras y hongos son sensibles a la sobrerregulación por TNF-α o incitan la producción de TNF-α en su huésped, por ejemplo, meningitis fúngica, particularmente cuando se administra conjuntamente con otros fármacos de elección para el tratamiento de las infecciones sistémicas por levaduras y hongos, incluyendo pero no limitadas a, polimixinas, por ejemplo, Polimicina B, imidazoles, por ejemplo, clotrimazol, econazol, miconazol y ketoconazol, triazoles, por ejemplo, fluconazol e itranazol así como anfotericinas, por ejemplo, Anfotericina B y Anfotericina B liposomal,
- daño por reperfusión-isquemia, cardiopatía isquémica, diabetes autoinmune, autoinmunidad retinal, leucemia linfocítica crónica, infecciones HIV, lupus eritematoso, enfermedad del uréter y riñón, trastornos gastrointestinales y urogenitales y enfermedades de próstata,
- reducción de la formación de cicatrices en el cuerpo de animales y humanos, tales como la formación de cicatrices en la curación de heridas agudas, y
- psoriasis, otros usos dermatológicos y cosméticos, incluyendo antiflogísticos, suavizantes de la piel, y productos con actividades que aumenten la elasticidad y humedad de la piel.

12. El uso de un compuesto de la fórmula (1) como se define en la reivindicación 1 o de una sal, forma derivada o composición farmacéuticamente aceptable del mismo, para

la fabricación de un fármaco que tiene una actividad inhibitoria de PDE4.

13. El uso de un compuesto de fórmula (1) como se define en la reivindicación 1 o de una sal, forma derivada o composición farmacéuticamente aceptable del mismo, para la fabricación de un fármaco para el tratamiento de enfermedades, trastornos y dolencias inflamatorias, respiratorias y alérgicas, y en el tratamiento de heridas.

14. El uso de un compuesto de fórmula (1) como se define en la reivindicación 1 o de una sal, solvato o composición farmacéuticamente aceptable del mismo, para la fabricación de un fármaco para el tratamiento de enfermedades, trastornos y dolencias seleccionadas del grupo descrito en la reivindicación 11.

15. Un método de tratamiento de un mamífero, incluyendo un ser humano, con un inhibidor de PDE4 incluyendo el tratamiento de dicho mamífero con una cantidad efectiva de un compuesto de fórmula (1) como se define en la reivindicación 1 o con una sal, forma derivada o composición farmacéuticamente aceptable del mismo.

16. Un método de acuerdo con la reivindicación 13 en que la enfermedad, trastorno o dolencia a tratar está seleccionada del grupo descrito en la reivindicación 11.

**RESUMEN**

La invención se refiere a derivados de nicotinamida y a procedimientos para su preparación, a intermedios utilizados en su preparación, a composiciones que los contienen y a los usos de dichos derivados. Los derivados de nicotinamida de acuerdo con la presente invención son útiles en numerosas enfermedades, trastornos y dolencias, en particular en enfermedades, trastornos y dolencias inflamatorios, alérgicos, respiratorios, así como en heridas.

**RESUMEN**

La invención se refiere a derivados de nicotinamida y a procedimientos para su preparación, a intermedios utilizados en su preparación, a composiciones que los contienen y a los usos de dichos derivados. Los derivados de nicotinamida de acuerdo con la presente invención son útiles en numerosas enfermedades, trastornos y dolencias, en particular en enfermedades, trastornos y dolencias inflamatorios, alérgicos, respiratorios, así como en heridas.

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference PC22066A | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/IB 03/00439 | International filing date *(day/month/year)* 03.02.2003 | Priority date *(day/month/year)* 11.02.2002 |
| International Patent Classification (IPC) or both national classification and IPC C07D213/00 | | |
| Applicant PFIZER LIMITED | | |

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 5 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 consist of a total of sheets.

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

   - I ☒ Basis of the opinion
   - 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 Rule 66.2(a)(ii) 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 |
|---|---|
| 18.03.2003 | 13.04.2004 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Johnson, C Telephone No. +49 89 2399-8287 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/00439

## I. Basis of the report

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

**Description, Pages**

1-233 as originally filed

**Claims, Numbers**

1-18 as originally filed

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

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

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

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

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

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY EXAMINATION REPORT** International application No. PCT/IB 03/00439

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-4 (part), 9-15 (part), 17 (part), 18

   because:

   ☒ the said international application, or the said claims Nos. 17,18 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-4 (part), 9-15 (part), 17 (part) are so unclear that no meaningful opinion could be formed *(specify)*:

   **see separate sheet**

   ☒ the claims, or said claims Nos. 1-4 (part), 9-15 (part), 17 (part) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

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

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 1-18 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-18 |
| Industrial applicability (IA) | Yes: | Claims | 1-16 |
| | No: | Claims | |

2. Citations and explanations

   **see separate sheet**

**III. Non-establishment of opinion**

Due to a lack of clarity and support (Articles 5 and 6 PCT), claims 1-4, 9-15 and 17 have only been partially searched (see International Search Report for details). The examination has been made for searched subject matter only.
Claims 17 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**V. Reasoned statement**

Reference is made to the following document:
D1: WO 98/45268

**Novelty**

The present formula (1) overlaps with formula (I) of D1. In order for a general formula to be considered a novel selection of the prior art, it must be narrow, sufficiently removed from the specific embodiments of the prior art, and it must be a purposive selection illustrating a new technical teaching. The latter criterion can be achieved, for example, by selecting a specific combination of substituents which is not illustrated in the prior art and which leads to a novel effect. In the present case, in view of the extensive variability of the substituents $R_1$-$R_4$, Y and Z, it is not clear which combination of substituents could be considered as the basis for a new structural sub-group. Furthermore, even if a new structural sub-group could be identified (which is not the case), evidence that such a sub-group is a purposive selection leading to a novel effect is lacking - it is simply stated on p. 4 of the application that there is a need for additional PDE4 inhibitors showing an improved therapeutic index with possibly less adverse effects. The requirements for a novel selection are hence not fulfilled and claims 1-18 do not fulfil the requirements of Article 33(2) PCT.

top large

**Inventive step**

The objective technical problem shown to have been solved by the present compounds is that of providing further PDE4 inhibitors. It would be obvious to solve this problem by selecting compounds already known to have this activity from D1. Thus, in the absence of data showing that the present compounds have an activity which is unexpected in light of D1, claims 1-18 do not fulfil the

requirements of Article 33(3) PCT.

**Industrial applicability**

Claims 1-16 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claims 17 and 18 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

# INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 03/00439

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/455 A61P29/00 A61P11/00 C07D405/12 C07D213/82
C07D401/12 C07D451/04

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, 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. |
|---|---|---|
| X | WO 98 45268 A (CHAMBERS ROBERT JAMES ;KLEINMAN EDWARD FOX (US); CHENG JOHN BIN (U) 15 October 1998 (1998-10-15) cited in the application claims 1,19 | 1-18 |

☐ Further documents are listed in the continuation of box C.

☒ 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 |
|---|---|
| 7 April 2003 | 17/04/2003 |

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040 Tx. 31 651 epo nl

Authorized officer

INTERNATIONAL SEARCH REPORT

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17 and 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-4(part), 9-15(part),17(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

International Application No. PCT/IB 03 00439



Continuation of Box I.2

Claims Nos.: 1-4(part), 9-15(part),17(part)

Claims 1-4 encompass metabolites of the compounds of formula (1). No further information is given as to the structure of these metabolites, hence these claims cover all possible metabolic products, regardless of whether they have been identified or isolated. It is considered an undue and impossible burden for the skilled person to determine the scope of the claims insofar as the metabolites are concerned, as he would have to administer all compounds of formula (1) to all biological systems and thereafter isolate and identify all metabolites. Thus these claims do not fulfil the requirements of Article 6 PCT. On p. 36-37 of the description, a few exemplary metabolites are defined, namely N-oxide, glucuronide and sulfonate derivatives. However, in view of the large number of possible substituents in various positions, it is not clear which positions and substituents would in fact metabolically form glucuronide or sulfonate derivatives. Thus the scope of the claims in which the metabolites are glucuronide or sulfonated derivatives is not clear. In contrast, the metabolites which are N-oxides of the compounds of formula (1) are considered to be limited and clearly defined. Thus the metabolites have only been searched insofar as they are N-oxides of the compounds of formula (1).

Claims 9-15 and 17 refer to compositions containing a compound of formula (1) as defined in claim 1 or a derived form thereof. Derived forms have only been searched insofar as they are covered by the definition in claim 1 (excluding metabolites except N-oxides, vide supra).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9845268 A | 15-10-1998 | AU 738037 B2 | 06-09-2001 |
| | | AU 6227398 A | 30-10-1998 |
| | | BG 103725 A | 31-07-2000 |
| | | BR 9810733 A | 12-09-2000 |
| | | CN 1254335 T | 24-05-2000 |
| | | EP 0971894 A1 | 19-01-2000 |
| | | HR 980181 A1 | 28-02-1999 |
| | | HU 0001243 A2 | 28-09-2000 |
| | | WO 9845268 A1 | 15-10-1998 |
| | | JP 2000510481 T | 15-08-2000 |
| | | NO 994791 A | 01-12-1999 |
| | | NZ 337698 A | 27-07-2001 |
| | | PL 336148 A1 | 05-06-2000 |
| | | SK 132899 A3 | 12-09-2000 |
| | | TR 9902432 T2 | 21-01-2000 |
| | | US 2002111495 A1 | 15-08-2002 |
| | | US 6380218 B1 | 30-04-2002 |
| | | ZA 9802853 A | 04-10-1999 |

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Fecha (AMD): 2004-08-11 17:01:05
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

# REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

Firma Responsable: Claudia M Neva

Fecha:

437

440

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER 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, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

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

CERTIFICADÓ

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. G210434
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

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

BOGOTÁ, D.C. - COLOMBIA
XIMENA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.
09 MAR 2005
FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

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

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 [illegible]

**OLARTERAISBECK**

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

## Power of Attorney

The undersigned,

Pfizer Inc.

domiciled in

235 East 42nd Street, New York, NY 10017 USA

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

## Poder

El suscrito,

Pfizer Inc.

domiciliado en

235 East 42nd Street, New York, NY 10017 USA

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

Signature/Firma: _____

Date/Fecha: July 14, 2003

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

BOGOTÁ, D.C. - COLOMBIA
XIMENA E. [illegible]
NOTARIA ONCE (11) E.
FOTOCOPIA CORRESPONDE CON EL ORIGINAL
03

# 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


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## 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 Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in New York, New York, 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 legitima.

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):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 24th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGLAND AND FREEMAN

**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 — G210434

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.

Industria y Comercio
SUPERINTENDENCIA

443

2020
Bogotá, D.C.,

**FOLIO 440**

**Doctor(a):**
CARLOS R OLARTE
Apoderado
PFIZER INC.

| **REFERENCIA:** | | |
|---|---|---|
| | Radicación N° | 04-78332 |
| | Solicitud internacional | PCT/IB03/00439 |
| | Fecha inicio fase nacional | 11/09/2004 |
| | Trámite | 011 |
| | Evento | 379 |
| | Actuación | 416 |
| | Oficio N° | 1467 |
| | 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, 17 SET. 2004.

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

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