



Industria y Comercio
SUPERINTENDENCIA

PCT

SOLICITUD

PATENTE DE INVENCION

03-90558

21. EXPEDIENTE N° 03-90558

54. TÍTULO DERIVADOS DE BIPERIDINILO Y SU USO COMO INHIBIDORES DE RECEPTORES
DE QUIMIOCINA.

51. CLASIFICACIÓN INTERNACIONAL C. 070211/50, A61K31/4468

71. SOLICITANTE NOVARTIS AG

DOMICILIO BASILEA, SUIZA

74. APODERADO JIMENA ESCOBAR URIBE

22. BOGOTÁ, D. C. OCTUBRE 10, 2003

CF
SS

Industria y Comercio
SUPERINTENDENCIA

03 090558 00



SUPERINTENDENCIA Y COMERCIO
Folios: 147
Radicación: 03090558 00000000
Fecha (AMD): 2003-10-10 15:12:40
Trámite: 011 PCT-PATENT 379 FASE INICI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1



Patente de invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

2

S LICITANTE
(71)

Nombre: **NOVARTIS AG**

Dirección: Lichtstrasse 35

Nacionalidad o Domicilio: CH-4056 Basilea,
Suiza.

Lugar de Constitución: Suiza

Teléfono: 41613241111 Fax: 41613227532

E-mail

IDENTIFICACIÓN

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Número

3

REPRESENTANTE
AP DERADO
(74)

Nombre: **JIMENA ESCOBAR URIBE**

Dirección: Cra. 11A No. 94-76 (Of. 305)

Teléfono: 6 162051/61 Fax: 6 161889

E-mail: tm-patent@escobaruribe.com

IDENTIFICACIÓN

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Número 39.779.452T.P 68228

4

INVENTOR (ES)
(72)

Nombre: **VER ANEXOS**

Dirección:

Nacionalidad o domicilio:

5

PCT (86)

Solicitud Internacional No. PCT/EP02/03871

Fecha Abril 8, 2002

Publicación Internacional No. WO 02/081449 A1

Fecha Octubre 17, 2002

6 TÍTULO (54) DERIVADOS DE BIPIPERIDINIL Y SU USO COMO INHIBIDORES DE
RECEPTORES DE QUIMIOCINA.

7 Clasificación Internacional (51) C 07D21/48 , A61K31/4468

8 Prioridad

(33) País de Origen

GRAN BRETAÑA

(32) Fecha

Abril 9, 2001

(31) Número de Solicitud

0108876.4

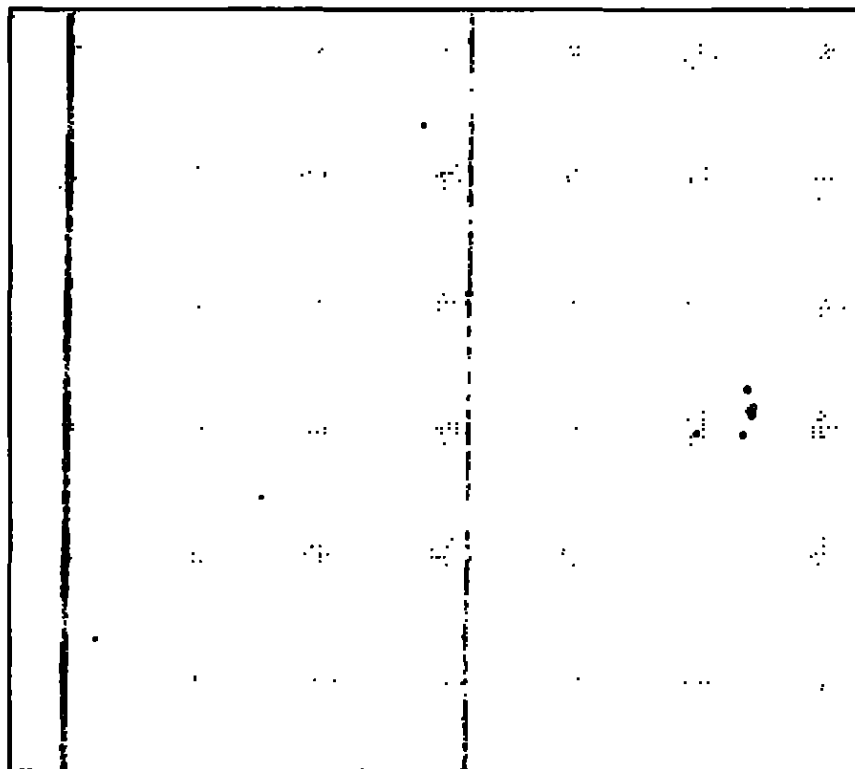
SI ☒ NO ☐

9 Comprobante de pago N. 03 - 63.519

Fecha Septiembre 8, 2003

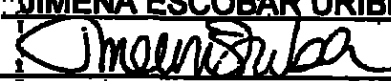
- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Prot. 17.398
- ☒ Poderes si fuere el caso Protocolo No. 17.398
- ☒ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ 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 de 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
- ☐ Otros

11 FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE: WIMENA ESCOBAR URIBE

FIRMA: 

C.G. 39.779.452 DE Usaquén T.P. 68.228

As. 2588/PCT

Radicacon : 03090558 00000000 Folios: 147
Fecha (AMB): 2003-10-10 15:12:40
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 000176089-2

RECIBO OFICIAL DE CAJA : 03 - 43,519
FECHA : SEPTIEMBRE 8 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4061886	05/09/2003	9,303,000.00

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

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 30003-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.
	TOTAL :	400,000.00

SOM: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXOS

INVENTORES

- 1.) **ALBERT, Rainer** ✓
(CH-4052 Basilea, Suiza);
- 2.) **BRUNS, Christian** ✓
(79110 Freiburg, Alemania);
- 3.) **NUNINGER, François**
(F-68270 Wittenheim, Francia);
- 4.) **STREIFF, Markus**
(CH-4127 Birsfelden, Suiza);
- 5.) **THOMA, Gebhard**
(D-79540 Lörrach, Alemania);
- 6.) **ZERWES, Hans-Günter**
(D-79539 Lörrach, Alemania).

Solicito expresamente a nombre de la sociedad **NOVARTIS AG**, sociedad constituida de conformidad con las leyes de Suiza, domiciliada en Lichtstrasse 35, CH-4056 Basilea, Suiza, el otorgamiento de Patente para la invención titulada **"DERIVADOS DE BIPERIDINILO Y SU USO COMO INHIBIDORES DE RESEPTORES DE QUIMIOCINA"**.

Clase: C 07


JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquen
T.P. 68.228

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
17 October 2002 (17.10.2002) ✓

PCT

(10) International Publication Number
WO 02/081449 A1 ✓(51) International Patent Classification²: C07D 211/58,
401/14, 211/96, 417/14, A61K 31/4468(CH) THOMA, Gebhard [DE/DE]; Talweg 32, D-79540
Lörrach (DE). ZERWES, Hans-Günter [DE/DE]; Holz-
gasse 55, D-79539 Lörrach (DE).

(21) International Application Number: PCT/EP02/03871 ✓

(74) Agent: BECKER, Konrad; Novartis AG, Corporate In-
tellectual Property, Patent & Trademark Dept., CH-4002
Basel (CH).

(22) International Filing Date: 8 April 2002 (08.04.2002) ✓

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0108876.4 9 April 2001 (09.04.2001) GB ✓(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH,
PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA,
US, UZ, VN, YU, ZA, ZW.(71) Applicant (for all designated States except AT, US): NO-
VARTIS AG [CH/CH]; Lichtstrasse 35, CH-4002 Basel
(CH).(84) Designated States (regional): Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, TR).(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN/
VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT];
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Published:

(72) Inventors; and

(75) Inventors/Applicants (for US only): ALBERT, Rainer
[AT/CH]; Wartenbergstrasse 21, CH-4052 Basel (CH).
BRUNS, Christian [DE/DE]; Ziegelhofstrasse 120, 79110
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rue de l'Entente, F-68270 Wittenheim (FR). STREIFF,
Markus [CH/CH]; Friedensgasse 15, CH-4127 Birsfelden— with international search report
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendmentsFor two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 02/081449 A1

(54) Title: BIPERIDINYL-DERIVATIVES AND THEIR USE AS CHEMOKINE RECEPTORS INHIBITORS

(57) Abstract: Piperidine derivatives of formula (I) as disclosed in the specification have interesting pharmaceutical properties e.g.
as CCR5 inhibitors.

5
6(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL TRATADO DE COOPERACION
EN MATERIA DE PATENTES (TCP)

OMPI

(19) Organización Mundial de la Propiedad Intelectual Oficina Internacional (43) Fecha de la Publicación Internacional: 17 de octubre de 2002 (17.10.2002)	TCP	(10) Número de la Publicación Internacional: WO 02/081449 A1
(51) Clasificación de Patente Internacional ¹ : C07D 211/58, 401/14, 211/56, 417/14, A61K 31/4468 (21) Número de Solicitud Internacional: PCT/EP02/03871 (22) Fecha de Presentación Internacional: 8 de abril de 2002 (08.04.2002) (25) Idioma de Presentación: Inglés (26) Idioma de Publicación: Inglés (30) Información de Prioridad: 0108876.4 9 de abril de 2001 (09.04.2001) GB (71) Solicitante: (para todos los Estados designados excepto AT, US): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4002 Basel (CH). (71) Solicitante: (solo para AT): NOVARTIS-ERFINDUGEN VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT]: Brunner Strasse 59, A-1230 Viena (AT). (72) Inventores; y (75) Inventores/Solicitantes (solo para US): ALBERT, Rainer [AT/CH]; Wartenbergstrasse 21, CH-4052 Basel (CH). BRUNS, Christian [DE/DE]; Ziegelhofstrasse 120, 79110 Freiburg (DE). NUNINGER, François [FR/FR]; 11, rue de l'Essence, F-68270 Wittenheim (FR). STREIFF, Markus [CH/CH]; Friedensgasse 15, CH-4127 Birsfelden (CH). THOMA, Gebhard [DE/DE]; Talweg 32, D-79540 Lörrach (DE). ZIERWES, Hans-Günter [DE/DE]; Holzgasse 55, D- 79539 Lörrach (DE).	(74) Agente: BECKER, Konrad; Novartis AG, Corporación de Propiedad Intelectual, Departamento de Patentes & Marcas, CH-4002 Basel (CH). (81) Estados Designados (nacionales): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW. (84) Estados Designados (regionales): Patente Eurspatica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR). Publicado: -con reporte de búsqueda internacional -antes del término del límite de tiempo para enmendar las reivindicaciones y para ser publicado en el evento de recepción de enmiendas. Para dos códigos de curias y otras abreviaturas, referir al "Guidance Notes on Codes and Abbreviations" que aparece al principio de cada derecho regular de la Gaceta TCP.	
(54) Título: DERIVADOS DE BIPERIDINILO Y SU USO COMO INHIBIDORES DE RECEPTORES DE QUIMIOCINA (57) Resumen: Los derivados de piperidina de la fórmula I, como se dan a conocer en la memoria descriptiva, tienen interesantes propiedades farmacéuticas, por ejemplo como inhibidores de CCR5.		

WO 02/081449 A1

PATENT COOPERATION TREATY

2588 BW 6 7

From the RECEIVING OFFICE

PCT

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

To:

Becker Konrad
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

Date of mailing
(day/month/year)

31 05. 2002

Applicant's or agent's file reference
4-31953A

IMPORTANT NOTIFICATION

International application No.

PCT/EP 02/ 03871 ✓

International filing date (day/month/year)

08/04/2002 ✓

Priority date (day/month/year)

09/04/2001 ✓

Applicant

NOVARTIS AG ET AL ✓

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.

3. ☐ Other: _____

P + TM Dept.

- 3. Juni 2002

as

APPL	M/D	F/L	PS/TS	
Kopien:				

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the Receiving Office

 European Patent Office, P.B. 5818 Patentaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

N. MAILLIARD
Tel.: (070) 340.28.55
The Hague

N. Mailliard

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 0 2 / 0 3 8 7 1
International Application No.(08 04 2002) 08 APR 2002
International Filing DateEUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"Applicant's or agent's file reference
(if desired) (12 characters maximum) 4-31953ABox No. I TITLE OF INVENTION
NOVEL PIPERIDINE DERIVATIVESBox No. II APPLICANT ☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Novartis AG
Lichtstrasse 35
4056 Basel
CHTelephone No.
+41 61 324 11 11Facsimile No.
+41 61 322 75 32

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:
CHState (that is, country) of residence:
CHThis person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
Brunner Strasse 59
1230 Vienna
AT

This person is:

☒ applicant only
☐ applicant and inventor
☐ inventor only (if this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
ATState (that is, country) of residence:
ATThis person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CHTelephone No.
+41 61 324 11 11Facsimile No.
+41 61 322 75 32

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) ALBERT, Rainer Wartenbergstrasse 21 4052 Basel CH	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: AT	State (that is, country) of residence: CH
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BRUNS, Christian Ziegelhofstrasse 120 79110 Freiburg DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) NUNINGER, François Rue de l'Entente 11 68270 Wittenhelm FR	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: FR	State (that is, country) of residence: FR
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) STREIFF, Markus Friedensgasse 15 4127 Blrsfelden CH	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: CH	State (that is, country) of residence: CH
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> THOMA, Gebhard Talweg 32 79540 Lörrach DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: DE	State <i>(that is, country)</i> of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> ZERWES, Hans-Günter Holzgasse 55 79539 Lörrach DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: DE	State <i>(that is, country)</i> of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
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- ☒ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|---|
| ☒ AE United Arab Emirates | ☐ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☒ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | ☐ SD Sudan |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SE Sweden |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SG Singapore |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SI Slovenia |
| ☒ BY Belarus | ☒ KR Republic of Korea | ☒ SK Slovakia |
| ☒ BZ Belize | ☒ KZ Kazakhstan | ☐ SL Sierra Leone |
| ☒ CA Canada | ☒ LC Saint Lucia | ☒ TJ Tajikistan |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☒ TM Turkmenistan |
| ☒ CN China | ☐ LR Liberia | ☒ TN Tunisia |
| ☒ CO Colombia | ☐ LS Lesotho | ☒ TR Turkey |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CU Cuba | ☒ LU Luxembourg | ☐ TZ United Republic of Tanzania |
| ☒ CZ Czech Republic | ☒ LV Latvia | ☒ UA Ukraine |
| ☒ DE Germany | ☒ MA Morocco | ☐ UG Uganda |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ US United States of America |
| ☒ DM Dominica | ☐ MG Madagascar | ☐ UZ Uzbekistan |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☒ EC Ecuador | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☒ EE Estonia | ☐ MW Malawi | ☒ ZA South Africa |
| ☒ ES Spain | ☒ MX Mexico | ☐ ZM Zambia |
| ☒ FI Finland | ☒ MZ Mozambique | ☒ ZW Zimbabwe |
| ☒ GB United Kingdom | ☒ NO Norway | |
| ☒ GD Grenada | | |
| ☒ GE Georgia | | |
| ☒ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

H
12**Supplemental Box***If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(1) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

Continuation of Box No. II

Novartis AG is applicant for all designated States with the exception of: AT (Austria) and US (USA)

- (i) *If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

Continuation of Box No. III

Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. is applicant for AT (Austria) only.

- (ii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

- (iii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor-applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

- (iv) *If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

- (v) *If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

- (vi) *If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	International application: receiving Office
item (1) 09 April 2001 (09.04.01)	0108876.4	GB		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)	Number	Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING																											
This international application contains: (a) the following number of sheets in paper form: request (including declaration sheets) : 7 description (excluding sequence listing part) : 29 claims : 4 abstract : 1 drawings : 0 Sub-total number of sheets : 41 sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) : 0 Total number of sheets : 41 (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">1. ☒ fee calculation sheet</td> <td style="width: 20%; text-align: right;">1</td> </tr> <tr> <td>2. ☒ original separate power of attorney</td> <td style="text-align: right;">1</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;"></td> </tr> <tr> <td>4. ☒ copy of general power of attorney; reference number, if any: AV. 36671 + 37586</td> <td style="text-align: right;">2</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;"></td> </tr> <tr> <td>6. ☒ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;">1</td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td style="text-align: right;"></td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;"></td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))</td> <td style="text-align: right;"></td> </tr> <tr> <td style="padding-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td> <td style="text-align: right;"></td> </tr> <tr> <td style="padding-left: 20px;">(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter</td> <td style="text-align: right;"></td> </tr> <tr> <td style="padding-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td> <td style="text-align: right;"></td> </tr> <tr> <td>10. ☐ other (specify):</td> <td style="text-align: right;"></td> </tr> </table>	1. ☒ fee calculation sheet	1	2. ☒ original separate power of attorney	1	3. ☐ original general power of attorney		4. ☒ copy of general power of attorney; reference number, if any: AV. 36671 + 37586	2	5. ☐ statement explaining lack of signature		6. ☒ priority document(s) identified in Box No. VI as item(s):	1	7. ☐ translation of international application into (language):		8. ☐ separate indications concerning deposited microorganism or other biological material		9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)		(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column		10. ☐ other (specify):	
1. ☒ fee calculation sheet	1																										
2. ☒ original separate power of attorney	1																										
3. ☐ original general power of attorney																											
4. ☒ copy of general power of attorney; reference number, if any: AV. 36671 + 37586	2																										
5. ☐ statement explaining lack of signature																											
6. ☒ priority document(s) identified in Box No. VI as item(s):	1																										
7. ☐ translation of international application into (language):																											
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(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column																											
10. ☐ other (specify):																											
Figure of the drawings which should accompany the abstract:	Language of filing of the international application:																										
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>																											
In the name of the applicants The representative 04.03.2002 BECKER, Konrad, AV 36671 + 37586																											

For receiving Office use only		
1. Date of actual receipt of the purported international application: 08 APR 2002 (08.04.02)	2. Drawings:	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	☐ received:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

PATENT COC

23.10.2002
4-31953A
Béatrice MolacVT
PCT
EP02/03871

2588

14
15

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

NOVARTIS AG
Corporate Intellectual Property
Attn. Becker, Konrad
Patent & Trademark Department
CH-4002 Basel
SWITZERLANDNOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

23/08/2002

Applicant's or agent's file reference

4-31953A

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 02/03871

International filing date

(day/month/year)

08/04/2002

Applicant

NOVARTIS AG

- 1.
- ☒
- The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

- 2.
- ☐
- The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

- 3.
- ☐
- With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 18 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 18 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Kerstin G^tz

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 18, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequences with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 18 may have to be furnished to the designated/elected Office, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-31953A	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 02/ 03871	International filing date (day/month/year) 08/04/2002	(Earliest) Priority Date (day/month/year) 09/04/2001
Applicant NOVARTIS AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search 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

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

BIPERIDINYL-DERIVATIVES AND THEIR USE AS CHEMOKINE RECEPTORS INHIBITORS

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 36.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

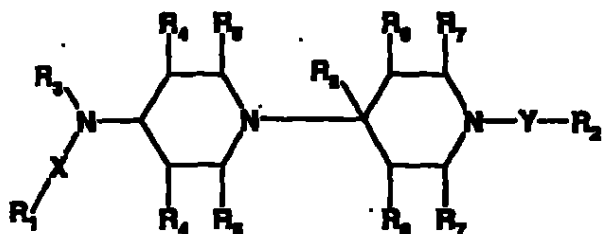
INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 02/03871

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Piperidine derivatives of formula I as disclosed in the specification have interesting pharmaceutical properties e.g. as CCR5 inhibitors.



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/03871

20

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/58 C07D401/14 C07D211/96 C07D417/14 A61K31/4468

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

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, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 66559 A (MCCOMBIE STUART W ;CLADER JOHN W (US); SCHERING CORP (US); JOSIEN) 9 November 2000 (2000-11-09) page 1, line 10 -page 2, line 22 claim 1	1-10
X	DE 196 43 331 A (THOMAE GMBH DR K) 23 April 1998 (1998-04-23) claim 1	1-4
A,P	WO 01 98268 A (DU PONT PHARM CO) 27 December 2001 (2001-12-27) claims 1,17	1,10
A	WO 00 76972 A (GUTHIKONDA RAVI N ;KIM DOOSEOP (US); OATES BRYAN (US); CHAPMAN KEV) 21 December 2000 (2000-12-21) claims 1,34	1,10
	— — — — — -/-	

☒ 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.

"Z" document member of the same patent family

Date of the actual completion of the international search

6 August 2002

Date of mailing of the international search report

23/08/2002

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,
Fax: (+31-70) 340-3016

Authorized officer

Fanni, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/03871

21

G.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 02 22592 A (SCHERING CORP) 21 March 2002 (2002-03-21) page 79; examples 286,287 claim 1	1
A	WO 98 11128 A (EBERLEIN WOLFGANG ; ENTZEROOTH MICHAEL (DE); HALLERMAYER GERHARD (DE) 19 March 1998 (1998-03-19) page 125; examples 565,566 claim 1 page 127; claims 584,587,588	1
A	WO 98 11082 A (DIMOUDIS NIKOLAOS ; FRIEBE WALTER GUNAR (DE); MICHAELIS UWE (DE); K) 19 March 1998 (1998-03-19) examples 20,27,32 claim 1	1

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.1

Although claim 10 is 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.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/03871

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. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
- 2. ☐ Claims Nos.:
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:
- 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 SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/03871

24

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0066559	A	09-11-2000	AU 4501000 A 17-11-2000
		BR 0010607 A 13-02-2002	
		CN 1349504 T 15-05-2002	
		CZ 20013941 A3 17-04-2002	
		EP 1175402 A1 30-01-2002	
		NO 20015365 A 03-01-2002	
		TR 200103213 T2 21-03-2002	
		WO 0066559 A1 09-11-2000	
DE 19643331	A	23-04-1998	DE 19643331 A1 23-04-1998
			AU 4867497 A 15-05-1998
			WO 9817646 A1 30-04-1998
WO 0198268	A	27-12-2001	AU 6860701 A 02-01-2002
			WO 0198268 A2 27-12-2001
WO 0076972	A	21-12-2000	AU 5472600 A 02-01-2001
			EP 1192133 A1 03-04-2002
			WO 0076972 A1 21-12-2000
			US 6358979 B1 19-03-2002
WO 0222592	A	21-03-2002	AU 9454701 A 26-03-2002
			WO 0222592 A2 21-03-2002
WO 9811128	A	19-03-1998	DE 19636623 A1 12-03-1998
			DE 19720011 A1 19-11-1998
			AU 721035 B2 22-06-2000
			AU 4119697 A 02-04-1998
			BG 103250 A 31-05-2000
			BR 9712023 A 31-08-1999
			CN 1230196 A 29-09-1999
			CZ 9900823 A3 16-06-1999
			EE 9900115 A 15-10-1999
			WO 9811128 A1 19-03-1998
			EP 0927192 A1 07-07-1999
			HR 970481 A1 31-08-1998
			JP 2000505100 T 25-04-2000
			NO 991130 A 05-05-1999
			NZ 334543 A 23-06-2000
			PL 331989 A1 16-08-1999
			SK 29799 A3 13-03-2000
			TR 9900537 T2 21-07-1999
			US 6344449 B1 05-02-2002
			ZA 9708083 A 17-12-1999
			HU 9904501 A2 28-04-2000
WO 9811082	A	19-03-1998	DE 19637043 A1 19-03-1998
			AU 741636 B2 06-12-2001
			AU 4384197 A 02-04-1998
			BR 9712818 A 21-12-1999
			CN 1237161 A , B 01-12-1999
			WO 9811082 A1 19-03-1998
			EP 0927174 A1 07-07-1999
			JP 2001504806 T 10-04-2001
			TR 9901200 T2 21-10-1999
			ZA 9708170 A 11-03-1999

PATENT COOPERATION TREATY

29.12.2002
4-31953A
Béatrice Molac

VT
PCT
EP02/03871

fu
...J...ORITY

2588
P + TM Dept.

31. Okt. 2002

PCT	M/D	F/L	PS/TS
Kopien:			

To:

Gros, Florent
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year) 29/10/2002

Applicant's or agent's file reference
4-31953A

REPLY DUE
within 2 / 00 months/days
from the above date of mailing

International application No.

PCT/EP 02/ 03871

International filing date (day/month/year)

08/04/2002

Priority date (day/month/year)

09/04/2001

International Patent Classification (IPC) or both national classification and IPC

C07D211/58

Applicant

NOVARTIS AG et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion 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

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09/08/2003

Name and mailing address of the IPEA/

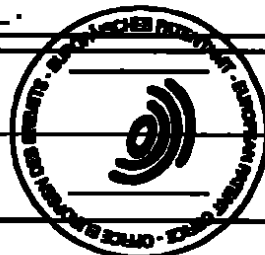


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Fax: (+49-89) 2399-4465

Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+49-89) 2399 2828



I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:
2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).
3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/_____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 4-31953A
International application No. PCT/EP 02/03871	International filing date (day/month/year) 08 April 2002 (08.04.02)	(Earliest) Priority date (day/month/year) 09 April 2001 (09.04.01)
Title of invention BIPIPERIDINYL-DERIVATIVES AND THEIR USE AS CHEMOKINE RECEPTORS INHIBITORS		

Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis AG Lichtstrasse 35 4056 Basel CH	Telephone No. +4161 324 11 11
	Facsimile No. +4161 322 75 32
	Teleprinter No.
	Applicant's registration No. with the Office
State (that is, country) of nationality: CH	State (that is, country) of residence: CH

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1230 Vienna AT	
State (that is, country) of nationality: AT	State (that is, country) of residence: AT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ALBERT, Rainer Wartenbergstrasse 21 4052 Basel CH	
State (that is, country) of nationality: AT	State (that is, country) of residence: CH

☒ Further applicants are indicated on a continuation sheet.

27
28

Sheet No. 2

International application No.
PCT/EP 02/03871

Continuation of Box No. II APPLICANT(S)

If none of the following sub-items is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BRUNS, Christian
Ziegelhofstrasse 120
79110 Freiburg
DE

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

NUNINGER, François
Rue de l'Entente 11
68270 Wittenheim
FR

State (that is, country) of nationality:
FR

State (that is, country) of residence:
FR

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

STREIFF, Markus
Friedensgasse 15
4127 Birsfelden
CH

State (that is, country) of nationality:
CH

State (that is, country) of residence:
CH

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

THOMA, Gebhard
Talweg 32
79540 Lörrach
DE

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

☒ Further applicants are indicated on another continuation sheet.

28
29

Sheet No. .3.

International application No.
PCT/EP 02/03871

Continuation of Box No. II APPLICANT(S)

If none of the following sub-items is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ZERWES, Hans-Günter
Holzgasse 55
79539 Lörrach
DE

State (that is, country) of nationality:
DE

State (that is, country) of residence:
DE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

29
30

Sheet No. 4

International application No.
PCT/EP 02/03871

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☒ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)

GROS, Florent
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CH

Telephone No.

+4161 324 11 11

Facsimile No.

+4161 322 75 32

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed

☐ as amended under Article 34

the claims ☐ as originally filed

☐ as amended under Article 19 (together with any accompanying statement)

☐ as amended under Article 34

the drawings ☐ as originally filed

☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English.....

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☒ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Sheet No. 5.

International application No.
PCT/EP 02/03871

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|---|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☒ other (specify): copy of general sub-authorisation |
| 4. ☐ copy of general power of attorney;
reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

In the name of the applicants
The representative



09.10.2002

GROS, Florent AV 36871 + 37586

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due
to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

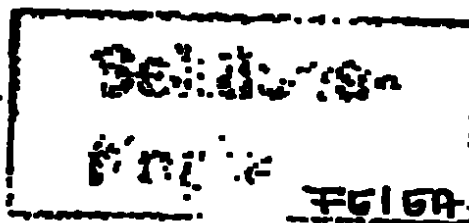
International application No. PCT/EP 02/03871		For International Preliminary Examining Authority use only	
Applicant's or agent's file reference 4-31953A		Date stamp of the IPEA	
Applicant Novartis AG et al.			
CALCULATION OF PRESCRIBED FEES			
1. Preliminary examination fee		EUR	1530.- P
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)		EUR	159.- H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box		EUR	1689.-
		TOTAL	
MODE OF PAYMENT			
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash		
☐ cheque	☐ revenue stamps		
☐ postal money order	☐ coupons		
☐ bank draft	☐ other (specify):		
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (This mode of payment may not be available at all IPEAs)			
☒ Authorization to charge the total fees indicated above.		IPEA/ <u>EP</u>	
☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.		Deposit Account No.: <u>2811 0031</u>	
		Date: <u>09.10.2002</u>	
		Name: <u>Novartis AG</u>	
		Signature: <u>E. Reichenauer</u>	



European Patent Office
D-80298 Munich

Thierry Holman
Intellectual Property Specialist

Novartis AG
Corporate Intellectual Property
CH-4002 Basel
Switzerland
Tel: +41 61 324 4428
Fax: +41 61 324 6104



Your Ref:

Our Ref:
HIO/GM

14 March 2000

General sub-authorisations

Dear Sirs,

I, Konrad Becker, authorised under the following General Authorisations:

Novartis AG	36671
Systemix Inc.	39505
Genetic Therapy Inc.	39407
Imutran Ltd.	39104
Biochemie GmbH	37946
The Scripps Research Institute	37685
Novartis Erfindungen Verwaltungsge. mbH	37686
Ciba-Geigy Japan Ltd.	37441
Novartis Consumer Health	37125

do hereby sub-authorise

Florent Gros (EPO code no. 87080)
c/o Novartis AG
Corporate Intellectual Property
Patent and Trademark Department
CH-4002 Basel
Switzerland

to represent the authorisers in all proceedings established by the EPC and to act for the authorisers in all patent transactions and to receive payments on their behalf. These sub-authorisations shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.

Yours faithfully
NOVARTIS AG

Dr. Konrad Becker
Head of Patent & Trademark Department

PATENT COOPERATION TREATY

2528

Corporate Intellectual Property				
29 Jan. 2003				
APPL	M/D	F/L	PS	Copy: 34

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
Gros, Florent
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 27/01/2003

Applicant's or agent's file reference
4-31953A.

IMPORTANT NOTIFICATION

International application No.
PCT/EP 02/ 03871

International filing date (day/month/year)
08/04/2002

Priority date (day/month/year)
09/04/2001

Applicant

NOVARTIS AG et al.

- The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/



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D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523636 epnu d
Fax: (+49-89) 2399-4465

Authorized officer

LAZARO ORTIZ A
Tel. (+49-89) 2399 2828



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 4-31953A	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IP/EA/416)
International application No. PCT/EP 02/ 03871	International filing date (day/month/year) 08/04/2002	Priority date (day/month/year) 09/04/2001
International Patent Classification (IPC) or national classification and IPC G07D211/58		
Applicant NOVARTIS AG et al.		

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

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

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

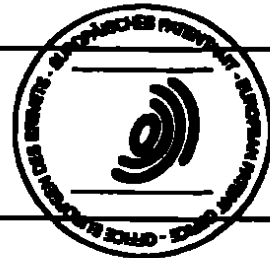
These annexes consists of a total of _____ sheets.

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

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 14/10/2002	Date of completion of this report 22/01/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523636 eponu d Fax: (+49-89) 2399-4465	Authorized officer GILLIE B R Tel. (+49-89) 2399 2828

Form PCT/IP/EA/409 (cover sheet) P20476 (October 2002)



I. Basis of the report

The basis of this International preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the International search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

**DOCUMENTO DE CESIÓN
ASSIGNMENT DOCUMENT**

El (los) suscrito (s), en su calidad de Inventor (es) de

declara (an) que cede (n) y traspasa (n) todos los derechos que les correspondan en y sobre el invento atrás mencionado a **NOVARTIS AG**, una compañía suiza constituida y existente bajo las leyes de Suiza, domiciliada en CH-4002 Basilea, Suiza, en cuanto se refiere a la República de Colombia.

The undersigned, as inventor (s) of

BIPIPERIDINYL-DERIVATIVES AND THEIR USE AS CHEMOKINE RECEPTORS INHIBITORS

hereby declare (s) that assign (s) all the rights in and to the aforementioned invention to **NOVARTIS AG**, a Swiss company incorporated and existing in conformity with the laws of Switzerland, domiciled at CH-4002 Basel, Switzerland, as far as the Republic of Colombia is concerned.



Rainer ALBERT
domiciled at
Wartenbergstrasse 21, 4052 Basel, Switzerland

FIRMA DEL CEDENTE
domicillado en



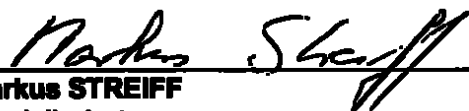
Christian BRUNS
domiciled at
Ziegelhofstrasse 120, 79110 Freiburg, Germany

FIRMA DEL CEDENTE
domicillado en



François NUNINGER
domiciled at
Rue de l'Entente 11, 68270 Wittenheim, France

FIRMA DEL CEDENTE
domicillado en



Markus STREIFF
domiciled at
Friedeneggasse 15, 4127 Birsfelden, Switzerland

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Gebhard Thoma

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Talweg 32, 79540 Lörrach, Germany

FIRMA DEL CEDENTE
domiciliado en

Hans-Günter Zerwes

Hans-Günter ZERWES
domiciled at
Holzgasse 55, 79539 Lörrach, Germany

FIRMA DEL CEDENTE
domiciliado en

Attestation

The undersigned notary public of Basel, Switzerland, hereby certify the authenticity of the signatures of **Mr. Rainer Albert**, Austrian citizen, residing in Basel, Switzerland, **Mr. Christian Bruns**, German citizen, residing in Freiburg, Germany, **Mr. François Nuninger**, French citizen, residing in Wittenheim, France, **Mr. Markus Streiff**, citizen of Schwanden/GL, Switzerland, residing in Birsfelden, Switzerland, **Mr. Gebhard Thoma**, German citizen, residing in Lörrach, Germany, and **Mr. Hans-Günter Zerwes**, German citizen, residing in Lörrach, Germany. The authenticity of the signatures was established by comparison.

BASEL, this 21st (twenty-first) of August 2003 (twothousandandthree)

A. Albrecht

Notar

Dr. A.C. Albrecht
Notar

Leg.Prot.Nr.: 444 / 2003

APOSTILLE
(Convention de la Haye du 5 octobre 1961)

1. Land: Schweiz (Suisse)
Diese öffentliche Urkunde

2. ist unterschrieben von *Dr. Albrecht*

3. in seiner Eigenschaft als *Notar*

4. sie ist versehen mit dem Siegel/Stempel des (der) *Gerichtes*

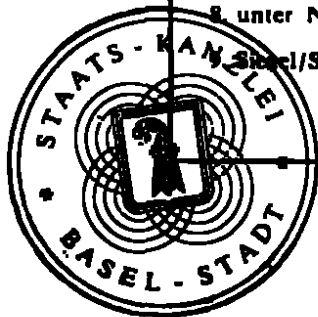
Bestätigt **21. Aug. 2003**

5. in Basel (Bâle) D. att.

7. durch die Staatskanzlei des Kantons Basel-Stadt

8. unter Nr. *6.942 / 1-878*

9. Siegel/Stempel: 10. Unterschrift: *Fischer*
Heidi Fischer



39
40

APOSTILLA

(Convention de la Haye du 5 octobre 1961)

1. País: Suiza

El presente documento público

2. Ha sido firmado por el Dr. iur. A. Albrecht

3. Actuando en calidad de: Notario público

4. Lleva el sello / estampilla del Notario Público en Basilea

Certificado

5. En Basilea

6. el 21 de agosto de 2003

7. Por la Cancillería de Estado del Cantón de Basilea - Ciudad

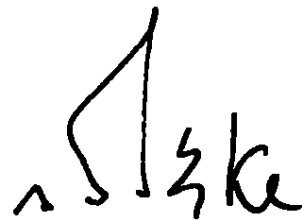
8. Bajo el No. 8942 / 11478

9. Sello/estampilla

10. Firmado

Sello de la Cancillería de Estado del
Cantón de Basilea - Ciudad

Heidi Fischer



ADOLF WATZKE
Traductor Oficial
Res. 8433 Minjusticia

MINISTERIO DE RELACIONES
EXTERIORES

666119

CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPENA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2003 SEP 12 A 10:28

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

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TRATAD DE COOPERACION EN MATERIA DE PATENTES
PCT

INFORME EXAMEN PRELIMINAR INTERNACIONAL
(PCT artículo 36 y regla 70)

(Reporte Racionalizado de acuerdo con la Notificación del Presidente de la OPE publicada en el Documento OJ11/2001)

Referencia del solicitante o agente 4-31853A	PARA PROSEGUIR Ver notificación de la transmisión del examen preliminar Internacional (formato PCT/IPEA/416)	
No. Solicitud Internacional PCT/EP 02/ 03871	Fecha de presentación internacional (día/mes/año) 08/04/2002	Fecha de prioridad (día/mes/año) 09/04/2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D211/58		
Solicitante NOVARTIS AG et al.		

1. Este examen preliminar internacional ha sido preparado por esta Autoridad encargada del Examen Preliminar Internacional y es transmitida al solicitante de acuerdo con el artículo 36.
2. Este INFORME consiste de un total de 2 páginas, incluyendo esta hoja.

— Este informe también está acompañado por ANEXOS, esto es hojas de la descripción, reivindicaciones y/o dibujos, los cuales han sido modificados y son la base para este informe y/o hojas que contienen rectificaciones presentadas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos consisten en un total de __ hojas.

3. Este informe contiene indicaciones que se relacionan con los siguientes puntos:

- I. ☒ Base del Informe
- II. ☐ Prioridad
- III. ☒ El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial
- IV. ☐ Falta de unidad de invención
- V. ☒ Declaración motivada bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación Industrial; citaciones y explicaciones que soportan dicha declaración
- VI. ☐ Ciertos documentos citados
- VII. ☐ Ciertos defectos en la solicitud internacional
- VIII. ☐ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 14/10/2002	Fecha en que se completó este informe 22/01/2003
Nombre y dirección de la autoridad encargada del examen preliminar internacional: Oficina de Patentes Europea D-80298 Munich Tel. +49 89 2399-0 Tx: 523656 epmu d Fax: +49 89 2399 – 4465	Oficial autorizado GELLIE B R Teléfono: +49 89 2399 2828

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

Solicitud internacional No. PCT/EP 02/03871

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42

I. BASE DEL INFORME

La base de este Informe del examen preliminar internacional es la solicitud como fue presentada originalmente.

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación Industrial

La pregunta de si la presente de invención reivindicada aparenta ser novedosa, si tiene altura inventiva, o es aplicable Industrialmente no ha sido objeto del examen preliminar internacional en relación con las reivindicaciones que no han sido buscadas (Art. 17(2) (a) o (3) y Regla 66.1 (e) PCT); ver también el informe de búsqueda internacional).

V. Declaración motivada bajo la Regla 66.2 (a) (II) con relación a la novedad, nivel inventivo o aplicación Industrial

Si se llevare a cabo el examen preliminar internacional (ver el ítem III mencionado anteriormente), se señala lo siguiente:

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención como está definida en por lo menos algunas de las reivindicaciones, las cuales han sido materia del Informe de búsqueda internacional, no aparentan cumplir con los criterios mencionados en el Artículo 33 (1) PCT, esto es, no aparenta ser novedosa y/o tener nivel inventivo (ver Informe de búsqueda internacional, en especial los documentos citados con X y/o Y, y las referencias de las reivindicaciones correspondientes).

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

INFORME EXAMEN PRELIMINAR INTERNACIONAL (PCT artículo 36 y regla 70)

(Reporte Racionalizado de acuerdo con la Notificación del Presidente de la OPE publicada en el Documento OJ11/2001)

Referencia del solicitante o agente 4-31953A	PARA PROSEGUIR Ver notificación de la transmisión del examen preliminar Internacional (formato PCT/IPEA/416)	
No. Solicitud Internacional PCT/EP 02/ 03871	Fecha de presentación Internacional (día/mes/año) 08/04/2002	Fecha de prioridad (día/mes/año) 09/04/2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D211/58		
Solicitante NOVARTIS AG et al.		

1. Este examen preliminar internacional ha sido preparado por esta Autoridad encargada del Examen Preliminar Internacional y es transmitida al solicitante de acuerdo con el artículo 36.
2. Este INFORME consiste de un total de 2 páginas, incluyendo esta hoja.

— Este informe también está acompañado por ANEXOS, esto es hojas de la descripción, reivindicaciones y/o dibujos, los cuales han sido modificados y son la base para este informe y/o hojas que contienen rectificaciones presentadas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos consisten en un total de __ hojas.

3. Este Informe contiene indicaciones que se relacionan con los siguientes puntos:

- I. ☒ Base del Informe
- II. ☐ Prioridad
- III. ☒ El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial
- IV. ☐ Falta de unidad de invención
- V. ☒ Declaración motivada bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración
- VI. ☐ Ciertos documentos citados
- VII. ☐ Ciertos defectos en la solicitud internacional
- VIII. ☐ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 14/10/2002	Fecha en que se completó este informe 22/01/2003
Nombre y dirección de la autoridad encargada del examen preliminar internacional: Oficina de Patentes Europea D-80298 Munich Tel. +49 89 2399-0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Oficial autorizado GELLIE B R Teléfono: +49 89 2399 2828

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

Solicitud internacional No. PCT/EP 02/03871

#3
44

I. BASE DEL INFORME

La base de este informe del examen preliminar internacional es la solicitud como fue presentada originalmente.

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación Industrial

La pregunta de si la presente de invención reivindicada aparenta ser novedosa, si tiene altura inventiva, o es aplicable industrialmente no ha sido objeto del examen preliminar internacional en relación con las reivindicaciones que no han sido buscadas (Art. 17(2) (a) o (3) y Regla 66.1 (e) PCT); ver también el informe de búsqueda internacional).

V. Declaración motivada bajo la Regla 66.2 (a) (II) con relación a la novedad, nivel inventivo o aplicación Industrial

Si se llevare a cabo el examen preliminar internacional (ver el ítem III mencionado anteriormente), se señala lo siguiente:

A la luz de los documentos citados en el Informe de búsqueda internacional, se considera que la invención como está definida en por lo menos algunas de las reivindicaciones, las cuales han sido materia del informe de búsqueda internacional, no aparentan cumplir con los criterios mencionados en el Artículo 33 (1) PCT, esto es, no aparenta ser novedosa y/o tener nivel inventivo (ver Informe de búsqueda internacional, en especial los documentos citados con X y/o Y, y las referencias de las reivindicaciones correspondientes).

44
45

A: Gros, Florent Novartis AG Corporate Intellectual Property Patent & Trademark Department CH-4002 Basilea Sulza	PCT OPINION ESCRITA (PCT Regla 66)	
	Fecha de Envío (día/mes/año) 29/10/2002	
	RESPUESTA VENCE dentro de 2 meses contados desde la fecha de envío	
Referencia del solicitante o agente 4-31953A	Fecha de presentación internacional (día/mes/año)	Fecha de prioridad (día/mes/año)
Solicitud Internacional No. PCT/EP 02/03871	08/04/2002	09/04/2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC CD7D211/58		
Solicitante NOVARTIS AG et al.		

1. Esta opinión escrita es la primera expedida por esta Autoridad encargada del Examen Preliminar Internacional.
2. Este opinión contiene indicaciones relacionadas con los siguientes puntos:
 - I. ☒ Base de la opinion
 - II. ☐ Prioridad
 - III. ☒ El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial
 - IV. ☐ Falta de unidad de Invención
 - V. ☒ Declaración motivada conforme a la Regla 66.2 (a)(ii) con relación a la novedad, nivel inventivo o aplicación Industrial; citas y explicaciones que soportan dicha declaración
 - VI. ☐ Ciertos documentos citados
 - VII. ☐ Ciertos defectos en la solicitud internacional
 - VIII. ☐ Ciertas observaciones en la solicitud internacional
3. El solicitante esta invitado a darle respuesta a esta opinión
 - Cuándo? Ver el tiempo limite indicado anteriormente. El solicitante podrá solicitar una prorrogas antes del vencimiento de este termino, ver regla 66.2 (d)
 - Cómo? Al suministrar una respuesta escrita, acompañada cuando sea apropiado de modificaciones de acuerdo con la regla 66.3. Para la forma e idioma de las modificaciones, ver regla 66.8 y 66.9.
 - Adicionalmente: Para una oportunidad adicional para someter modificaciones ver regla 66.4
Para la obligación del examinador de considerar modificaciones y/o argumentos ver regla 66.4bi
Para una comunicación informal con el examinador ver regla 66.6
- Si no se presenta una respuesta, el informe del examen preliminar internacional será establecido con base en esta opinión.
4. La fecha final para la cual el informe del examen preliminar internacional debe ser establecido conforme a la regla 69.2 es: 09/08/2003.

Nombre y dirección de la autoridad encargada del examen preliminar internacional:	Oficial Autorizado/ Examinador
Oficina de Patentes Europea D-80298 Munich Tel: +49 89 2399-0 Tx: 523658 epmu d Fax: +49 89 2399-4465	Oficial de formalidades (incluyendo prorrogas de términos)
	Teléfono: (+49- 89) 2399 2828

OPINION ESCRITA

Solicitud internacional No. PCT/EP 02/03871

I. Base del Informe

1. La base de esta opinión escrita es la solicitud de patente como fue presentada originalmente.

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación Industrial

2. La pregunta de si la presente invención reivindicada aparenta ser novedosa, si tiene altura inventiva, o es aplicable industrialmente no ha sido ni será materia del examen preliminar internacional (Art. 34 (a) (i) (ii) PCT; ver también el informe de búsqueda Internacional) en relación a:

V. Declaración motivada conforme a la Regla 66.2 (a)(ii) con relación a la novedad, nivel inventivo o aplicación Industrial

1. Si fuera llevado a cabo el examen internacional preliminar (ver el punto III), se señala lo siguiente:
2. A la luz de los documentos citados en el informe de búsqueda Internacional, se considera que la invención, tal como es reivindicada, en por lo menos una de sus reivindicaciones independientes no aparenta cumplir los criterios mencionados en el Artículo 33 (1) PCT, esto es, no aparenta ser novedosa y/o tener nivel inventivo. (ver reporte Internacional de búsqueda, en particular los documentos citados con X y/o Y y las correspondientes reivindicaciones en referencia).
3. Si se presentan modificaciones el Solicitante debe cumplir con los requisitos de la Regla 66.6 PCT e indicar la base de las modificaciones realizadas en la solicitud de patente original (Art. 34 (2) (b) PCT) de lo contrario, estas modificaciones no serán tenidas en cuenta para efecto del examen preliminar internacional. Se le llama la atención al solicitante respecto a que si la solicitud contiene una pluralidad de reivindicaciones independientes injustificadas no se llevará a cabo el examen de ninguna de las reivindicaciones.

NB: Si el solicitante decide pedir un examen de patentabilidad detallado, entonces un reporte del examen preliminar internacional será normalmente establecido directamente. Excepcionalmente el examinador podrá redactar una segunda opinión escrita, si se hace solicitud expresa de lo mismo.

TRATADO DE COOPERACION EN MATERIA DE PATENTES

46
47

A: Gros, Florent Novartis AG Corporate Intellectual Property Patent & Trademark Department CH-4002 Basilea Suiza	PCT OPINION ESCRITA (PCT Regla 66)	
Referencia del solicitante o agente 4-31953A Solicitud Internacional No. PCT/EP 02/03871	Fecha de Envío (día/mes/año) 29/10/2002	
	RESPUESTA VENCE dentro de 2 meses contados desde la fecha de envío	
	Fecha de presentación internacional (día/mes/año) 08/04/2002	Fecha de prioridad (día/mes/año) 09/04/2001
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC CD7D211/58		
Solicitante NOVARTIS AG et al.		

1. Esta opinión escrita es la primera expedida por esta Autoridad encargada del Examen Preliminar Internacional.

2. Este opinión contiene indicaciones relacionadas con los siguientes puntos:

- I. X Base de la opinion
- II. Prioridad
- III. X El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial
- IV. Falta de unidad de invención
- V. X Declaración motivada conforme a la Regla 66.2 (a)(ii) con relación a la novedad, nivel inventivo o aplicación Industrial; citaciones y explicaciones que soportan dicha declaración
- VI. Ciertos documentos citados
- VII. Ciertos defectos en la solicitud internacional
- VIII. Ciertas observaciones en la solicitud internacional

3. El solicitante esta invitado a darle respuesta a esta opinión

Cuándo? Ver el tiempo limite indicado anteriormente. El solicitante podrá solicitar una prorroga antes del vencimiento de este termino, ver regla 66.2 (d)

Cómo? Al suministrar una respuesta escrita, acompañada cuando sea apropiado de modificaciones de acuerdo con la regla 66.3. Para la forma e idioma de las modificaciones, ver regla 66.8 y 66.9.

Adicionalmente: Para una oportunidad adicional para someter modificaciones ver regla 66.4
 Para la obligación del examinador de considerar modificaciones y/o argumentos ver regla 66.4bi
 Para una comunicación informal con el examinador ver regla 66.6

Si no se presenta una respuesta, el Informe del examen preliminar internacional será establecido con base en esta opinión.

4. La fecha final para la cual el informe del examen preliminar internacional debe ser establecido conforme a la regla 69.2 es: 09/08/2003.

Nombre y dirección de la autoridad encargada del examen preliminar internacional:	Oficial Autorizado/ Examinador
Oficina de Patentes Europea D-80298 Munich Tel: +49 89 2399-0 Tx: 523656 epmu d Fax: +49 89 2399-4465	Oficial de formalidades (incluyendo prorrogas de términos) Teléfono: (+49- 89) 2399 2828

I. Base del Informe

1. La base de esta opinión escrita es la solicitud de patente como fue presentada originalmente.

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial

2. La pregunta de si la presente invención reivindicada aparenta ser novedosa, si tiene altura inventiva, o es aplicable industrialmente no ha sido ni será materia del examen preliminar internacional (Art. 34 (a) (i) (ii) PCT; ver también el Informe de búsqueda internacional) en relación a:

V. Declaración motivada conforme a la Regla 66.2 (a)(II) con relación a la novedad, nivel inventivo o aplicación industrial

1. Si fuera llevado a cabo el examen internacional preliminar (ver el punto III), se señala lo siguiente:
2. A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención, tal como es reivindicada, en por lo menos una de sus reivindicaciones independientes no aparenta cumplir los criterios mencionados en el Artículo 33 (1) PCT, esto es, no aparenta ser novedosa y/o tener nivel inventivo. (ver reporte internacional de búsqueda, en particular los documentos citados con X y/o Y y las correspondientes reivindicaciones en referencia).
3. Si se presentan modificaciones el Solicitante debe cumplir con los requisitos de la Regla 66.8 PCT e indicar la base de las modificaciones realizadas en la solicitud de patente original (Art. 34 (2) (b) PCT) de lo contrario, estas modificaciones no serán tenidas en cuenta para efecto del examen preliminar internacional. Se le llama la atención al solicitante respecto a que si la solicitud contiene una pluralidad de reivindicaciones independientes injustificadas no se llevará a cabo el examen de ninguna de las reivindicaciones.

NB: Si el solicitante decide pedir un examen de patentabilidad detallado, entonces un reporte del examen preliminar internacional será normalmente establecido directamente. Excepcionalmente el examinador podrá redactar una segunda opinión escrita, si se hace solicitud expresa de lo mismo.

Forma de Patentes 1/77

(Emblema)

(Logotipo); **Error! Marcador no definido.**

INVERSIONISTA EN LA GENTE

LA OFICINA DE PATENTES

La Oficina de Patentes
Concept House
Cardiff Road
Newport
Gales del Sur
NP10 8QQ

Yo, el suscrito, siendo un funcionario debidamente autorizado de acuerdo con la Sección 74(1) y (4) de la Ley de Desregulación y Contratación Externa de 1994, para firmar y expedir certificados a nombre del Contralor General, mediante la presente certifico que el anexo es una copia fiel de los documentos tal como se presentaron originalmente en relación con la Solicitud de Patente identificada en los mismos.

De acuerdo con las Reglas de Patentes (Re-registro de Sociedades) de 1982, si una sociedad nombrada en este certificado y en cualesquiera documentos acompañantes, se ha re-registrado, de acuerdo con la Ley de Sociedades de 1980, con el mismo nombre que aquél con el que se registró inmediatamente antes del re-registro, salvo por la sustitución como, o la inclusión como, la última parte del nombre con las palabras "sociedad pública limitada" o sus equivalentes en Galo, las referencias al nombre de la sociedad en este certificado y en cualesquiera documentos acompañantes, se tratarán como referencias al nombre con el cual así se re-registró.

De acuerdo con las reglas, las palabras "sociedad pública limitada" pueden ser reemplazadas por s.p.l., spl, S.P.L., ó SPL.

El re-registro según la Ley de Sociedades no constituye una nueva entidad legal, sino que meramente sujeta a la sociedad a ciertas reglas adicionales de la ley de sociedades.

Firma: (Firmado)

Fecha: 14 de febrero de 2002

(Aparece un sello móvil de la Oficina de Patentes).

Forma de Patentes 1/77

Forma de Patentes 1/77

1/77

(Ilegible) E620766-1 DO0524
P01/7700.0 00-0108876.4

Ley de Patentes de 1977
(Regla 16)

(Aparece un sello ovalado impreso con la siguiente leyenda:
LA OFICINA DE PATENTES
09 DE ABRIL DE 2001
RECIBIDO PERSONALMENTE).

LA OFICINA DE PATENTES

La Oficina de Patentes
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1. Su referencia: **4-31953P1**
2. Número de Solicitud de Patente:
(La Oficina de Patentes llenará esta parte)
0108876.4
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NOVARTIS AG
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Número ADP de Patentes (si lo conoce):
7125487002
Si el solicitante es un cuerpo corporativo, dé el país/estado de su incorporación:
SUIZA
4. Título de la invención:
Compuestos Orgánicos

50
51

5. Nombre de su agente (si tiene alguno):
B. A. YORKE & CO.
AGENTES DE PATENTES AUTORIZADOS

"Dirección para notificaciones" en el Reino Unido, a donde se debe enviar toda la correspondencia (incluyendo el código postal):

**COOMB HOUSE, 7 ST. JOHN'S ROAD
ISLEWORTH
MIDDLESEX TW7 6NH**

Número ADP de Patentes (si lo conoce):
1800001

6. Si está declarando prioridad a partir de una o más solicitudes de patente anteriores, dé el país y la fecha de presentación de cada una de estas solicitudes anteriores, y (si lo conoce) cada número de solicitud:

País: - - -

Número de solicitud de prioridad (si lo sabe): - - -

Fecha de presentación (día/mes/año): - - -

7. Si esta solicitud está dividida o se deriva de otra manera de una solicitud anterior del Reino Unido, dé el número y la fecha de presentación de la solicitud anterior:

Número de solicitud anterior: - - -

Fecha de presentación (día/mes/año): - - -

8. Es una declaración de invención y del derecho de otorgar una patente requerida en apoyo de esta solicitud? (Conteste "Sí" en el caso de que:

a) cualquier solicitante nombrado en la parte 3 no sea un inventor, ó

b) haya un inventor que no esté nombrado como un solicitante, ó

c) cualquier solicitante nombrado sea un cuerpo corporativo.

Ver la nota (d)): **Sí**

9. Anote el número de páginas para cualquiera de los siguientes artículos que esté presentando con esta forma. No cuente las copias del mismo documento.

Forma de Patentes 1/77

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Resumen	--
Dibujo(s)	--

10. Si también está presentando cualquiera de los siguientes, informe cuántas en cada uno de los puntos.

Documentos de prioridad: --

Traducción de documentos de prioridad: --

Declaración de invención y derecho a la concesión de una patente (Forma de Patentes 7/77): --

Solicitud de examen preliminar y búsqueda (Forma de Patentes 9/77): **UNA**

Solicitud de examen sustantivo (Forma de Patentes 10/77): --

Cualesquiera otros documentos (por favor especifique):

11. Solicitamos la concesión de una patente con base en esta solicitud.

Firma: **B. A. Yorke & Co.**
(Firmado)

Fecha: **09 de abril de 2001**

12. Nombre y número telefónico diurno de la persona para hacer contacto en el Reino Unido:

SRA. E. CHEETHAM
020 8560 5847

Advertencia

Después de que se haya presentado una solicitud de patente, el Contralor de la Oficina de Patentes considerará si se debe prohibir o restringir la publicación o comunicación de la invención, de acuerdo con la Sección 22 de la Ley de Patentes de 1977. Se le informará si es necesario prohibir o restringir su invención de esta manera. Además, si usted vive en el Reino Unido, la Sección 23 de la Ley de Patentes de 1977 le impide solicitar una patente en el extranjero sin obtener primero un permiso por escrito de la Oficina de Patentes, a menos que se haya presentado una solicitud cuando menos 6 semanas antes en el Reino Unido para una patente para la misma invención, y no se hayan dado instrucciones que prohíban la publicación o la comunicación, o se hayan revocado dichas instrucciones.

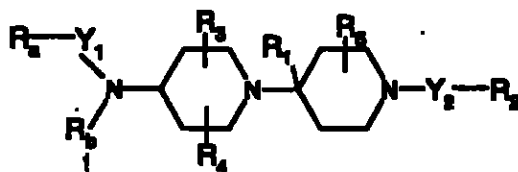
Forma de Patentes 1/77

Notas

- a) Si necesita ayuda para llenar esta forma, o tiene alguna pregunta, por favor haga contacto con la Oficina de Patentes al 0645 500505.
- b) Escriba sus respuestas en letras mayúsculas, utilizando tinta negra, o puede mecanografiarlas.
- c) Si no hay suficiente espacio para todos los detalles pertinentes en cualquier parte de esta forma, por favor continúe en una hoja de papel separada, y escriba "ver página de continuación" en las partes pertinentes. Cualquier página de continuación se debe adjuntar a esta forma.
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REIVINDICACIONES

1. Un compuesto de la fórmula I:



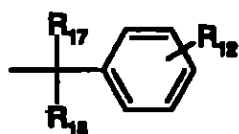
en donde:

Y_1 es O; CH_2 ; o un enlace directo;

Y_2 es $-CO-$; $-CS-$; $-CO-NR_6-$; $-CS-NR_6-$; $-CO-O-$; o $-SO_2-$;

R_1 es H, alquilo de 1 a 6 átomos de carbono, alquienilo de 2 a 6 átomos de carbono, o fenilo;

R_2 es fenilo, heteroarilo de 6 miembros, o N-óxido de heteroarilo de 6 miembros, cada uno siendo sustituido por R_7 , R_8 y R_9 ; R_{10} , R_{11} -heteroarilo sustituido de 5 miembros, naftilo; fluorenilo; difenilmetilo;



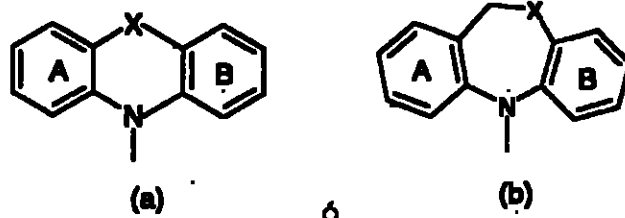
o



cada uno de R_3 , R_4 y R_5 , independientemente es H; o alquilo de 1 a 6 átomos de carbono; y

cada uno de R_7 y R_8 , independientemente, está sustituido o insustituido por arilo, o heteroarilo; o R_7 y R_8 for-

man juntos con el nitrógeno al que están unidos un radical de la fórmula (a) o (b)



R_6 es H; o alquilo de 1 a 4 átomos de carbono;

cada uno de R_7 y R_8 , independientemente, es halógeno; alquilo de 1 a 6 átomos de carbono; $NR_{20}R_{21}$; OH; CF_3 ; OCH_3 ; -O-acilo, y OCF_3 ;

R_9 es R_7 ; H; fenilo; NO_2 ; CN; CH_2F ; CHO; $-CH=NOR_{20}$; piridilo; N-óxido de piridilo, pirimidinilo; piracinilo; $-N(R_{20})CONR_1R_{22}$; $-NHCONH$ (cloroalquilo de 1 a 6 átomos de carbono); $-NHCONH$ (cicloalquilo de 3 a 10 átomos de carbono)(alquilo de 1 a 6 átomos de carbono); $NHCO$ (alquilo de 1 a 6 átomos de carbono); $-NHCOCF_3$; $-NHSO_2N$ (alquilo de 1 a 6 átomos de carbono); $-OSO_2$ (alquilo de 1 a 6 átomos de carbono); OSO_2CF_3 ; hidroxialquilo de 1 a 6 átomos de carbono; $-CONR_{20}R_{21}$; $-CON(CH_2CH_2-O-CH_3)_2$; $-OCONH$ (alquilo de 1 a 6 átomos de carbono); $-CO_2R_{20}$; $-Si(CH_3)_3$ o $-B(OC(CH_3)_2)_2$;

R_{10} es alquilo de 1 a 6 átomos de carbono; NH_2 ; o R_{12} -fenilo;

R_{11} es H; o alquilo de 1 a 6 átomos de carbono;

R_{12} es de 1 a 3 sustituyentes independientemente se-

leccionados a partir del grupo que consiste de H; alquilo de 1 a 6 átomos de carbono; CH₃; -CO₂R₂₀; CN; alcoxilo de 1 a 6 átomos de carbono; y halógeno.

cada uno de R₁₇ y R₁₈, independientemente, es H; alquilo de 1 a 6 átomos de carbono; o R₁₇ y R₁₈ juntos son alquilenos de 2 a 5 átomos de carbono, y con el átomo de carbono con el que están unidos forman un anillo espiro de 3 a 6 átomos de carbono.

cada uno de R₂₀, R₂₁ y R₂₂, independientemente es H, o alquilo de 1 a 6 átomos de carbono;

R₂₃ es alquilo de 1 a 6 átomos de carbono; o fenilo;

X es O; -NR_c- en donde R_c es H o alquilo de 1 a 4 átomos de carbono; S; o CH₂;

cada uno de los anillos A y B, independientemente están opcionalmente sustituidos;

en forma libre o en forma de sal.

2. Un compuesto de la fórmula I, sustancialmente como se define o se describe en la presente.

3. Un compuesto de la fórmula I, de acuerdo con la reivindicación 1 ó 2, o una sal farmacéuticamente aceptable del mismo, para utilizarse como un producto farmacéutico.

4. Una composición farmacéutica que comprende un compuesto de la fórmula I, de acuerdo con la reivindicación 1 ó 2, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o vehículo farmacéuticamente acepta-

ble del mismo.

5. Un método para prevenir o tratar desórdenes o enfermedades mediadas por las interacciones entre receptores de quimiocina y sus ligandos, por ejemplo, como se describe en la presente, en un sujeto que necesite de este tratamiento, cuyo método comprende administrar al sujeto una cantidad efectiva de un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo.

6. Un método de acuerdo con la reivindicación 5, el cual comprende co-administración, por ejemplo, de manera concomitante, o en secuencia, de una cantidad no tóxica terapéuticamente efectiva de un compuesto de la fórmula I, de acuerdo con la reivindicación 1 ó 2, o una sal farmacéuticamente aceptable del mismo, y cuando menos una segunda sustancia de fármaco.

7. Un compuesto de la fórmula I, de acuerdo con la reivindicación 1 ó 2, o una sal farmacéuticamente aceptable del mismo, para utilizarse en la preparación de una composición farmacéutica para utilizarse en cualquier método como se define en la reivindicación 5.

8. Una combinación farmacéutica, por ejemplo, un estuche, que comprenda, a) un primer agente que es un compuesto de la fórmula I, de acuerdo con la reivindicación 1 ó 2, o una sal farmacéuticamente aceptable del mismo, y b) cuando menos un co-agente.

Yo, ANA ELENA FERRER RAMÍREZ, Perita Traductora Autorizada por el Tribunal Superior de Justicia del D.F., y miembro de la Organización Mexicana de Traductores, A.C., con domicilio en Av. Clavería 224-205, Col. Clavería, México, D.F. 02080, Tels. 5396 2669 y 5396 5201, certifico que el documento precedente es, a mi leal saber y entender, una traducción fiel y exacta del documento original en idioma inglés que tuve a la vista.

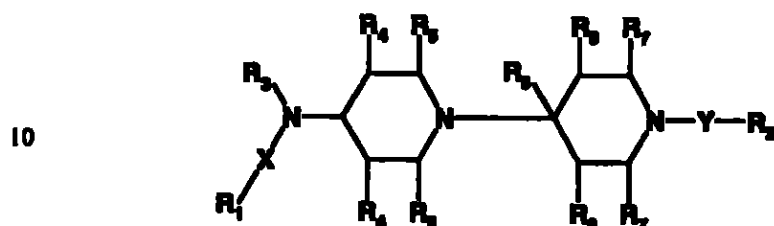
México, D. F., 29 de agosto de 2003

ANA ELENA FERRER R.
Perita Traductora
Autorizada por el Tribunal
Superior de Justicia del D.F.
Ana Elena Ferrer Ramírez

DERIVADOS DE BIPIPERIDINILO Y SU USO COMO
INHIBIDORES DE RECEPTORES DE QUIMIOTINA

La presente invención se refiere a derivados de piperidina, a un proceso para su producción, a sus usos, y a composiciones farmacéuticas que los contienen.

De una manera más particular, la presente invención proporciona un compuesto de la fórmula I:



en donde:

X es un enlace directo; $-CH_2-$; $-CH_2-CH_2-$; $CH(R_9)-$
 15 ; $-C(O)-$; $-O-$; $-NH-$ ó NR_9 ;

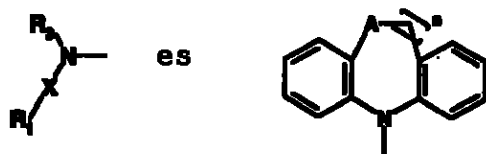
R_1 es fenilo opcionalmente sustituido por R_{10} y/o R_{11} ; heteroarilo opcionalmente sustituido por R_{10} y/o R_{11} ; N-óxido de heteroarilo opcionalmente sustituido por R_{10} y/o R_{11} ; o naftilo opcionalmente sustituido por R_{10} y/o R_{11} ;

20 R_2 tiene uno de los significados dados para R_1 ; o es fluorenilo opcionalmente sustituido por R_{10} y/o R_{11} ; alquilo de 1 a 6 átomos de carbono opcionalmente sustituido por R_{10} ; alquenilo de 2 a 6 átomos de carbono opcionalmente sustituido por R_{10} ; cicloalquilo de 3 a 6 átomos de carbono opcionalmente
 25 sustituido por R_{10} ; adamantilo opcionalmente sustituido por

R_{10} ; o cicloalqueno de 4 a 6 átomos de carbono opcionalmente sustituido por R_{10} ;

R_3 tiene uno de los significados dados para R_1 ; o es fluorenilo opcionalmente sustituido por R_{10} y/o R_{11} ; alquilo de 1 a 6 átomos de carbono sustituido por R_{10} ; alqueno de 2 a 6 átomos de carbono opcionalmente sustituido por R_{10} ; cicloalquilo de 3 a 6 átomos de carbono opcionalmente sustituido por R_{10} ; adamantilo opcionalmente sustituido por R_{10} ; o cicloalqueno de 4 a 8 átomos de carbono opcionalmente sustituido por R_{10} ;

ó



15

en donde A es $-\text{CH}_2-$, $-\text{NH}-$, $-\text{NR}_9-$, $-\text{S}-$, $-\text{SO}-$, SO_2- u $-\text{O}-$; n es 0, 1, ó 2, y los anillos aromáticos están cada uno independientemente opcionalmente sustituidos por R_{10} ;

cada uno de R_4 tiene independientemente uno de los significados de R_5 ; ó es CN ; OH ; OR_9 ; F ; Cl ; Br ; ó I ;

cada uno de R_5 es independientemente H; alquilo de 1 a 6 átomos de carbono; hidroxialquilo de 1 a 6 átomos de carbono; alcoxialquilo de 2 a 6 átomos de carbono; haloalquilo de 1 a 6 átomos de carbono; fenilo; bencilo; o heteroarilo;

25

cada uno de R_6 tiene independientemente uno de los significados dados para R_4 ;

cada uno de R_7 tiene independientemente uno de los significados dados para R_5 ;

5 R_8 es H; alquilo de 1 a 6 átomos de carbono; alquenilo de 2 a 6 átomos de carbono; alquinilo de 2 a 6 átomos de carbono; fenilo; bencilo; CN; CH_2NH_2 ; CH_2NHR_9 ; $CH_2NR_9R_9$; $CH_2NHC(O)R_9$; $CH_2NR_9C(O)R_9$; $CH_2NHC(O)NHR_9$; $CH_2NR_9C(O)NHR_9$; $CH_2NR_9C(O)NR_9R_9$; $CH_2NHC(O)OR_9$; $CH_2NR_9C(O)OR_9$;
10 $CH_2NHOSO_2R_9$; $CH_2N(SO_2R_9)_2$; ó $CH_2NR_9SO_2R_9$;

cada R_9 es independientemente alquilo de 1 a 6 átomos de carbono; cicloalquilo de 3 a 6 átomos de carbono; alquenilo de 2 a 6 átomos de carbono; alquinilo de 2 a 6 átomos de carbono; fenilo; bencilo; heteroarilo; o CF_3 ;

15 R_{10} representa de 1 a 4 sustituyentes independientemente seleccionados a partir de alquilo de 1 a 6 átomos de carbono; hidroxialquilo de 1 a 6 átomos de carbono; alcoxialquilo de 2 a 6 átomos de carbono; haloalquilo de 1 a 6 átomos de carbono; cicloalquilo de 3 a 6 átomos de carbono; alquenilo de 2 a 6 átomos de carbono; cicloalquenilo de 3 a 6 átomos de carbono; alquinilo de 2 a 6 átomos de carbono; fenilo; heteroarilo; N-óxido de heteroarilo; F; Cl; Br; I; OH; OR_9 ; $CONH_2$; $CONHR_9$; $CONR_9R_9$; $OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9 ; $COOH$; $COOR_9$; CF_3 ; CHF_2 ; CH_2F ; CN; NO_2 ; NH_2 ;
20 NHR_9 ; NR_9R_9 ; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$;

$\text{NR}_9\text{C}(\text{O})\text{NHR}_9$; $\text{NR}_9\text{C}(\text{O})\text{NR}_9\text{R}_9$; $\text{NHC}(\text{O})\text{OR}_9$; $\text{NR}_9\text{C}(\text{O})\text{OR}_9$; NHSO_2R_9 ;
 $\text{N}(\text{SO}_2\text{R}_9)_2$; $\text{NR}_9\text{SO}_2\text{R}_9$; SR_9 ; $\text{S}(\text{O})\text{R}_9$; SO_2R_9 ; $\text{Si}(\text{CH}_3)_3$ y $\text{B}(\text{OC}(\text{CH}_3)_2)_2$;

R_{11} represente dos sustituyentes adyacentes que forman un anillo no aromático anulado de 4 a 7 miembros que contiene opcionalmente hasta dos heteroátomos seleccionados independientemente a partir de N, O, y S; e

Y es un enlace directo; $-\text{C}(\text{O})-$; $-\text{C}(\text{O})\text{CH}_2-$ $-\text{S}(\text{O})-$;
 $-\text{S}(\text{O}_2)-$; $-\text{C}(\text{S})-$; $-\text{CH}_2-$; $-\text{C}(-\text{CH}_2-\text{CH}_2)-$; $-\text{CH}(\text{R}_4)-$ ó $-\text{C}(\text{R}_5)_2-$,
 en forma libre o en forma de sal.

Cualquier alquilo, alqueniilo, o alquiniilo puede ser lineal o ramificado. Halógeno es F, Cl, Br, ó I.

Heteroarilo significa un sistema de anillo aromático que comprende sistemas mono-, bi-, ó tricíclicos que contienen hasta 4 heteroátomos independientemente seleccionados a partir de N, O, y S, tales como por ejemplo furilo, tienilo, pirrolilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, tetrazinilo, indolilo, benzotiofenilo, benzofuranilo, bencimidazolilo, indazolilo, benzotriazolilo, benzotiazolilo, benzoxazolilo, quinolinilo, isoquinolinilo, ptalazinilo, quinoxalinilo, quinazolinilo, cinolinilo o naftiridinilo.

El anillo no aromático anulado de 4 a 7 miembros preferido representado por R_{11} es un anillo no aromático anu-

lado de 5 ó 6 miembros que contiene opcionalmente uno o dos átomos de oxígeno, e incluye, por ejemplo, $-O-CH_2-O-$ u $-O-CH_2-CH_2-O-$, unidos a 2 átomos de carbono adyacentes.

Los compuestos de la fórmula I pueden existir en forma libre o en forma de sal, por ejemplo como sales de adición con, por ejemplo, ácidos orgánicos e inorgánicos, por ejemplo ácido clorhídrico, ácido acético cuando R_1 , R_2 , y/o R_3 comprenden un grupo amino opcionalmente sustituido o un residuo heterocíclico que pueda formar sales de adición. Cuando los compuestos de la fórmula I tienen uno o más centros asimétricos en la molécula, por ejemplo cuando un anillo de piperidina está sustituido, se debe entender que la presente invención abarca los diferentes isómeros ópticos, así como los racematos, diaetereoisómeros, y mezclas de los mismos.

En los compuestos de la fórmula I, se prefieren los siguientes significados individualmente o en cualquier subcombinación:

1. R_1 es fenilo opcionalmente sustituido por R_{10} ; heteroarilo opcionalmente sustituido por R_{10} ; o fenilo opcionalmente sustituido por R_{11} .

2. R_2 es fenilo opcionalmente sustituido por R_{10} ; heteroarilo opcionalmente sustituido por R_{10} ; N-óxido de heteroarilo opcionalmente sustituido por R_{10} ; o naftilo opcionalmente sustituido por R_{10} .

3. R_3 es fenilo opcionalmente sustituido por R_{10} ;

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heteroarilo opcionalmente sustituido por R_{10} ; o naftilo opcionalmente sustituido por R_{10} .

4. Cada uno de R_4 , R_5 , R_6 , ó R_7 , es independiente-
mente H; alquilo de 1 a 6 átomos de carbono; o bencilo.

5 5. R_8 es H; alquilo de 1 a 6 átomos de carbono; o alquénilo de 2 a 6 átomos de carbono.

6. R_9 es alquilo de 1 a 6 átomos de carbono; cicloalquilo de 3 a 6 átomos de carbono; alquénilo de 2 a 6 átomos de carbono; alquinilo de 2 a 6 átomos de carbono; fe-
nilo; bencilo; heteroarilo; o CF_3 .
10

7. R_{10} representa de 1 a 3 sustituyentes indepen-
dientemente seleccionados a partir de alquilo de 1 a 6 átomos
de carbono; hidroxialquilo de 1 a 6 átomos de carbono; al-
coxialquilo de 2 a 6 átomos de carbono; haloalquilo de 1 a 6
15 átomos de carbono; cicloalquilo de 3 a 6 átomos de carbono;
alquénilo de 2 a 6 átomos de carbono; cicloalquénilo de 3 a 6
átomos de carbono; alquinilo de 2 a 6 átomos de carbono; fe-
nilo; heteroarilo; N-óxido de heteroarilo; F; Cl; Br; I; OH;
OR₉; CONH₂; CONHR₉; CONR₉R₉; OC(O)R₉; OC(O)OR₉; OC(O)NHR₉;
20 OC(O)NR₉R₉; OSO₂R₉; COOH; COOR₉; CF₃; CHF₂; CH₂F; CN; NO₂; NH₂;
NHR₉; NR₉R₉; NHC(O)R₉; NR₉C(O)R₉; NHC(O)NHR₉; NHC(O)NH₂;
NR₉C(O)NHR₉; NR₉C(O)NR₉R₉; NHC(O)OR₉; NR₉C(O)OR₉; NH₂SO₂R₉;
N(SO₂R₉)₂; NR₉SO₂R₉; SR₉; S(O)R₉; SO₂R₉; y Si(CH₃)₃

8. R_{11} representa -O-CH₂-O- unido a 2 átomos de
25 carbono adyacentes.

9. X es un enlace directo ó -CH₂-.

10. Y es -C(O)-.

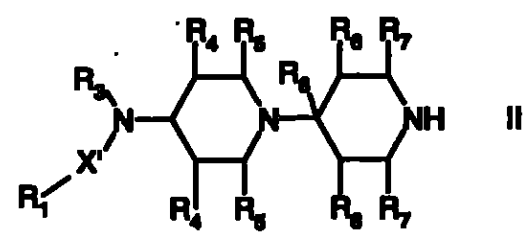
En los compuestos preferidos de la fórmula I, R₁₀ puede representar de 1 a 3 sustituyentes seleccionados a partir de alquilo de 1 a 6 átomos de carbono; fenilo; heteroarilo; N-óxido de heteroarilo; F; Cl; Br; I; OH; OR₉; CONH₂; CONHR₉; CONR₉R₉; COOH; COOR₉; CF₃; CHF₂; CH₂F; NH₂; NHR₉; NR₉R₉; NHC(O)R₉; NR₉C(O)R₉; NHC(O)NHR₉; NHC(O)NH₂; NR₉C(O)NHR₉; NR₉C(O)NR₉R₉; NHC(O)OR₉ y NR₉C(O)OR₉.

10 R₉ es de preferencia alquilo de 1 a 6 átomos de carbono; cicloalquilo de 3 a 6 átomos de carbono; fenilo; bencilo; o heteroarilo; más preferiblemente alquilo de 1 a 6 átomos de carbono.

La presente invención también incluye un proceso para la preparación de un compuesto de la fórmula I, cuyo proceso comprende:

a) para la preparación de un compuesto de la fórmula I, en donde X es un enlace directo, -CH₂-, -CH₂CH₂- ó -CHR₉- e Y es -CO-, -C(O)CH₂-, -S(O)- ó -S(O₂)-,

20 amidar un compuesto de la fórmula II:



en donde R_1 y R_3 a R_8 son como se indica anteriormente, y X' es un enlace directo, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$ ó $-\text{CHR}_9-$ con un compuesto de la fórmula III:

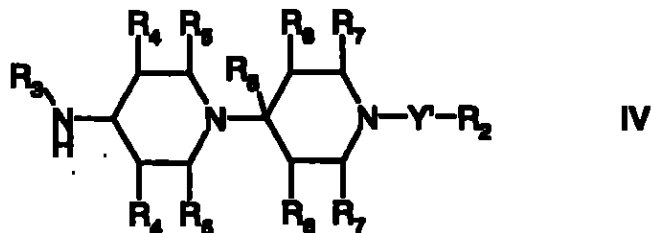


5 en donde R_2 es como se define anteriormente, Y' es $-\text{CO}-$, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{S}(\text{O})-$ ó $-\text{S}(\text{O}_2)-$ y A' es un grupo saliente, por ejemplo Cl ó Br,

b) para la preparación de un compuesto de la fórmula I, en donde X es un enlace directo, e Y es $-\text{CH}_2-$, someter a un compuesto de la fórmula II como se define anteriormente, en donde X' es un enlace directo, a una aminación reductiva; o

c) para la preparación de un compuesto de la fórmula I, en donde X es CH_2- , $-\text{CH}_2\text{CH}_2-$ ó $-\text{CHR}_9-$ e Y es $-\text{CO}-$, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{S}(\text{O})-$, ó $-\text{S}(\text{O}_2)-$,

15 hacer reaccionar un compuesto de la fórmula IV:



20 en donde R_2 a R_8 e Y' son como se definen anteriormente, con un compuesto de la fórmula V:



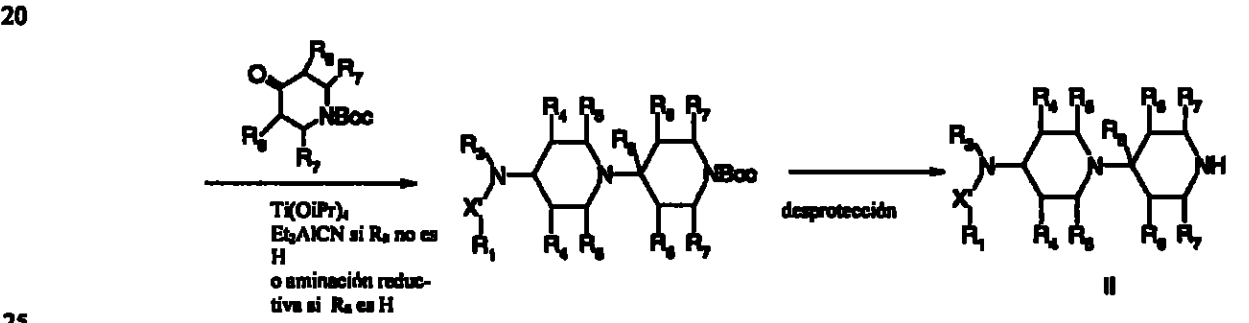
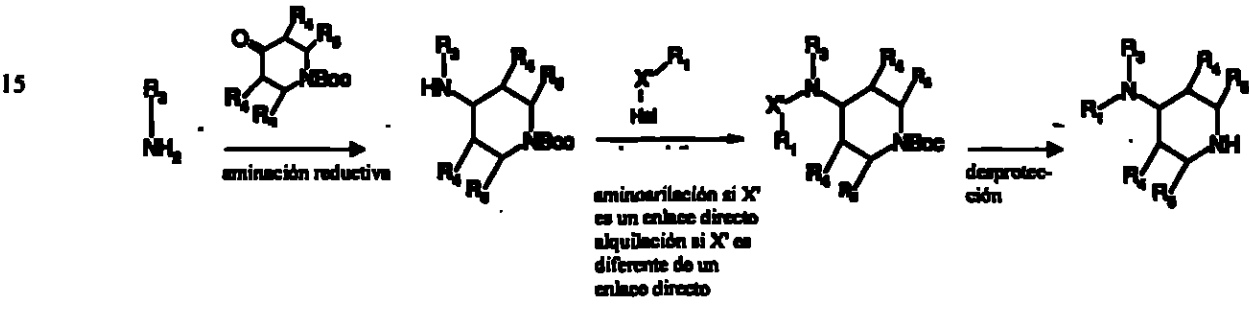
25 en donde R_1 es como se define anteriormente, y X''

es CH_2- ó $-\text{CHR}_9-$;

y, en donde se requiera, convertir el compuesto resultante de la fórmula I obtenido en forma libre en la forma de sal deseada, o viceversa.

5 Los pasos de reacción a), b), ó c) se pueden realizar de acuerdo con los métodos conocidos en la técnica, o como se da a conocer en los ejemplos que se encuentran más adelante. Cuando R_6 comprende un grupo que no deba participar en la reacción, este grupo se puede proteger de acuerdo con
10 los métodos conocidos en este campo.

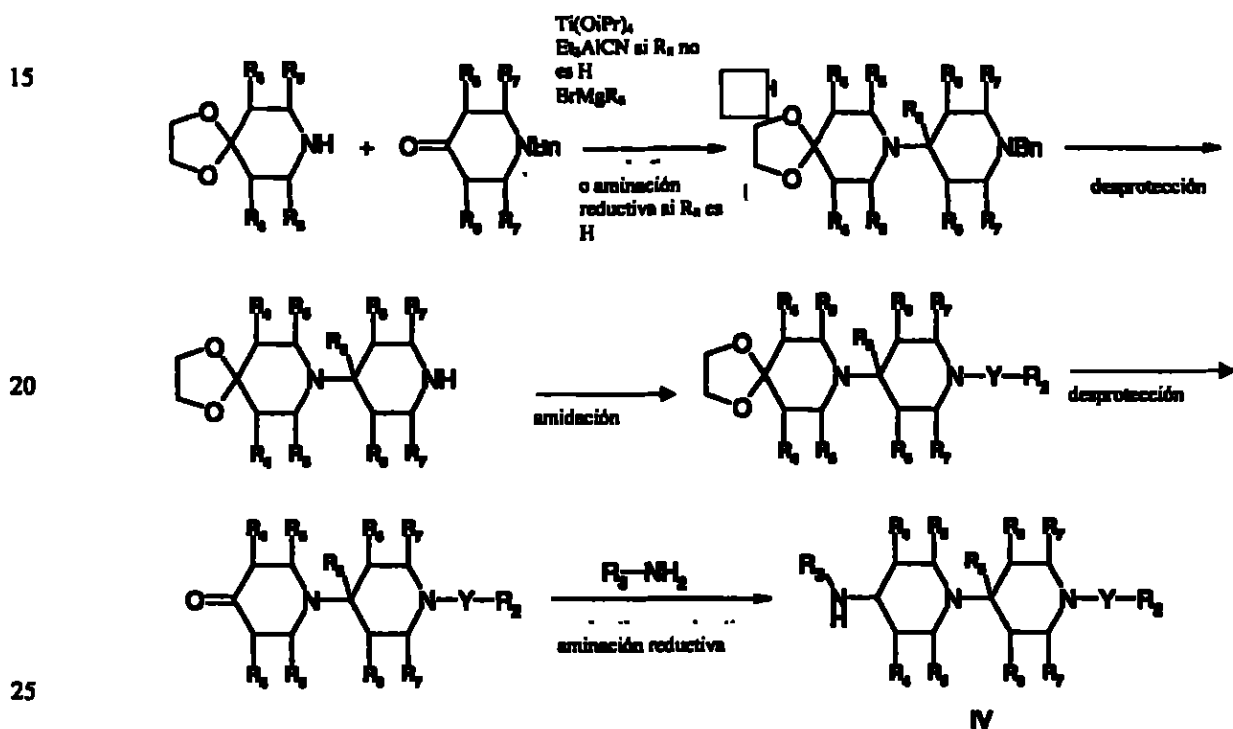
Los compuestos de la fórmula II, utilizados como material de partida, se pueden preparar como sigue:



67
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en donde X' y R_1 a R_8 son como se definen anteriormente, y Hal es Cl, Br, ó I. En las fórmulas anteriores, Boc es un grupo protector, que significa terbutiloxicarbonilo. Este grupo protector puede ser reemplazado en el esquema de reacción anterior por cualquier grupo protector de amino, por ejemplo como se da a conocer en "Protective Groups in Organic Síntesis" por T.W. Greene, J. Wiley & Sons NY, 2ª edición, capítulo 7, 1991, y las referencias en el mismo, por ejemplo benciloxicarbonilo o 9-fluorenilmetoxicarbonilo.

Los compuestos de la fórmula IV, utilizados como material de partida, se pueden preparar como sigue:



en donde R₂ a R₈ e Y son como se definen anteriormente, y Bn es bencilo.

Las reacciones anteriores se pueden realizar de acuerdo con los métodos conocidos en la materia, o como se da a conocer posteriormente en la presente.

Hasta donde no se describa particularmente la producción de los materiales de partida, los compuestos son conocidos o se pueden preparar de una manera análoga a los métodos conocidos en la técnica, o como se describe posteriormente en la presente.

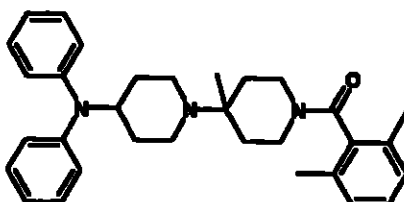
Los siguientes ejemplos son ilustrativos de la invención sin limitación. Se utilizan las siguientes abreviaturas:

15

Bn	= Bencilo
Boc	= Terbutoxicarbonilo
DMF	= Dimetilformamida
DMSO	= Sulfoxido de dimetilo
20 BINAP	= 2,2'-bis(difenilfosfino)-1,1'-binaftilo
THF	= Tetrahydrofurano
TFA	= Acido trifluoroacético
TA	= Temperatura ambiente

25

Ejemplo 1: (2,6-dimetil-fenil)-(4-difenilamino-4'-metil-1-[1,4']bipiperidinil-1'-il)-metanona



Una mezcla (4'-metil-[1,4']bipiperidinil-4-il)-
 10 difenil-amina (0.25 gramos, 0.71 milimoles), ácido 2,6-
 dimetilbenzoico (0.32 gramos, 2.13 milimoles), tetrafluorobo-
 rato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio
 (0.57 gramos, 1.5 milimoles), EtN(i-Pr)₂ (0.6 mililitros), y
 dimetilformamida (5 mililitros), se agita durante 16 horas a
 15 20°C. La mezcla se diluye con t-butilmetiléter (25 milili-
 tros), se lava con NaOH 2N (25 mililitros) y salmuera (25 mi-
 lilitros), y se seca con sulfato de sodio. El solvente se
 remueve, y el residuo se purifica mediante cromatografía
 (SiO₂, t-butilmetiléter/ciclohexano, 1:4 -> 1:0). El com-
 20 puesto del título se aísla como un sólido incoloro. MS/ESI
 482 (M+H)+;

¹H-RMN (400 MHz, DMSO) δ = 0.89 (3 H, s), 1.14 -1.25
 (3 H, m), 1.39 (1 H, m), 1.59 (1 H, m), 1.75 (1 H, m), 1.83-
 1.95 (2 H, m), 2.01 (3 H, s), 2.13 (3 H, s), 2.11-2.24 (2 H,
 25 m), 2.85 (2 H, m), 2.95 (1 H, m), 3.01 (1 H, m), 3.35 (1 H,

70
71

m), 3.70-3.83 (2 H, m), 6.77 (4 H, m), 6.92-7.05 (4 H, m), 7.12 (1H, m), 7.26 (4 H, m).

La (4'-metil[1,4']bipiperidinil-4-il)-difenil-
amina, utilizada como material de partida, se puede preparar
5 como sigue:

a) Una mezcla de fenil-piperidin-4-il-amina (4.14
gramos; 15.0 milimoles), yodobenceno (3.06 gramos; 15.0
milimoles), Pd(OAc)₂ (0.14 gramos; 0.63 milimoles); BINAP
(0.43 gramos; 0.69 milimoles), t-BuOK (17.5 mililitros de una
10 solución 1M en tetrahidrofurano) en tolueno (20 mililitros),
se calienta a 110°C durante 5 horas. La mezcla se diluye con
acetato de etilo, se extrae con carbonato ácido de sodio y
salmuera, y se seca con sulfato de sodio. El solvente se re-
mueve, y el residuo se somete a cromatografía (SiO₂, t-
15 butilmetiléter/ciclohe-xano 1:9 -> 1:1). El terbutiléster
del ácido 4-difenilamino-piperidin-1-carboxílico se aísla co-
mo un sólido amarillo. MS/ESI 353 (M+H)⁺.

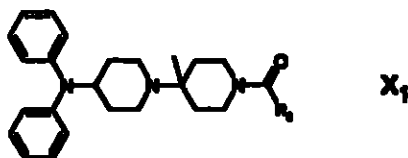
b) Una mezcla de TFA (5 mililitros), cloruro de
metileno (5 mililitros), agua (0.25 mililitros), y terbuti-
20 léster del ácido 4-difenilamino-piperidin-1-carboxílico (1.5
gramos; 4.2 milimoles), se agita durante 2 horas a 20°C. Se
agrega hidróxido de sodio (4N), y la mezcla se extrae con
acetato de etilo. La fase orgánica se seca con sulfato de
sodio, y se remueve el solvente. La difenil-piperidin-4-il-
25 amina se aísla como un aceite incoloro. MS/ESI 253 (M+H)⁺.

c) Una suspensión de difenil-piperidin-4-il-amina (1.26 gramos, 5.00 milimoles), 1-(terbutiloxicarbonil)-4-piperidona (1.00 gramos, 5.00 milimoles), e isopropóxido de titanio (IV) (1.42 gramos, 5.00 milimoles) en 1,2-dicloroetano (25 mililitros), se agita durante 1 hora a 80°C, y luego durante 16 horas a 20°C. Se agrega cianuro de dietilaluminio (10 mililitros de una solución 1M en tolueno), y la mezcla se agita durante 24 horas adicionales. El solvente se remueve, y el material crudo se disuelve en tetrahidrofurano (25 mililitros). Se agrega por goteo bromuro de metilmagnesio (8.7 mililitros de una solución 3M en éter), y la mezcla se agita durante 3 horas a 20°C. Se agregan cloruro de amonio (solución al 10 por ciento, 50 mililitros) y acetato de etilo (50 mililitros), la fase orgánica se lava con cloruro de amonio (solución al 10 por ciento, 50 mililitros) y carbonato ácido de sodio (solución al 10 por ciento, 50 mililitros), se seca con sulfato de sodio, y se remueve el solvente. El residuo se somete a cromatografía (SiO₂, acetato de etilo/ciclohexano, 1:9 -> 1:1). El terbutiléster del ácido 4-difenilamino-4'-metil-[1,4']bipiperidinil-1'-carboxílico se aísla como un sólido incoloro. MS/ESI 450 (M+H)⁺.

d) Una mezcla de ácido trifluoroacético (2 mililitros) y agua (0.1 mililitros) se agrega por goteo a una solución del compuesto a) anterior (0.81 gramos, 1.80 milimoles) en cloruro de metileno (5 mililitros), y la mezcla se

agita durante 3 horas a 20°C. Se agregan carbonato ácido de sodio (solución al 10 por ciento, 10 mililitros) y acetato de etilo (20 mililitros), y la fase orgánica se seca con sulfato de sodio. El solvente se remueve, y el residuo se somete a cromatografía (RP-18, metanol/H₂O, 1:3->0:1). El compuesto del título se aísla como un aceite incoloro. MS/ESI 350 (M+H)⁺; ¹H-RMN (400 MHz, CDCl₃) δ = 0.88 (3 H, s), 1.35 (4 H, m), 1.60 (4 H, m), 1.93 (2 H, m), 2.15 (2 H, m), 2.58 (2 H, m), 2.87 (2 H, m), 2.96 (2 H, m), 3.76 (1 H, m), 6.78 (4 H, m), 6.94 (2 H, m), 7.22 (4 H, m).

Siguiendo el procedimiento del Ejemplo 1, y utilizando como material de partida la (4'-metil-[1,4']bipiperidinil-4-il)-difenil-amina, se pueden preparar los compuestos de la fórmula X₁:



en donde R₂ tiene los significados dados en la Tabla 1.

Tabla 1

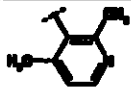
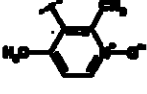
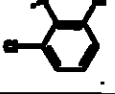
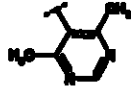
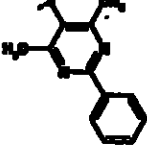
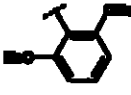
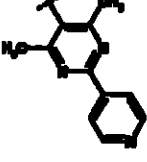
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Ejemplo	R ₂	MS/ESI (M+H) ⁺
2		483
3		499
4		480
5		454
6		470
7		522
8		488
9		484
10		580
11		514
12		581
13		488

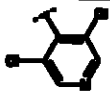
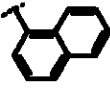
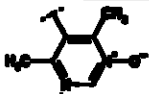
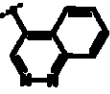
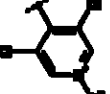
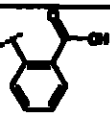
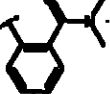
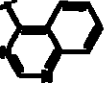
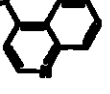
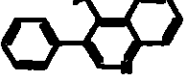
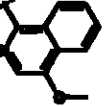
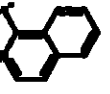
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15

20

25

14		523
15		504
16		500
17		506
18		539
19		496
20		525
21		488
22		506
23		505
24		581
25		535
26		505

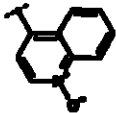
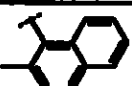
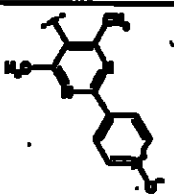
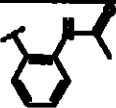
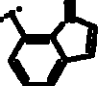
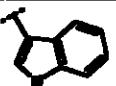
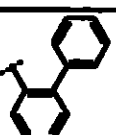
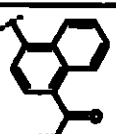
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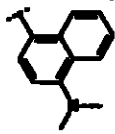
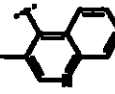
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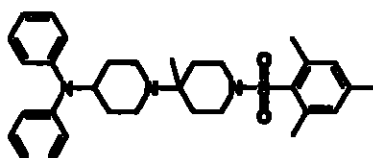
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25

27		506
28		521
29		505
30		505
31		518
32		577
33		511
34		493
35		493
36		530
37		528
38		548

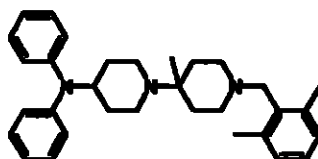
39		547
40		519

Ejemplo 41: [4'-metil-1'-(2,4,6-trimetil-bencensulfonil)-[1,4']bipiperidinil-4-il]-difenilamina



Una mezcla de (4'-metil-[1,4']bipiperidinil-4-il)-difenil-amina (70 miligramos, 0.20 milimoles), y cloruro de 2,4,6-trimetil-bencensulfonilo (65 miligramos, 0.30 milimoles), y di-isopropiletilamina (0.50 mililitros) en cloruro de metileno (3 mililitros), se agita durante 4 horas a temperatura ambiente. La mezcla se diluye con acetato de etilo, se extrae con carbonato ácido de sodio (solución al 10 por ciento), y se seca con sulfato de sodio. El solvente se remueve, y el residuo se somete a cromatografía (SiO₂, t-butilmetiléter/ciclohexano, 1:9->1:0). El compuesto del título se aísla como un sólido incoloro. MS/ESI 532 (M+H)⁺.

Ejemplo 42: [1'-(2,6-dimetilbencil)-4'-metil-

[1,4']bipiperidinil-4-il]-difenil-amina

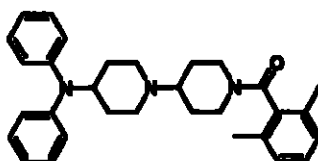
5

Una mezcla de (4'-metil-[1,4']bipiperidinil-4-il)-difenil-amina (70 miligramos, 0.20 milimoles) y 2,6-dimetilbenzaldehído (34 miligramos, 0.25 milimoles) y Na(OAc)₃BH (53 miligramos, 0.25 milimoles) en 1,2-dicloroetano (10 mililitros), se agita a temperatura ambiente durante 16 horas. La mezcla se diluye con acetato de etilo, se extrae con carbonato ácido de sodio (solución al 10 por ciento), y se seca con sulfato de sodio. El solvente se re-

15 mueve, y el residuo se somete a cromatografía (SiO₂, terbutilmetiléter/metanol 1:0 -> 10:1). El compuesto del título se aísla como un sólido incoloro. MS/ESI 468 (M+H)⁺.

Ejemplo 43: (2,6-dimetil-fenil)-(4-difenilamino-[1,4']-bipi-peridinil-1'-il)-metanona

20



25

Una mezcla de sal de TFA de [1,4']bipiperidinil-4-

il-difenil-amina (77 miligramos, 0.23 milimoles), ácido 2,6-dimetilbenzoico (100 miligramos, 0.67 milimoles), tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3-tetrametiluronio (254 miligramos, 0.67 milimoles), EtN(i-Pr)₂ (2 mililitros),
5 y dimetilformamida (3 mililitros), se agita durante 5 horas a temperatura ambiente. La mezcla se diluye con terbutilmetiléter (10 mililitros), se lava con NaOH 2N y salmuera, y se seca con sulfato de sodio. El solvente se remueve, y el residuo se purifica mediante cromatografía (SiO₂, t-butilmetiléter/ciclohexano 1:1 -> acetato de etilo -> acetato de etilo/H₂O, 98:2). El compuesto del título se aísla como un sólido incoloro. MS/ESI 468 (M+H)⁺.
10

La [1,4']bipiperidinil-4-il-difenilamina, utilizada
15 como material de partida, se puede preparar como sigue:

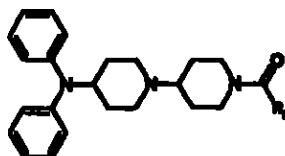
a) Una mezcla de difenil-piperidin-4-il-amina (1.06 gramos; 4.2 milimoles), terbutiléster del ácido 4-oxopiperidin-1-carboxílico (1.0 gramos; 5.0 milimoles), AcOH (0.62 gramos; 10.3 milimoles), y Na(OAc)₃BH (1.0 gramos; 4.7 milimoles) en 1,2-dicloroetano (15 mililitros), se agita durante 4 horas a 65°C. La mezcla se diluye con t-butilmetiléter, se extrae con NaOH 1N, y se seca con sulfato de sodio. El solvente se remueve, y el residuo se somete a
25 cromatografía (SiO₂, t-butilmetiléter/ciclohexano 1:9 ->

1:0). El terbutiléster del ácido 4-difenilamino-[1,4']bipiperidinil-1'-carboxílico se aísla como un sólido incoloro. MS/ESI 436 (M+H)⁺.

5 b) Una mezcla de terbutiléster del ácido 4-difenilamino-[1,4']bipiperidinil-1'-carboxílico (1.06 gramos; 2.4 milimoles), TFA (2.5 mililitros), H₂O (0.25 mililitros), y cloruro de metileno (5 mililitros), se agita a temperatura ambiente durante 4 horas. La mezcla se agrega por goteo a
10 éter, y el precipitado formado se filtra. La sal de TFA de [1,4']bipiperidinil-4-il-difenil-amina se aísla como un sólido incoloro. MS/ESI 336 (M+H)⁺.

 Siguiendo el procedimiento del Ejemplo 2 anterior,
15 y utilizando como material de partida la [1,4']bipiperidinil-4-il-difenil-amina, se pueden preparar los compuestos de la fórmula X₂:

20

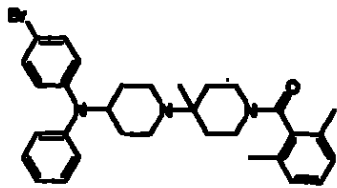


 en donde R₂ tiene uno de los significados dados en
25 las Tabla 2.

Tabla 2

Ejemplo	R ₉	MS/ESI
44		469
45		465
46		470
47		509
48		466
49		547
50		525

Ejemplo 51: {4-[(4-bromofenil)-fenil-amino]-4'-
metil[1,4']-bipiperidinil-1'-il}-(2,6-dimetil-fenil)-metanona



Una mezcla de [4-(4-bromo-fenilamino)-4'-metil-[1,4']bipiperidinil-1'-il]-(2,6-dimetil-fenil)-metanona (97 miligramos; 0.20 milimoles), yodobenceno (41 miligramos; 0.20 milimoles), Pd (OAc)₂ (1.9 miligramos; 0.008 milimoles), BINAP (5.7 miligramos; 0.009 milimoles), y t-BuOK (0.23 mililitros de una solución 1M sobre tetrahidrofurano) en tolueno (3 mililitros), se calienta a 110°C durante 16 horas. La mezcla se diluye con acetato de etilo y se filtra. La solución resultante se extrae con NaOH 2N y salmuera, y se seca con sulfato de sodio. El solvente se remueve, y el residuo se somete a cromatografía (primero SiO₂, t-butilmetiléter/ciclohexano, 1:4 -> 1:0, y subsecuentemente RP-18, metanol/H₂O, 7:3). El compuesto del título se aísla como un sólido incoloro. MS/ESI 560 (M+H)⁺.

La [4-(4-bromo-fenilamino)-4'-metil-[1,4]bipiperidinil-1'-il]-(2,6-dimetilfenil)-metanona, utilizada como material de partida, se puede preparar como sigue:

a) El 8-(1-bencil-4-metil-piperidin-4-il)-1,4-dioxa-8-aza-espiro[4.5]decano se prepara a partir de 1,4-dioxa-8-aza-espiro[4.5]decano y 1-bencil-piperidin-4-ona, siguiendo un procedimiento como se describe en el Ejemplo 1c). MS/ESI 331 (M+H)⁺.

b) Una mezcla de 8-(1-bencil-4-metil-piperidin-4-il)-1,4-dioxa-8-aza-espiro[4.5]decano (2.0 gramos, 0.1 milimoles) y Pd(OH)₂ (20 por ciento) sobre carbón (1 gramo) en

metanol (30 mililitros) se hidrogena durante 16 horas a temperatura ambiente. El catalizador se filtra, y se remueve el solvente. El 8-(4-metil-piperidin-4-il)-1,4-dioxa-8-aza-espiro[4.5]decano crudo se aísla como un aceite amarillo.
5 MS/ESI 241 (M+H)⁺.

c) La (2,6-dimetil-fenil)-[4-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-4-metil-piperidin-1-il]-metanona se obtiene a partir de 8-(4-metil-piperidin-4-il)-1,4-dioxa-8-aza-espiro[4.5]decano crudo y ácido 2,6-dimetil-benzoico, siguiendo un procedimiento como se describe en el Ejemplo 1.
10 MS/ESI 373 (M+H)⁺.

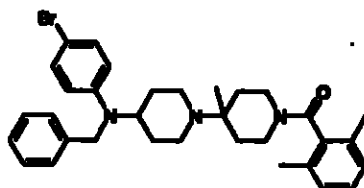
d) Una solución de (2,6-dimetil-fenil)-[4-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-4-metil-piperidin-1-il]-meta-nona (915 miligramos; 2.46 milimoles) en dioxano (30 mililitros) y HCl (6N; 30 mililitros), se agita durante 4 horas a 50°C. La mezcla se diluye con acetato de etilo (50 mililitros), se extrae con NaOH 2N y salmuera, y se seca con sulfato de sodio. La remoción del solvente proporciona la 1'-(2,6-dimetil-benzoil)-4'-metil-[1,4']bipiperidinil-4-ona como
15 un sólido incoloro. MS/ESI 329 (M+H)⁺.

e) Una mezcla de 1'-(2,6-dimetil-benzoil)-4'-metil-[1,4']bipiperidinil-4-ona (49.3 miligramos; 0.15 milimoles), 4-bromo-fenilamina (29 miligramos, 0.165 milimoles), ácido acético (18 miligramos; 0.30 milimoles), y NaBH(OAc)₃
25 (35 miligramos; 0.165 milimoles) en (CH₂Cl)₂ (4 mililitros),

43
84

se agita durante 16 horas a temperatura ambiente. La mezcla se diluye con acetato de etilo, se extrae con NaOH 2N y salmuera, y se seca con sulfato de sodio. El solvente se remueve, y el residuo se somete a cromatografía (RP-18, metanol/H₂O, 8:2->1:0). La [4-(4-bromo-fenil-amino)-4'-metil-[1,4]bipiperidinil-1'-il]-(2,6-dimetil-fenil)-metanona se aísla como un sólido incoloro. MS/ESI 484 (M+H)⁺.

Ejemplo 52: {4-[bencil-(4-bromo-fenil)-amino]-4'-metil-[1,4']bipiperidinil-1'-il]-(2,6-dimetil-fenil)-metanona



15

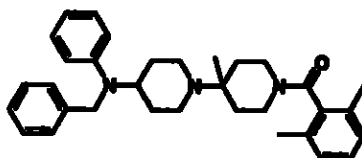
Una mezcla de {4-[(4-bromo-fenil)-fenil-amino]-4'-metil-[1,4']bipiperidinil-1'-il]-(2,6-dimetil-fenil)-metanona (97 miligramos; 0.20 milimoles), bromometil-benceno (376 miligramos, 2.2 milimoles), y K₂CO₃ (138 miligramos; 1.0 milimoles) en dimetilformamida (3 mililitros), se agita a 100°C durante 16 horas. La mezcla se diluye con acetato de etilo, se extrae con NaOH 2N y salmuera, y se seca con sulfato de sodio. El solvente se remueve, y el residuo se somete a cromatografía (primero SiO₂, t-butilmetiléter, y subsecuentemente RP-18, metanol/H₂O 8:2). El compuesto del título se aísla

25

como un sólido incoloro. MS/ESI 574 (M+H)⁺.

Ejemplo 53: [4-(bencil-fenil-amino)-4'-metil-[1,4']bipiperi-dinil-1'-il]-(2,6-dimetil]-fenil)-metanona

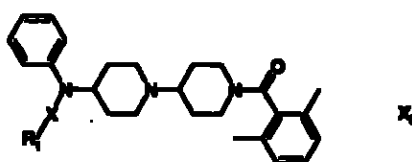
5



Se prepara a partir de (2,6-dimetil-fenil)-(4'-metil-4-fenilamino-[1,4']bipiperidinil-1'-il)-metanona y bromuro de bencilo, siguiendo un procedimiento similar al descrito en el Ejemplo 52. MS/ESI 496 (M+H)⁺. El material de partida se puede preparar a partir de 1'-(2,6-dimetil-benzoil)-4'-metil-[1,4']bipiperidinil-4-ona, siguiendo un procedimiento similar al descrito en el Ejemplo 51e). MS/ESI 406 (M+H)⁺.

Siguiendo el procedimiento del Ejemplo 53 anterior, y utilizando los materiales de partida apropiados, se pueden preparar los compuestos de la fórmula X₃.

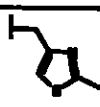
25



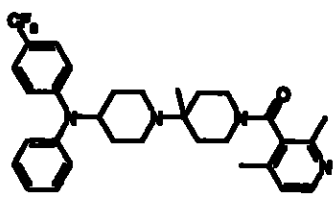
45
88

en donde -X-R₁ tiene los significados indicados en la siguiente Tabla 3.

Tabla 3

Ejemplo	-X-R ₁	MS/ESI (M+H) ⁺
54		517
55		487

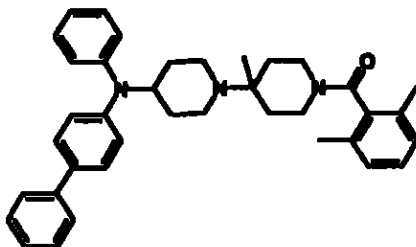
Ejemplo 56: (2,4-dimetil-piridin-3-il)-(4'-metil-4-[fenil-(4-trifluorometil-fenil)-amino]-[1,4']bipiperidinil-1'-il)-metanona



Se prepara a partir de terbutiléster del ácido 4-(4-trifluorometil-fenilamino)-piperidin-1-carboxílico, mediante la utilización de un procedimiento como se describe en el Ejemplo 1. MS/ESI 551 (M+H)⁺. El material de partida se prepara a partir de 4-trifluorometilfenilamina y terbutiléster del ácido 4-oxo-piperidin-1-carboxílico, siguiendo un

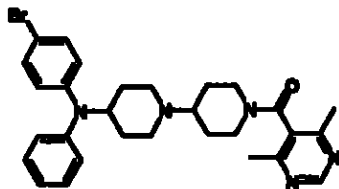
procedimiento como se describe en el Ejemplo 51e). MS/ESI 345 (M+H)⁺.

Ejemplo 57: [4-(bifenil-4-il-fenil-amino)-4'-metil-[1,4']-bipiperidinil-1'-il]-(2,6-dimetil-fenil)-metanona



Se prepara a partir de terbutiléster del ácido 4-fenilamino-piperidin-1-carboxílico y 4-bromobifenilo, mediante la utilización de un procedimiento como se describe en el Ejemplo 1. MS/ESI 558 (M+H)⁺.

Ejemplo 58: {4[(4-bromo-fenil)-fenil-amino]-[1,4']bipiperidinil-1'-il}-(4,6-dimetil-pirimidin-5-il)-metanona.



Se prepara a partir de [1,4']bipiperidinil-4-il-(4-bromo-fenil)-fenil-amina y ácido 4,6-dimetil-pirimidin-5-carboxílico, siguiendo un procedimiento como se describe en el

Ejemplo 1. MS/ESI 548 (M+H)⁺.

La [1,4']bipiperidinil-4-il-(4-bromo-fenil)-fenil-amina utilizada como material de partida, se puede preparar como sigue:

5 a) El terbutiléster del ácido 4-(4-bromo-fenilamino)-piperidin-1-carboxílico se prepara a partir de 4-bromo-fenilamina y terbutiléster del ácido 4-oxo-piperidin-1-carboxílico, como se describe en el Ejemplo 51e). MS/ESI 355 (M+H)⁺.

10 b) El terbutiléster del ácido 4-[(4-bromo-fenil)-fenil-amino]-piperidin-1-carboxílico se prepara a partir de terbutiléster del ácido 4-(4-bromo-fenilamino)-piperidin-1-carboxílico y yodo-benceno, como se describe en el Ejemplo 51. MS/ESI 431 (M+H)⁺.

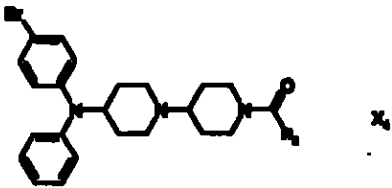
15 c) La (4-bromo-fenil)-fenil-piperidin-4-il-amina se prepara a partir de terbutiléster del ácido 4-[(4-bromo-fenil)-fenil-amino]-piperidin-1-carboxílico como se describe en el Ejemplo 1b). MS/ESI 331 (M+H)⁺.

20 d) El terbutiléster del ácido 4-[(4-bromo-fenil)-fenil-amino]-[1,4']bipiperidinil-1'-carboxílico se prepara a partir de (4-bromo-fenil)-fenil-piperidin-4-il-amina y terbutiléster del ácido 4-oxo-piperidin-1-carboxílico como se describe en el Ejemplo 43a). MS/ESI 514 (M+H)⁺.

25 e) La [1,4']bipiperidinil-4-il-(4-bromo-fenil)-fenil-amina se prepara a partir de terbutiléster del ácido 4-

{(4-bromo-fenil)-fenil-amino}-[1,4']bipiperidinil-1'-carboxílico como se describe en el Ejemplo 1b). MS/ESI 414 (M+H)⁺.

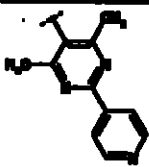
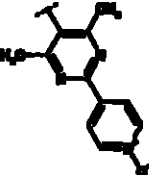
Utilizando un procedimiento como se da a conocer anteriormente, y los materiales de partida correspondientes, se pueden preparar los compuestos de la fórmula X₄:



en donde R₂ es como se define en la siguiente Tabla 4.

Tabla 4

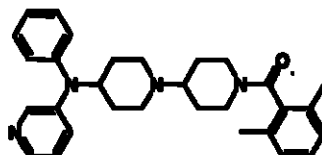
Ejemplo	R ₂	MS/ESI (M+H) ⁺
59		546
60		567
61		603
62		563
63		564
64		548

65		625
66		641

5

10

Ejemplo 67: (2,6-dimetil-fenil)-[4-(fenil-piperidin-3-il-amino)-[1,4']bipiperidinil-1'-il]-metanona

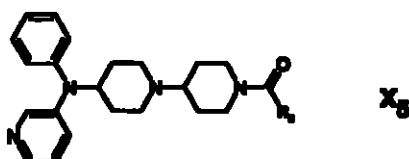


15

Se prepara a partir de terbutiléster del ácido 4-fenilamino-piperidin-1-carboxílico y 3-bromo-piridina, utilizando un procedimiento como se describe en los Ejemplos 58 y 58b) a e). MS/ESI 469 (M+H)⁺.

20

Siguiendo un procedimiento como se da a conocer anteriormente, se pueden preparar los compuestos de la fórmula X₅.

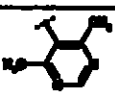
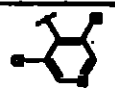
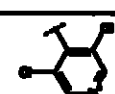
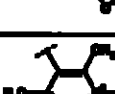


25

en donde R₂ es como se da en la siguiente Tabla 5.

Tabla 5

5

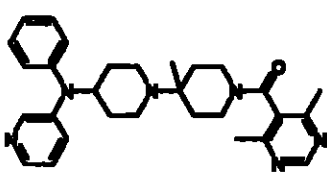
Ejemplo	R ₂	MS/ESI (M+H) ⁺
68		471
69		510
70		526
71		486
72		487

10

15

Ejemplo 73: (4,6-dimetil-pirimidin-5-il)-[4'-metil-4-(fenil-piperidin-3-il-amino)-[1,4']bipiperidinil-1'-il]-metanona

20

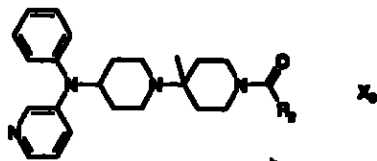


25

Se prepara a partir de fenil-piperidin-4-il-piridin-3-il-amina y terbutiléster del ácido 4-fenilamino-

piperidin-1-carboxílico, utilizando un procedimiento como se describe en los Ejemplos 1, 1c) y 1d). MS/ESI 485 (M+H)⁺.

Siguiendo el procedimiento como se da a conocer en el Ejemplo 73, se pueden preparar los compuestos de la fórmula X₆:

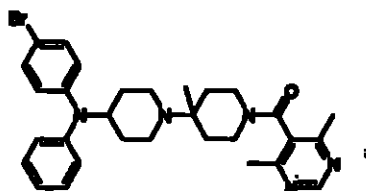


en donde R₂ tiene los significados indicados en la Tabla 6.

Tabla 6

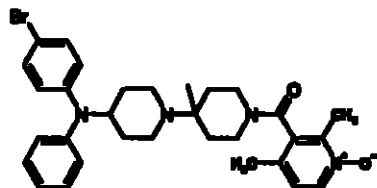
Ejemplo	R ₂	MS/ESI (M+H) ⁺
74		500
75		540
76		483

Ejemplo 77: (4-[(4-bromo-fenil)-fenil-amino]-4'-metil-[1,4']bipiperidinil-1'-il)-(4,6-dimetil-piperimidin-5-il)-metanona



Se prepara a partir de (4-bromo-fenil)-fenil-
 5 piperidin-4-il-amina y terbutiléster del ácido 4-fenilamino-
 piperidin-1-carboxílico, utilizando un procedimiento como se
 describe en los Ejemplos 1, 1c) y 1d). MS/ESI 562 (M+H)⁺.

Ejemplo 78: {4-[4-bromo-fenil)-fenil-amino)-4'-metil-
 10 [1,4']bipiperidinil-1'-il)-(2,4-dimetil-1-oxipiridin-3-
 il)metanona

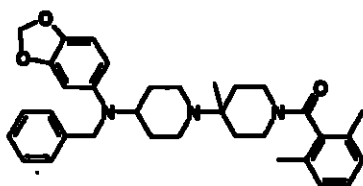


15

Se prepara a partir de (4-bromo-fenil)-fenil-
 piperidin-4-il-amina y terbutiléster del ácido 4-fenilamino-
 piperidin-1-carboxílico, utilizando un procedimiento como se
 describe en los Ejemplos 1, 1c), y 1d). MS/ESI 577 (M+H)⁺.

20

Ejemplo 79: [4-(benzo[1,3]dioxol-5-il-bencil-amino)-4'-
 metil-[1,4']bipiperidinil-1'-il)-(2,6-dimetil-fenil)-metanona



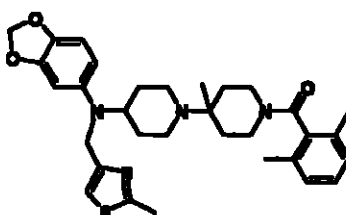
25

Se prepara a partir de 1'-(2,6-dimetil-benzoil)-4'-metil-[1,4']bipiperidinil-4-ona y benzo[1,3]dioxol-5-ilamina, siguiendo un procedimiento como se describe en los Ejemplos 51 y 52. MS/ESI 540 (M+H)⁺.

5

Ejemplo 80: {4-[1,3-benzodioxol-5-il-(2-metil-tiazol-4-ilmetil)-amino]-4'-metil-1,4'-bipiperidinil-1'-il}-(2,6-dimetil-fenil)-metanona

10

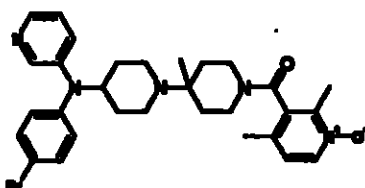


Se prepara a partir de 1'-(2,6-dimetil-benzoil)-4'-metil-[1,4']bipiperidinil-4-ona y benzo-[1,3]dioxol-5-ilamina, siguiendo un procedimiento como se describe en los Ejemplos 51 y 52. MS(ESI) (M+H)⁺.

15

Ejemplo 81: {4-[(4-bromo-fenil)-piridin-3-il-amino]-4'-metil-[1,4']bipiperidinil-1'-il}-(2,4-dimetil-1-oxi-piridin-3-il)-metanona

20



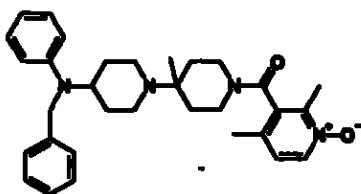
25

Se prepara a partir de terbutiléster del ácido 4-(piridin-3-ilamino)-piperidin-1-carboxílico y 1,4-dibromobenceno, siguiendo un procedimiento como se describe en el Ejemplo 1. MS/ESI 578 (M+H)⁺.

5

Ejemplo 82: [4-(bencil-fenil-amino)-4'-metil-[1,4']bipiperidinil-1'-il]-(2,4-dimetil-1-oxi-piridin-3-il)-metanona

10

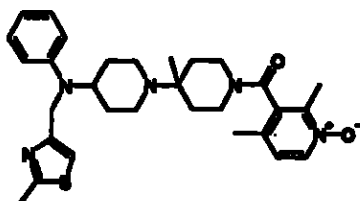


15

Se prepara a partir de fenil-piperidin-4-il-amina, siguiendo un procedimiento como se describe en los Ejemplos 52 y 1. MS/ESI 513 (M+H)⁺.

Ejemplo 83: (2,4-dimetil-1-oxi-piridin-3-il)-[4'-[(2-metil-tiazol-4-ilmetil)-fenil-amino]-[1,4']bipiperidinil-1'-il]-metanona

20



25

Se prepara a partir de (4'-metil-

[1,4']bipiperidinil-4-il)-)-(2-metil-tiazol-4-ilmetil)-fenil-
amina utilizando un procedimiento como se describe en el
Ejemplo 1. MS/ESI 534 (M+H)⁺.

La (4'-metil-[1,4']bipiperidinil-4-il)-(2-metil-
5 tiazol-4-ilmetil)-fenil-amina, utilizada como material de
partida, se obtiene como sigue: una mezcla de terbutiléster
del ácido 4-(bencil-fenilamino)-4'-metil-[1,4']bipiperidinil-
1'-carboxílico (1.0 gramos, 2.16 milimoles), formato de amo-
nio (0.5 gramos, 7.92 milimoles), y Pd(OH)₂ (20 por ciento)
10 sobre carbón (0.25 gramos) en metanol (25 mililitros), se ca-
lienta bajo reflujo durante 3 horas. El catalizador se fil-
tra y se lava con metanol. El solvente se remueve, y el re-
siduo se disuelve en acetato de etilo. La solución orgánica
se extrae con NaOH 1N y salmuera, y se seca con sulfato de
15 sodio. La remoción del solvente da el terbutiléster del áci-
do 4'-metil-4-fenilamino-[1,4']bipiperidinil-1'-carboxílico
crudo, el cual se utiliza en el siguiente paso sin mayor pu-
rificación. MS/ESI 374 (M+H)⁺.

El terbutiléster del ácido 4'-metil-4-fenilamino-
20 [1,4']bipiperidinil-1'-carboxílico se convierte en la (4'-
metil-[1,4']bipiperidinil-4-il)-(2-metil-tiazol-4-ilmetil)-
fenil-amina, utilizando un procedimiento como se describe en
los Ejemplos 52 y 1d).

Los compuestos de la fórmula I en forma libre o en
25 forma de sal farmacéuticamente aceptable, exhiben valiosas

propiedades farmacológicas, por ejemplo como antagonistas de CCR5, por ejemplo como se indica en las pruebas *in vitro*, y por consiguiente, se indican para terapia.

5 a) Ensayo de enlace de membrana CCR5

Se utiliza CCR5 humana para generar transfectantes estables en células CHO K1. Las membranas preparadas a partir de estos transfectantes CCR5 se utilizan en un ensayo de enlace de radioligando utilizando 125-I MIP-1 α como un ligando, y se prueban los compuestos de la fórmula I para determinar su actividad inhibidora. Los datos se reportan como IC₅₀, es decir, la concentración del compuesto requerida para alcanzar una inhibición del 50 por ciento del enlace de [I-125]MIP-1 α . En este ensayo, los compuestos de la fórmula I
10 tienen una IC₅₀ $\leq$ 1 μ M. Los compuestos de los Ejemplos 16, 53, y 83, tienen una IC₅₀ de 2 a 3 nM, respectivamente.

b) Ensayo funcional de CCR5 - movilización de Ca²⁺

Se utiliza CCR5 humana para generar transfectantes estables en células CHO K1. Estos transfectantes CCR5 se utilizan para evaluar la movilización de Ca²⁺ en respuesta al estímulo por parte de los ligandos de CCR5, MIP-1 α , MIP-1 β , HCC-1(9-74) ó RANTES. Para el ensayo, las células se cargan con un fluorocromo sensible a Ca²⁺ (Fluo3 ó Fluo4). Se utilizan concentraciones de ligando entre 0.01 y 100 nM para indu-
20
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cir la movilización de Ca^{2+} , que se monitorea en un fluorómetro con las posiciones apropiadas.

Para evaluar la actividad de los compuestos que se van a probar, se toma una lectura de fluorescencia de la línea base, después de lo cual se agregan los compuestos en la concentración deseada a las células, y se registra adicionalmente la fluorescencia durante cierto tiempo para evaluar si los compuestos muestran efectos agonistas. Enseguida, se agrega el agonista a la mezcla y se monitorea la fluorescencia. La inhibición del flujo de Ca^{2+} en la presencia de los compuestos que se van a probar, se calcula a partir de la inhibición de la máxima fluorescencia inducida por el agonista. Los valores IC_{50} se calculan a partir de las curvas de respuesta a la dosis obtenidas con los compuestos. En este ensayo, los compuestos de la fórmula I tienen una $\text{IC}_{50} \leq 1\mu\text{M}$. Por ejemplo, los compuestos de los Ejemplos 1, 18, y 52 tienen una IC_{50} de 10, 9, y 4, respectivamente.

c) Ensayo funcional de CCR5 - quimiotaxis

Se generan transfectantes de CCR5 en células Jurkat T o en la línea celular pre-B de ratón L1.2. La migración de los transfectantes CCR5 se prueba en un sistema de insertos de cámara de tejido transpozos con el agonista de CCR5, MIP-1 α , en concentraciones de 1 a 100 nM. Las células migradas en respuesta al agonista, comparándose con un control regula-

dor, se cuantifican en un citómetro de flujo. Los compuestos que se van a probar se agregan a las células y a los compartimientos de agonista. Los valores IC_{50} se calculan a partir de las curvas de concentración-respuesta obtenidas con los compuestos en la presencia de MIP-1 α . En este ensayo, los compuestos de la fórmula I tienen una $IC_{50} \leq 1\mu M$.

d) Los experimentos realizados en modelos animales de murino muestran que se inhibe de una manera significativa la remodelación de la pared del vaso después de una lesión experimental (por ejemplo, inducida mediante alotrasplante) en ausencia de las CCR5 funcional.

Por consiguiente, los compuestos de la fórmula I son útiles en la prevención y/o el tratamiento de enfermedades o desórdenes mediados por las interacciones entre los receptores de quimiocina, por ejemplo CCR5, y sus ligandos, por ejemplo en trasplante, tales como rechazo agudo o crónico de alo- o xenoinjertos de órganos, tejidos o células, o función de injerto demorada, enfermedades autoinmunes, por ejemplo artritis reumatoide, lupus eritematoso sistémico, tiroiditis de Hashimoto, esclerosis múltiple, miastenia gravis, diabetes tipo I ó II y los desórdenes asociados con la misma, vasculitis, anemia perniciosa, síndrome de Sjogren, uveítis, psoriasis, alopecia areata, y otras; enfermedades alérgicas, por ejemplo asma alérgico, dermatitis atópica, rinitis/conjuntivitis alérgica, dermatitis alérgica por contacto,

enfermedades inflamatorias opcionalmente con reacciones aberrantes subyacentes, por ejemplo enfermedad inflamatoria del intestino, enfermedad de Crohn o colitis ulcerativa, asma intrínseco, lesión inflamatoria del pulmón, lesión inflamatoria del hígado, lesión inflamatoria glomerular, aterosclerosis, osteoartritis, por contacto irritante, y además dermatitis eczematosas, dermatitis seborreica, manifestaciones cutáneas de desórdenes inmunológicamente mediados, enfermedad inflamatoria de los ojos, queraconjuntivitis, miocarditis o hepatitis, lesión por isquemia/reperfusión, por ejemplo infarto del miocardio, embolia, isquemia del intestino, insuficiencia renal o choque hemorrágico, choque traumático y otros, cáncer, por ejemplo tumores sólidos o cáncer linfático, tal como linfomas de células T, o leucémicas de células T, metástasis o angiogénesis, enfermedades infecciosas, por ejemplo choque tóxico (por ejemplo inducido por superantígeno), choque séptico, síndrome de insuficiencia respiratoria de adultos o infecciones virales, por ejemplo sida. Transplante significa alo-xeno-injertos, por ejemplo de células, tejidos, u órganos sólidos, por ejemplo islotes pancreáticos, células de tallo, médula ósea, tejido córneo, tejido neuronal, corazón, pulmón, corazón-pulmón combinados, riñón, hígado, intestino, páncreas, tráquea, o esófago. Al rechazo crónico también se le denomina enfermedad de vasos de injerto.

Para los usos anteriores, la dosificación requeri-

da, por supuesto, variará dependiendo del modo de administración, de la condición particular que se vaya a tratar, y del efecto deseado. En general, se indica que se obtienen resultados satisfactorios sistémicamente en dosificaciones diarias de aproximadamente 0.01 a 10 miligramos/kilogramo de peso del cuerpo. Una dosificación diaria indicada en el mamífero superior, por ejemplo en el ser humano, está en el rango de aproximadamente 0.5 miligramos a aproximadamente 1,000 miligramos, convenientemente administrados, por ejemplo, en dosis divididas hasta 4 veces al día, o en una forma retardada. Las formas de dosificación unitaria adecuadas para administración oral comprenden de aproximadamente 1 a 500 miligramos de ingrediente activo.

Los compuestos de la fórmula I se pueden administrar mediante cualquier vía convencional, en particular enteralmente, por ejemplo oralmente, por ejemplo en la forma de tabletas o cápsulas, o parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables, tópicamente, por ejemplo en la forma de lociones, geles, ungüentos, o cremas, o en una forma nasal o de supositorio. Las composiciones farmacéuticas que comprenden un compuesto de la fórmula I en forma libre o en forma de sal farmacéuticamente aceptable en asociación con cuando menos un vehículo o diluyente farmacéuticamente aceptable, se pueden fabricar de una manera convencional mezclándose con un vehículo o diluyente farmacéuti-

camente aceptable.

Los compuestos de la fórmula I se pueden administrar en forma libre o en forma de sal farmacéuticamente aceptable, por ejemplo como se indica anteriormente. Estas sales
5 se pueden preparar de una manera convencional, y exhiben el mismo orden de actividad que los compuestos libres.

De acuerdo con lo anterior, la presente invención proporciona además:

1.1 Un método para prevenir o tratar desórdenes o
10 enfermedades mediadas por las interacciones entre los receptores de quimiocina y sus ligandos, por ejemplo tales como se indican anteriormente, en un sujeto que necesita dicho tratamiento, cuyo método comprende administrar a este sujeto una cantidad efectiva de un compuesto de la fórmula I o una sal
15 farmacéuticamente aceptable del mismo.

1.2 Un método para prevenir o tratar rechazo de transplante agudo o crónico o enfermedades inflamatorias o autoinmunes, por ejemplo como se indica anteriormente, en un sujeto que necesite dicho tratamiento, cuyo método comprende
20 administrar a este sujeto una cantidad efectiva de un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo.

2. Un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo, para utilizarse como
25 un producto farmacéutico, por ejemplo en cualquiera de los métodos indicados en 1.1 ó 1.2 anteriores.

dos indicados en 1.1 ó 1.2 anteriores.

3. Una composición farmacéutica, por ejemplo para utilizarse en cualquiera de los métodos como en 1.1 ó 1.2 anteriores, la cual comprende un compuesto de la fórmula I o una sal farmacéuticamente aceptable de mismo, en asociación con un diluyente o vehículo farmacéuticamente aceptable para el mismo.

4. Un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo, para utilizarse en la preparación de una composición farmacéutica para uso en cualquier método como en 1.1 ó 1.2 anteriores.

Los compuestos de la fórmula I se pueden administrar como el único ingrediente activo, o en conjunto con, por ejemplo, como un adyuvante para, otros fármacos, por ejemplo en regímenes inmunosupresivos o inmunomoduladores, u otros agentes anti-inflamatorios, por ejemplo para el tratamiento o la prevención de rechazo agudo o crónico de alo- o xenoinjerto o desórdenes inflamatorios o autoinmunes, un agente quimioterapéutico o un agente anti-infeccioso, por ejemplo un agente antiviral, tal como, por ejemplo, un agente anti-retroviral o un antibiótico. Por ejemplo, los compuestos de la fórmula I, se pueden utilizar en combinación con un inhibidor de calcineurina, por ejemplo ciclosporina A ó FK 506; una lactona macrocíclica que tenga propiedades inmunosupresoras, por ejemplo rapamicina, 40-O-(2-hidroxietil)-rapamicina,

CC1779 ó ABT578; una ascomicina que tenga propiedades inmuno-
supresoras, por ejemplo ABT-281, ASM981, etcétera; corticos-
teroides; ciclofosfamida; azatioprina; metotrexato; lefluno-
mida; mizoribina; ácido micofenólico; micofenolato-mofetil;
5 15-desoxiespergualina o un homólogo, análogo, o derivado in-
munosupresor de la misma; un agente iniciador de la acelera-
ción de linfocitos, por ejemplo FTY720; anticuerpos monoclo-
nales para receptores de leucocitos, por ejemplo MHC, CD2,
CD3, CD4, CD7, CD8, CD11a/CD18, CD25, CD27, CD28 CD40, CD45,
10 CD58, CD80, CD86, CD137, ICOS, CD150 (SLAM), OX40, 4-1BB, o
sus ligandos, por ejemplo CD154, o antagonistas de los mis-
mos; otros compuestos inmunomoduladores, por ejemplo una mo-
lécula de enlace recombinante que tenga cuando menos una por-
ción del dominio extracelular de CTLA4 o un mutante de la
15 misma, por ejemplo cuando menos una porción extracelular de
CLTA4 o un mutante de la misma unido a una secuencia que no
sea de la proteína CTLA4, por ejemplo CTLA4Ig (por ejemplo,
la designada ATCC 68629) o un mutante de la misma, por ejem-
plo LEA29Y; inhibidores de moléculas de adhesión, por ejemplo
20 antagonistas de LFA-1, antagonistas de ICAM-1 ó -3, antago-
nistas de VCAM-4, o antagonistas de VLA-4; o anticuerpos an-
tiquimiocina o anticuerpos de receptores antiquimiocina, o
antagonistas de receptores de quimiocina de bajo peso molecu-
lar, por ejemplo anticuerpos anti-MCP-1.

25 Cuando los compuestos de la fórmula I se adminis-

tran en conjunto con otra terapia inmunosupresora/inmunomoduladora, anti-inflamatoria o quimioterapéutica, las dosificaciones del compuesto inmunosupresor, inmunomodulador, anti-inflamatorio, o quimioterapéutico co-administrado, por supuesto, variarán dependiendo del tipo de co-fármaco empleado, por ejemplo, si es un esteroide o un inhibidor de calcineurina, del fármaco específico empleado, de la condición que se esté tratando, etcétera. De acuerdo con lo anterior, la presente invención proporciona, en un aspecto todavía adicional:

5. Un método como se define anteriormente, el cual comprende la co-administración, por ejemplo de una manera concomitante o en secuencia, de una cantidad no tóxica terapéuticamente efectiva de un compuesto de la fórmula I y cuando menos una segunda sustancia de fármaco, por ejemplo un fármaco inmunosupresor, anti-inflamatorio, anti-infeccioso, o quimioterapéutico, por ejemplo como se indica anteriormente.

6. Una combinación farmacéutica, por ejemplo un estuche, que comprende: a) un primer agente que es un antagonista de CCR5, por ejemplo un compuesto de la fórmula I como se da a conocer en la presente, en forma libre o en forma de sal farmacéuticamente aceptable, y b) cuando menos un co-agente, por ejemplo un fármaco inmunosupresor, inmunomodulador, anti-inflamatorio, anti-infeccioso, o quimioterapéutico. El estuche puede comprender instrucciones para su administra-

ción.

Los términos "co-administración" o "administración combinada", o similares, como se utiliza en la presente, abarcan la administración de los agentes terapéuticos seleccionados a un solo paciente, y pretenden incluir los regímenes de tratamiento en donde los agentes no necesariamente se administran por la misma vía de administración o al mismo tiempo.

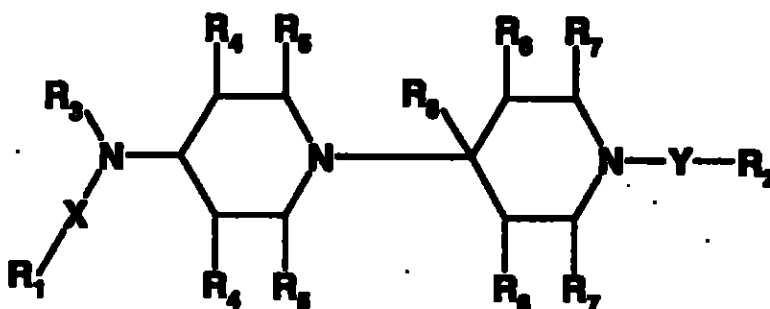
El término "combinación farmacéutica", como se utiliza en la presente, significa un producto que resulta de la mezcla o combinación de más de un ingrediente activo, e incluye tanto combinaciones fijas como no fijas de los ingredientes activos. El término "combinación fija" significa que los ingredientes activos, por ejemplo un compuesto de la fórmula I y un co-agente, se administran ambos a un paciente de una manera simultánea en la forma de una sola entidad o dosificación. El término "combinación no fija" significa que los ingredientes activos, por ejemplo un compuesto de la fórmula I y un co-agente, se administran ambos a un paciente como entidades separadas, ya sea de una manera simultánea, concurrente, o en secuencia, sin límites de tiempo específicos, en donde esta administración proporciona niveles terapéuticamente efectivos de los dos compuestos en el cuerpo del paciente. Esto último también se aplica a una terapia de cóctel, por ejemplo la administración de 3 ó más ingredientes activos.

REIVINDICACIONES

1. Un compuesto de la fórmula I:

5

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en donde:

X es un enlace directo; -CH₂-; -CH₂-CH₂-; CHR₉-
 15 ; -C(O)-; -O-; -NH- ó NR₉;

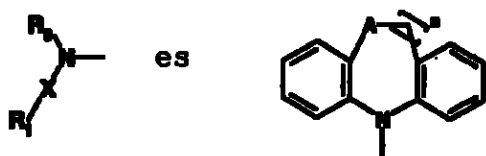
R₁ es fenilo opcionalmente sustituido por R₁₀ y/o R₁₁; heteroarilo opcionalmente sustituido por R₁₀ y/o R₁₁; N-
 óxido de heteroarilo opcionalmente sustituido por R₁₀ y/o R₁₁;
 o naftilo opcionalmente sustituido por R₁₀ y/o R₁₁;

20 R₂ tiene uno de los significados dados para R₁; o es fluorenilo opcionalmente sustituido por R₁₀ y/o R₁₁; alquilo de 1 a 6 átomos de carbono opcionalmente sustituido por R₁₀; alquenilo de 2 a 6 átomos de carbono opcionalmente sustituido por R₁₀; cicloalquilo de 3 a 6 átomos de carbono opcionalmente
 25 sustituido por R₁₀; adamantilo opcionalmente sustituido por

R_{10} ; o cicloalqueno de 4 a 6 átomos de carbono opcionalmente sustituido por R_{10} ;

R_3 tiene uno de los significados dados para R_1 ; o es fluorenilo opcionalmente sustituido por R_{10} y/o R_{11} ; alquilo de 1 a 6 átomos de carbono sustituido por R_{10} ; alqueno de 2 a 6 átomos de carbono opcionalmente sustituido por R_{10} ; cicloalquilo de 3 a 6 átomos de carbono opcionalmente sustituido por R_{10} ; adamantilo opcionalmente sustituido por R_{10} ; o cicloalqueno de 4 a 8 átomos de carbono opcionalmente sustituido por R_{10} ;

ó



15

en donde A es $-\text{CH}_2-$, $-\text{NH}-$, $-\text{NR}_3-$, $-\text{S}-$, $-\text{SO}-$, SO_2- u $-\text{O}-$; n es 0, 1, ó 2, y los anillos aromáticos están cada uno independientemente opcionalmente sustituidos por R_{10} ;

cada uno de R_4 tiene independientemente uno de los significados de R_5 ; ó es CN ; OH ; OR_3 ; F ; Cl ; Br ; ó I ;

cada uno de R_5 es independientemente H; alquilo de 1 a 6 átomos de carbono; hidroxialquilo de 1 a 6 átomos de carbono; alcoxialquilo de 2 a 6 átomos de carbono; haloalquilo de 1 a 6 átomos de carbono; fenilo; bencilo; o heteroarilo;

25

cada uno de R_6 tiene independientemente uno de los significados dados para R_4 ;

cada uno de R_7 tiene independientemente uno de los significados dados para R_5 ;

5 R_8 es H; alquilo de 1 a 6 átomos de carbono; alqueni-
lo de 2 a 6 átomos de carbono; alquinilo de 2 a 6
átomos de carbono; fenilo; bencilo; CN; CH_2NH_2 ; CH_2NHR_9 ;
 $\text{CH}_2\text{NR}_9\text{R}_9$; $\text{CH}_2\text{NHC}(\text{O})\text{R}_9$; $\text{CH}_2\text{NR}_9\text{C}(\text{O})\text{R}_9$; $\text{CH}_2\text{NHC}(\text{O})\text{NHR}_9$;
 $\text{CH}_2\text{NR}_9\text{C}(\text{O})\text{NHR}_9$; $\text{CH}_2\text{NR}_9\text{C}(\text{O})\text{NR}_9\text{R}_9$; $\text{CH}_2\text{NHC}(\text{O})\text{OR}_9$; $\text{CH}_2\text{NR}_9\text{C}(\text{O})\text{OR}_9$;
10 $\text{CH}_2\text{NH}\text{SO}_2\text{R}_9$; $\text{CH}_2\text{N}(\text{SO}_2\text{R}_9)_2$; ó $\text{CH}_2\text{NR}_9\text{SO}_2\text{R}_9$;

cada R_9 es independientemente alquilo de 1 a 6 áto-
mos de carbono; cicloalquilo de 3 a 6 átomos de carbono; al-
queni-
lo de 2 a 6 átomos de carbono; alquinilo de 2 a 6 átomos
de carbono; fenilo; bencilo; heteroarilo; o CF_3 ;

15 R_{10} representa de 1 a 4 sustituyentes independiente-
mente seleccionados a partir de alquilo de 1 a 6 átomos de
carbono; hidroxialquilo de 1 a 6 átomos de carbono; alcoxial-
quilo de 2 a 6 átomos de carbono; haloalquilo de 1 a 6 átomos
de carbono; cicloalquilo de 3 a 6 átomos de carbono; alqueni-
20 lo de 2 a 6 átomos de carbono; cicloalqueni-
lo de 3 a 6 átomos de carbono; alquinilo de 2 a 6 átomos de carbono; fenilo;
heteroarilo; N-óxido de heteroarilo; F; Cl; Br; I; OH; OR_9 ;
 CONH_2 ; CONHR_9 ; CONR_9R_9 ; $\text{OC}(\text{O})\text{R}_9$; $\text{OC}(\text{O})\text{OR}_9$; $\text{OC}(\text{O})\text{NHR}_9$;
 $\text{OC}(\text{O})\text{NR}_9\text{R}_9$; OSO_2R_9 ; COOH ; COOR_9 ; CF_3 ; CHF_2 ; CH_2F ; CN; NO_2 ; NH_2 ;
25 NHR_9 ; NR_9R_9 ; $\text{NHC}(\text{O})\text{R}_9$; $\text{NR}_9\text{C}(\text{O})\text{R}_9$; $\text{NHC}(\text{O})\text{NHR}_9$; $\text{NHC}(\text{O})\text{NH}_2$;

$\text{NR}_9\text{C}(\text{O})\text{NHR}_9$; $\text{NR}_9\text{C}(\text{O})\text{NR}_9\text{R}_9$; $\text{NHC}(\text{O})\text{OR}_9$; $\text{NR}_9\text{C}(\text{O})\text{OR}_9$; NHSO_2R_9 ;
 $\text{N}(\text{SO}_2\text{R}_9)_2$; $\text{NR}_9\text{SO}_2\text{R}_9$; SR_9 ; $\text{S}(\text{O})\text{R}_9$; SO_2R_9 ; $\text{Si}(\text{CH}_3)_3$ y $\text{B}(\text{OC}(\text{CH}_3)_2)_2$;

R_{11} represente dos sustituyentes adyacentes que forman un anillo no aromático anulado de 4 a 7 miembros que contiene opcionalmente hasta dos heteroátomos seleccionados independientemente a partir de N, O, y S; e

Y es un enlace directo; $-\text{C}(\text{O})-$; $-\text{C}(\text{O})\text{CH}_2-$ $-\text{S}(\text{O})-$;
 $-\text{S}(\text{O}_2)-$; $-\text{C}(\text{S})-$; $-\text{CH}_2-$; $-\text{C}(-\text{CH}_2-\text{CH}_2)-$; $-\text{CH}(\text{R}_4)-$ ó $-\text{C}(\text{R}_5)_2-$,
 en forma libre o en forma de sal.

2. Un compuesto de acuerdo con la reivindicación 1, en donde R_1 es fenilo o heteroarilo, estando cada uno opcionalmente sustituido por R_{10} ; o fenilo opcionalmente sustituido por R_{11} ; en donde R_{10} representa de 1 a 3 sustituyentes independientemente seleccionados a partir de alquilo de 1 a 6 átomos de carbono; hidroxialquilo de 1 a 6 átomos de carbono; alcoxialquilo de 2 a 6 átomos de carbono; haloalquilo de 1 a 6 átomos de carbono; cicloalquilo de 3 a 6 átomos de carbono; alquenilo de 2 a 6 átomos de carbono; cicloalquenilo de 3 a 6 átomos de carbono; alquinilo de 2 a 6 átomos de carbono; fenilo; heteroarilo; N-óxido de heteroarilo; F; Cl; Br; I; OH; OR_9 ; CONH_2 ; CONHR_9 ; CONR_9R_9 ; $\text{OC}(\text{O})\text{R}_9$; $\text{OC}(\text{O})\text{OR}_9$; $\text{OC}(\text{O})\text{NHR}_9$; $\text{OC}(\text{O})\text{NR}_9\text{R}_9$; OSO_2R_9 ; COOH ; COOR_9 ; CF_3 ; CHF_2 ; CH_2F ; CN ; NO_2 ; NH_2 ; NHR_9 ; NR_9R_9 ; $\text{NHC}(\text{O})\text{R}_9$; $\text{NR}_9\text{C}(\text{O})\text{R}_9$; $\text{NHC}(\text{O})\text{NHR}_9$; $\text{NHC}(\text{O})\text{NH}_2$; $\text{NR}_9\text{C}(\text{O})\text{NHR}_9$; $\text{NR}_9\text{C}(\text{O})\text{NR}_9\text{R}_9$; $\text{NHC}(\text{O})\text{OR}_9$; $\text{NR}_9\text{C}(\text{O})\text{OR}_9$; NHSO_2R_9 ; $\text{N}(\text{SO}_2\text{R}_9)_2$; $\text{NR}_9\text{SO}_2\text{R}_9$; SR_9 ; $\text{S}(\text{O})\text{R}_9$; SO_2R_9 ; y $\text{Si}(\text{CH}_3)_3$, y R_{11} un ani-

llo no aromático anulado de 5 ó 6 miembros que contiene opcionalmente 1 ó 2 átomos de oxígeno, y que está unido a dos átomos de carbono adyacentes.

3. Un compuesto de acuerdo con la reivindicación 1, en donde cada uno de R_4 , R_5 , R_6 , ó R_7 es independientemente H, alquilo de 1 a 6 átomos de carbono; o bencilo.

4. Un compuesto de acuerdo con la reivindicación 1, en donde R_8 es H; alquilo de 1 a 6 átomos de carbono; o alquenilo de 2 a 6 átomos de carbono.

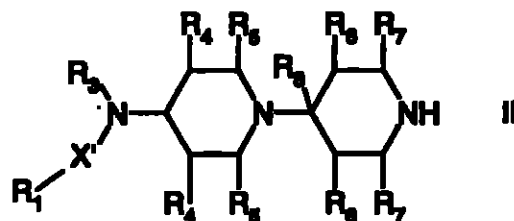
5. Un compuesto de acuerdo con la reivindicación 1, en donde X es un enlace directo o $-\text{CH}_2-$, y/o Y es $-\text{C}(\text{O})-$.

6. Un proceso para la preparación de un compuesto de la fórmula I de acuerdo con la reivindicación 1, cuyo proceso comprende:

a) para la preparación de un compuesto de la fórmula I, en donde X es un enlace directo, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$ ó $-\text{CHR}_9-$ e Y es $-\text{CO}-$, $-\text{C}(\text{O})\text{CH}_2-$, $-\text{S}(\text{O})-$ ó $-\text{S}(\text{O}_2)-$,

amidar un compuesto de la fórmula II:

20



en donde R_1 y R_3 a R_9 son como se indica anteriormente, y X' es un enlace directo, $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$ ó $-\text{CHR}_9-$

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con un compuesto de la fórmula III:

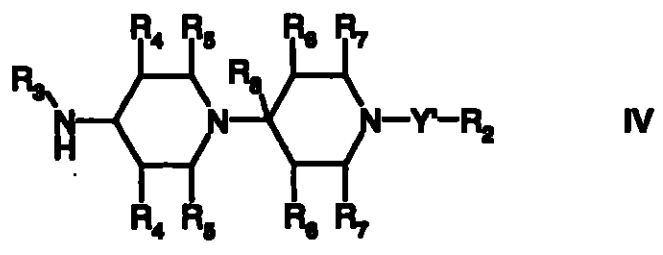


en donde R_2 es como se define anteriormente, Y' es $-CO-$, $-C(O)CH_2-$, $-S(O)-$ ó $-S(O_2)-$ y A' es un grupo saliente, por ejemplo Cl, Br, u OH,

b) para la preparación de un compuesto de la fórmula I, en donde X es un enlace directo, e Y es $-CH_2-$, someter a un compuesto de la fórmula II como se define anteriormente, en donde X' es un enlace directo, a una aminación reductiva; o

c) para la preparación de un compuesto de la fórmula I, en donde X es CH_2- , $-CH_2CH_2-$ ó $-CHR_9-$ e Y es $-CO-$, $-C(O)CH_2-$, $-S(O)-$, ó $-S(O_2)-$,

hacer reaccionar un compuesto de la fórmula IV:



en donde R_2 a R_8 e Y' son como se definen anteriormente, con un compuesto de la fórmula V:



en donde R_1 es como se define anteriormente, y X'' es CH_2- ó $-CHR_9-$;

y, en donde se requiera, convertir el compuesto re-

sultante de la fórmula I obtenido en forma libre en la forma de sal deseada, o viceversa.

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, o una sal farmacéuticamente aceptable del mismo, para utilizarse como un producto farmacéutico.

8. Una composición farmacéutica que comprende un compuesto de la fórmula I de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o vehículo farmacéuticamente aceptable para el mismo.

9. Una combinación farmacéutica que comprende:

- a) un primer agente es un compuesto de la fórmula I de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y
- b) cuando menos un co-agente.

10. Un método para prevenir o tratar desórdenes o enfermedades mediadas mediante interacciones entre receptores de quimiocina y sus ligandos, en un sujeto que necesite de este tratamiento, cuyo método comprende administrar al sujeto una cantidad efectiva de un compuesto de la fórmula I, de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

RESUMEN

Los derivados de piperidina de la fórmula I, como
5 se dan a conocer en la memoria descriptiva, tienen interesan-
tes propiedades farmacéuticas, por ejemplo como inhibidores
de CCR5.

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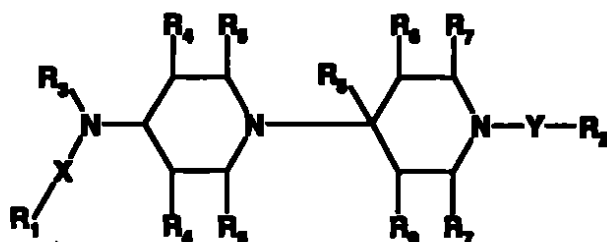
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BIPIPERIDINYL-DERIVATIVES AND THEIR USE AS CHEMOKINE RECEPTORS INHIBITORS**~~Novel Piperidine Derivatives~~**

The present invention relates to piperidine derivatives, process for their production, their uses and pharmaceutical compositions containing them.

More particularly, the present invention provides a compound of formula I



wherein

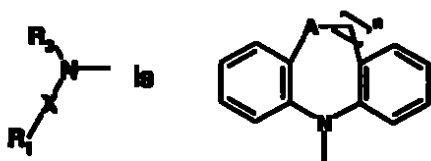
X is a direct bond; $-\text{CH}_2-$; $-\text{CH}_2\text{CH}_2-$; $-\text{CHR}_9-$; $-\text{C}(\text{O})-$; $-\text{O}-$; $-\text{NH}-$ or NR_9 ;

R_1 is optionally R_{10} and/or R_{11} -substituted phenyl; optionally R_{10} and/or R_{11} -substituted heteroaryl; optionally R_{10} and/or R_{11} -substituted heteroaryl N-oxide; or optionally R_{10} and/or R_{11} -substituted naphthyl;

R_2 has one of the significances given for R_1 ; or is optionally R_{10} and/or R_{11} -substituted fluorenyl; optionally R_{10} -substituted C_1-C_8 alkyl; optionally R_{10} -substituted C_2-C_8 alkenyl; optionally R_{10} -substituted C_3-C_8 cycloalkyl; optionally R_{10} -substituted adamantyl; or optionally R_{10} -substituted C_4-C_8 cycloalkenyl;

R_3 has one of the significances given for R_1 ; or is optionally R_{10} and/or R_{11} -substituted fluorenyl; R_{10} -substituted C_1-C_8 alkyl; optionally R_{10} -substituted C_2-C_8 alkenyl; optionally R_{10} -substituted C_3-C_8 cycloalkyl; optionally R_{10} -substituted adamantyl; or optionally R_{10} -substituted C_4-C_8 cycloalkenyl;

or



wherein A is $-\text{CH}_2-$, $-\text{NH}-$, $-\text{NR}_9-$, $-\text{S}-$, $-\text{SO}-$, SO_2 or $-\text{O}-$, n is 0, 1 or 2, and the aromatic rings are each, independently optionally R_{10} -substituted;

each of R_4 , independently, has one of the significances of R_6 ; or is CN; OH; OR_9 ; F; Cl; Br; or I;

each of R_5 , independently, is H; C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; phenyl; benzyl; or heteroaryl;

each of R_6 , independently, has one of the significances given for R_4 ;

each of R_7 , independently, has one of the significances given for R_5 ;

R_8 is H; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; CN; CH_2NH_2 ; CH_2NHR_9 ; $CH_2NR_9R_9$; $CH_2NHC(O)R_9$; $CH_2NR_9C(O)R_9$; $CH_2NHC(O)NHR_9$; $CH_2NR_9C(O)NHR_9$; $CH_2NR_9C(O)NR_9R_9$; $CH_2NHC(O)OR_9$; $CH_2NR_9C(O)OR_9$; $CH_2NHSO_2R_9$; $CH_2N(SO_2R_9)_2$; or $CH_2NR_9SO_2R_9$;

each R_9 , independently, is C_1-C_6 alkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; heteroaryl; or CF_3 ;

R_{10} represents 1 to 4 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_9 ; $CONH_2$; $CONHR_9$; $CONR_9R_9$; $OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9 ; $COOH$; $COOR_9$; CF_3 ; CHF_2 ; CH_2F ; CN; NO_2 ; NH_2 ; NHR_9 ; NR_9R_9 ; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$; $NR_9C(O)OR_9$; $NHSO_2R_9$; $N(SO_2R_9)_2$; $NR_9SO_2R_9$; SR_9 ; $S(O)R_9$; SO_2R_9 ; $Si(CH_3)_3$ and $B(OC(CH_3)_2)_2$;

R_{11} represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; and

Y is a direct bond; $-C(O)-$; $-C(O)CH_2-$; $-S(O)-$; $-S(O)_2-$; $-C(S)-$; $-CH_2-$; $-C(-CH_2CH_2-)-$; $-CH(R_4)-$ or $-C(R_4)_2-$,

in free form or in salt form.

Any alkyl, alkenyl or alkynyl may be linear or branched. Halogeno is F, Cl, Br or I.

By heteroaryl is meant an aromatic ring system comprising mono-, bi- or tricyclic systems which contains up to 4 heteroatoms independently selected from N, O and S, such as for example furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, benzothiophenyl, benzofuranyl, benzimidazolyl, indazolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl or naphthyridinyl.

Preferred annulated 4-7membered non-aromatic ring as represented by R_{11} is annulated 5 or 6 membered non aromatic ring optionally containing 1 or 2 oxygen and include e.g.

$\text{-O-CH}_2\text{-O-}$ or $\text{-O-CH}_2\text{-CH}_2\text{-O-}$, attached to 2 adjacent carbon atoms.

The compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid when R_1 , R_2 , and/or R_3 comprises an optionally substituted amino group or a heterocyclic residue which can form addition salts. When the compounds of formula I have one or more asymmetric centers in the molecule, e.g. when a piperidine ring is substituted, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof.

In the compounds of formula I, the following significances are preferred individually or in any sub-combination:

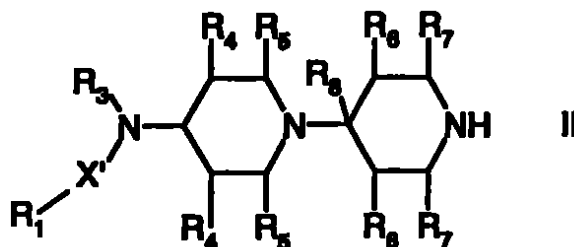
1. R_1 is optionally R_{10} -substituted phenyl; optionally R_{10} -substituted heteroaryl; or optionally R_{11} -substituted phenyl.
2. R_2 is optionally R_{10} -substituted phenyl; optionally R_{10} -substituted heteroaryl; optionally R_{10} -substituted heteroaryl N-oxide; or optionally R_{10} -substituted naphthyl.
3. R_3 is optionally R_{10} -substituted phenyl; optionally R_{10} -substituted heteroaryl; or optionally R_{10} -substituted naphthyl.
4. Each of R_4 , R_5 , R_6 or R_7 , independently, is H; $C_1\text{-C}_6$ alkyl; or benzyl.
5. R_8 is H; $C_1\text{-C}_6$ alkyl; or $C_2\text{-C}_6$ alkenyl.
6. R_9 is $C_1\text{-C}_6$ alkyl; $C_3\text{-C}_6$ cycloalkyl; $C_2\text{-C}_6$ alkenyl; $C_2\text{-C}_6$ alkynyl; phenyl; benzyl; heteroaryl; or CF_3 .
7. R_{10} represents 1 to 3 substituents independently selected from $C_1\text{-C}_6$ alkyl; $C_1\text{-C}_6$ hydroxyalkyl; $C_2\text{-C}_6$ alkoxyalkyl; $C_1\text{-C}_6$ halogenoalkyl; $C_3\text{-C}_6$ cycloalkyl; $C_2\text{-C}_6$ alkenyl; $C_3\text{-C}_6$ cycloalkenyl; $C_2\text{-C}_6$ alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_6 ; CONH_2 ; CONHR_6 ; CONR_6R_6 ; OC(O)R_6 ; OC(O)OR_6 ; OC(O)NHR_6 ; $\text{OC(O)NR}_6\text{R}_6$; OSO_2R_6 ; COOH ; COOR_6 ; CF_3 ; CHF_2 ; CH_2F ; CN ; NO_2 ; NH_2 ; NHR_6 ; NR_6R_6 ; NHC(O)R_6 ; $\text{NR}_6\text{C(O)R}_6$; NHC(O)NHR_6 ; NHC(O)NH_2 ; $\text{NR}_6\text{C(O)NHR}_6$; $\text{NR}_6\text{C(O)NR}_6\text{R}_6$; NHC(O)OR_6 ; $\text{NR}_6\text{C(O)OR}_6$; NHSO_2R_6 ; $\text{N(SO}_2\text{R}_6)_2$; $\text{NR}_6\text{SO}_2\text{R}_6$; SR_6 ; S(O)R_6 ; SO_2R_6 and $\text{Si(CH}_3)_3$.
8. R_{11} represents $\text{-O-CH}_2\text{-O-}$ attached on 2 adjacent carbon atoms.
9. X is a direct bond or $\text{-CH}_2\text{-}$.
10. Y is -C(O)- .

In the preferred compounds of formula I, R_{10} may represent 1-3 substituents selected from from C_{1-8} alkyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_9 ; $CONH_2$; $CONHR_9$; $CONR_9R_9$; $COOH$; $COOR_9$; CF_3 ; CHF_2 ; CH_2F ; NH_2 ; NHR_9 ; NR_9R_9 ; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$ and $NR_9C(O)OR_9$.

R_9 is preferably C_1-C_8 alkyl; C_3-C_8 cycloalkyl; phenyl; benzyl; or heteroaryl; more preferably C_1-C_8 alkyl.

The present invention also includes a process for the preparation of a compound of formula I which process comprises

- a) for the preparation of a compound of formula I wherein X is a direct bond, $-CH_2-$, $-CH_2CH_2-$ or $-CHR_9-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O_2)-$, amidating a compound of formula II

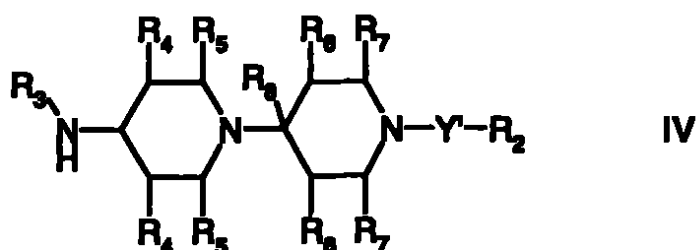


wherein R_1 and R_3 to R_8 are as indicated above and X' is a direct bond, $-CH_2-$, $-CH_2CH_2-$ or $-CHR_9-$ with a compound of formula III



wherein R_2 is as defined above, Y' is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O_2)-$ and A' is a leaving group, e.g. Cl or Br,

- b) for the preparation of a compound of formula I wherein X is a direct bond and Y is $-CH_2-$, submitting a compound of formula II as defined above wherein X' is a direct bond, to a reductive amination; or
- c) for the preparation of a compound of formula I wherein X is CH_2- , $-CH_2CH_2-$ or $-CHR_9-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O_2)-$, reacting a compound of formula IV



wherein R_2 to R_9 and Y' are as defined above, with a compound of formula V

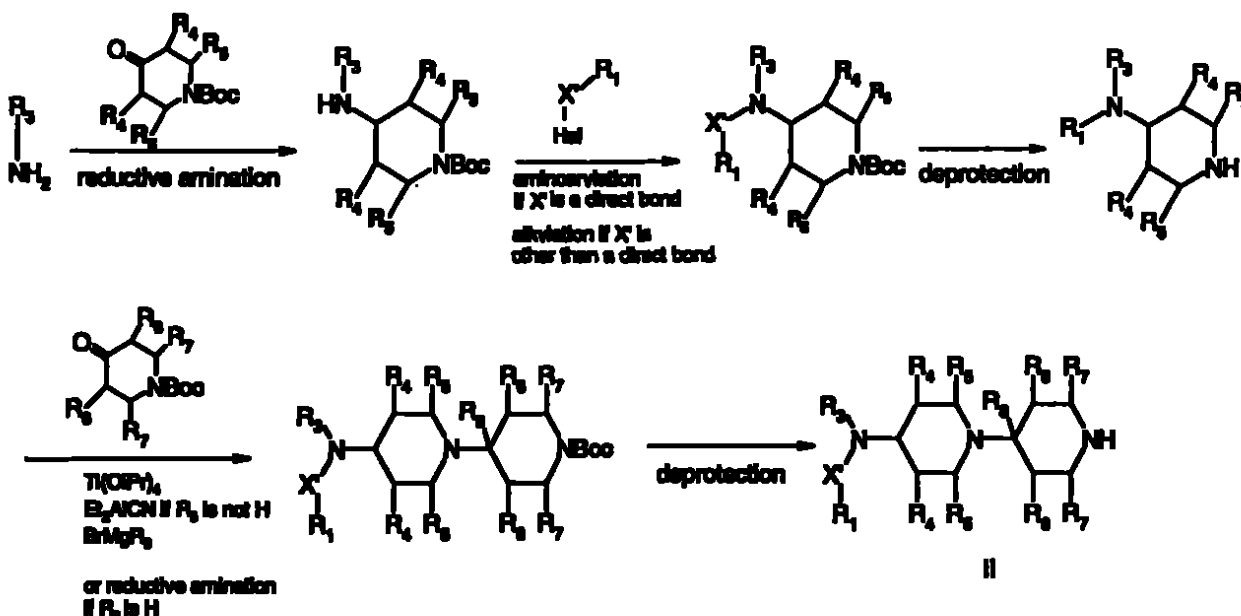


wherein R_1 is as defined above and X'' is CH_2 or $-\text{CHR}_9$;

and, where required, converting the resulting compound of formula I obtained in free form into the desired salt form, or vice versa.

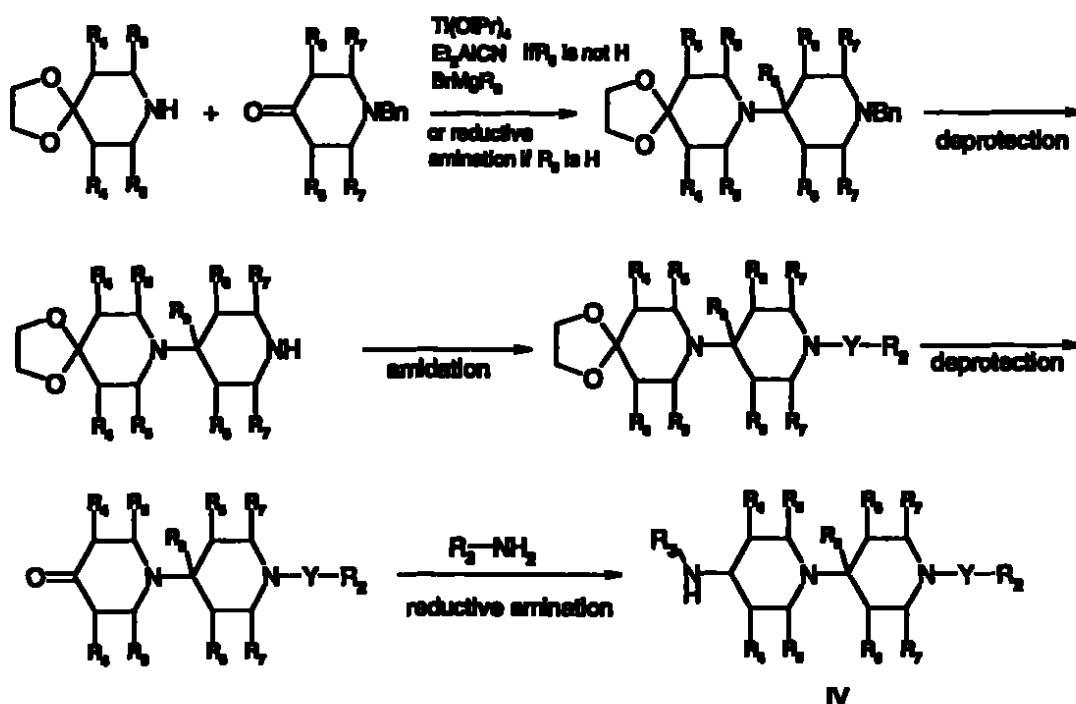
The reaction steps a), b) or c) may be performed in accordance with methods known in the art or as disclosed in the Examples below. When R_9 comprises a group which should not participate in the reaction, this group may be protected in accordance with methods known in the art.

Compounds of formula II, used as starting material may be prepared as follows:



wherein X' and R_1 to R_9 are as defined above and Hal is Cl, Br or I. In above formulae, Boc is a protecting group which means tert.-butoxycarbonyl. This protecting group may be replaced in above reaction scheme by any amino protecting group, e.g. as disclosed in "Protective Groups in Organic Synthesis" by T. W. Greene, J. Wiley & Sons NY, 2nd ed., Chapter 7, 1991 and references therein, e.g. benzyloxycarbonyl or 9-fluorenylmethoxy carbonyl.

Compounds of formula IV, used as starting material, may be prepared as follows:



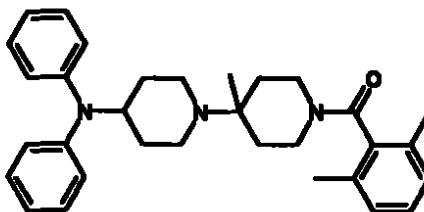
wherein R_2 to R_9 and Y are as defined above and Bn is benzyl.

Above reactions may be carried out in accordance with methods known in the art or as disclosed hereafter.

Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as described hereafter.

The following Examples are illustrative of the invention, without limitation. Following abbreviations are used:

Bn	= Benzyl
Boc	= tert.-Butoxycarbonyl
DMF	= Dimethylformamide
DMSO	= Dimethylsulfoxide
BINAP	= 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
THF	= Tetrahydrofuran
TFA	= Trifluoroacetic acid
RT	= Room temperature

Example 1: (2,6-Dimethyl-phenyl)-(4-diphenylamino-4'-methyl-[1,4']bipiperidinyl-1'-yl)-methanone

A mixture of (4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (0.25 g, 0.71 mmol), 2,6-dimethylbenzoic acid (0.32 g, 2.13 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.57 g, 1.5 mmol), EtN(*i*-Pr)₂ (0.6 ml) and DMF (5 ml) is stirred for 16 h at 20°C. The mixture is diluted with *t*-butyl methylether (25 ml), washed with 2N NaOH (25 ml) and brine (25 ml) and dried with sodium sulfate. The solvent is removed and the residue purified by chromatography (SiO₂, *t*-butyl methylether/cyclohexane 1:4→1:0). The title compound is isolated as a colorless solid. MS/ESI 482 (M+H)⁺; ¹H NMR (400 MHz, DMSO) δ= 0.89 (3 H, s), 1.14-1.25 (3 H, m), 1.39 (1 H, m), 1.59 (1 H, m), 1.75 (1 H, m), 1.83-1.95 (2 H, m), 2.01 (3 H, s), 2.13 (3 H, s), 2.11-2.24 (2 H, m), 2.85 (2 H, m), 2.95 (1 H, m), 3.01 (1 H, m), 3.35 (1 H, m), 3.70-3.83 (2 H, m), 6.77 (4 H, m), 6.92-7.05 (4 H, m), 7.12 (1 H, m), 7.26 (4 H, m).

(4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine, used as starting material may be prepared as follows:

a) A mixture of phenyl-piperidin-4-yl-amine (4.14 g; 15.0 mmol), iodobenzene (3.06 g; 15.0 mmol), Pd(OAc)₂ (0.14 g; 0.63 mmol); BINAP (0.43 g; 0.69 mmol), *t*-BuOK (17.5 ml of 1M solution in THF) in toluene (20 ml) is heated at 110°C for 5 h. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, *t*-butyl methylether /cyclohexane 1:9→1:1). 4-Diphenylamino-piperidine-1-carboxylic acid *tert*-butyl ester is isolated as a yellow solid. MS/ESI 353 (M+H)⁺

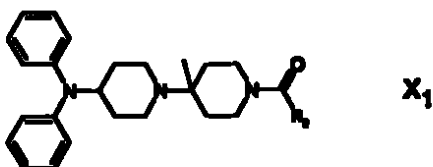
b) A mixture of TFA (5 ml), methylene chloride (5 ml) water (0.25 ml) and 4-diphenylamino-piperidine-1-carboxylic acid *tert*-butyl ester (1.5 g; 4.2 mmol) is stirred for 2 h at 20°C. Sodium hydroxide (4N) is added and the mixture extracted with ethyl acetate. The organic

phase is dried with sodium sulfate and the solvent removed. Diphenyl-piperidin-4-yl-amine is isolated as a colorless oil. MS/ESI 253 (M+H)⁺

c) A suspension of diphenyl-piperidin-4-yl-amine (1.26 g, 5.00 mmol), 1-(tert-butyl oxycarbonyl)-4-piperdone (1.00 g, 5.00 mmol), and titanium(IV) isopropoxide (1.42 g, 5.00 mmol) in 1,2-dichloroethane (25 ml) is stirred for 1 h at 80°C and then for 16 h at 20°C. Diethylaluminum cyanide (10 ml 1M solution in toluene) is added and the mixture stirred for additional 24 h. The solvent is removed and the crude material dissolved in tetrahydrofuran (25 ml). Methylmagnesium bromide (8.7 ml 3M solution in ether) is added dropwise and the mixture stirred for 3 h at 20°C. Ammonium chloride (10 % solution, 50 ml) and ethyl acetate (50 ml) are added, the organic phase washed with ammonium chloride (10 % solution, 50 ml) and sodium hydrogencarbonate (10 % solution, 50 ml), dried with sodium sulfate and the solvent removed. The residue is subjected to chromatography (SiO₂, ethyl acetate/cyclohexane 1:9→1:1). 4-Diphenylamino-4'-methyl-[1,4']bipiperidinyl-1'-carboxylic acid tert.-butyl ester is isolated as a colorless solid MS/ESI 450 (M+H)⁺.

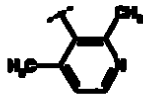
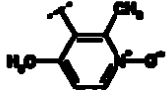
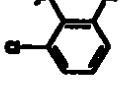
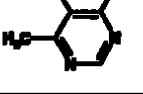
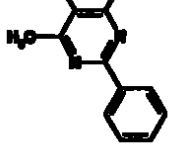
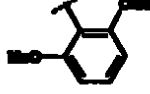
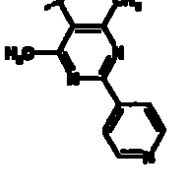
d) A mixture of trifluoroacetic acid (2 ml) and water (0.1 ml) is added dropwise to a solution of compound a) above (0.81 g, 1.80 mmol) in methylene chloride (5 ml) and the mixture stirred for 3 h at 20°C. Sodium hydrogencarbonate (10% solution, 10 ml) and ethyl acetate (20ml) are added and the organic phase dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (RP-18, methanol/H₂O 1:3→0:1). The title compound is isolated as a colorless oil. MS/ESI 350 (M+H)⁺; ¹H NMR (400 MHz, CDCl₃) δ = 0.88 (3 H, s), 1.35 (4 H, m), 1.60 (4 H, m), 1.93 (2 H, m), 2.15 (2 H, m), 2.58 (2 H, m), 2.87 (2 H, m), 2.98 (2 H, m), 3.76 (1 H, m), 6.78 (4 H, m), 6.94 (2 H, m), 7.22 (4 H, m).

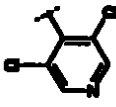
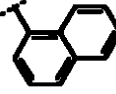
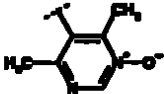
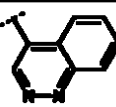
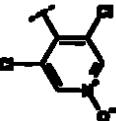
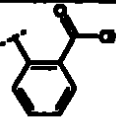
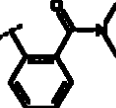
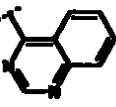
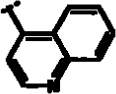
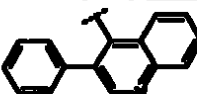
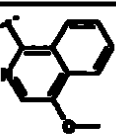
By following the procedure of Example 1 and using as starting material (4'-methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine, the compounds of formula X₁

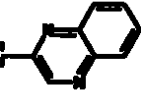
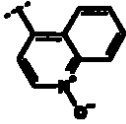
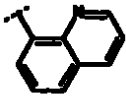
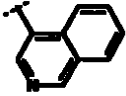
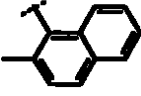
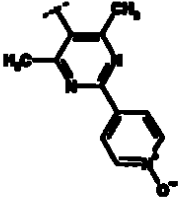
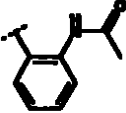
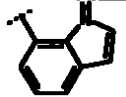
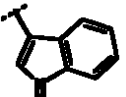
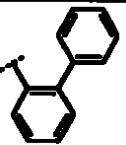
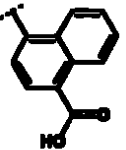


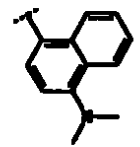
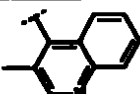
wherein R₂ has the significances as given in Table 1, may be prepared.

Table 1

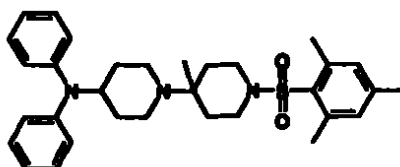
Example	R ₂	MS/ESI (M+H) ⁺
2		483
3		499
4		460
5		454
6		470
7		522
8		468
9		484
10		560
11		514
12		561
13		488

14		523
15		504
16		500
17		508
18		539
19		498
20		525
21		488
22		506
23		505
24		581
25		535
26		505

27		508
28		521
29		505
30		505
31		518
32		577
33		511
34		493
35		493
36		530
37		528
38		548

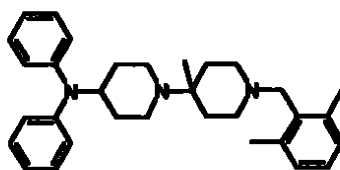
39		547
40		519

Example 41: [4'-Methyl-1'-(2,4,6-trimethyl-benzenesulfonyl)-[1,4']bipiperidinyl-4-yl]-diphenyl-amine



A mixture of (4'-methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (70 mg, 0.20 mmol) and 2,4,6-trimethyl-benzenesulfonyl chloride (65 mg, 0.30 mmol) and diisopropyl ethylamine (0.50 ml) in methylene chloride (3 ml) is stirred for 4h at RT. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate (10 % solution) and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, t-butyl methylether/cyclohexane 1:9→1:0). The title compound is isolated as a colorless solid. MS/ESI 532 (M+H)⁺

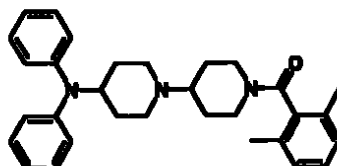
Example 42: [1'-(2,6-Dimethyl-benzyl)-4'-methyl-[1,4']bipiperidinyl-4-yl]-diphenyl-amine



A mixture of (4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (70 mg, 0.20 mmol) and 2,6-dimethyl-benzaldehyde (34 mg, 0.25 mmol) and Na(OAc)₃BH (53 mg, 0.25 mmol) in 1,2-dichloroethane (10 ml) is stirred at RT for 16 h. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate (10 % solution) and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, tert-butyl

methylether/methanol 1:0→10:1). The title compound is isolated as a colorless solid. MS/ESI 468 (M+H)⁺

Example 43: (2,6-Dimethyl-phenyl)-(4-diphenylamino-[1,4']bipiperidiny-1'-yl)-methanone



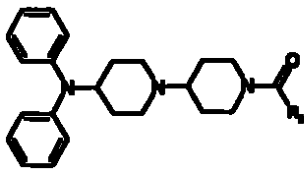
A mixture of TFA salt of [1,4']bipiperidiny-4-yl-diphenyl-amine (77 mg, 0.23 mmol), 2,6-dimethylbenzoic acid (100 mg, 0.67 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (254 mg, 0.67 mmol), EtN(i-Pr)₂ (2 ml) and DMF (3 ml) is stirred for 5 h at RT. The mixture is diluted with tert-butyl methylether (10 ml), washed with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue purified by chromatography (SiO₂, t-butyl methylether/cyclohexane 1:1→ethyl acetate→ethyl acetate/H₂O 98:2). The title compound is isolated as a colorless solid. MS/ESI 468 (M+H)⁺

[1,4'] Bipiperidiny-4-yl-diphenylamine, used as starting materials, may be prepared as follows:

a) A mixture of diphenyl-piperidin-4-yl-amine (1.06 g; 4.2 mmol), 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (1.0 g; 5.0 mmol), AcOH (0.62 g; 10.3 mmol) and Na(OAc)₃BH (1.0 g; 4.7 mmol) in 1,2-dichloroethane (15 ml) is stirred for 4h at 65°C. The mixture is diluted with t-butyl methylether, extracted with 1N NaOH and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO₂, t-butyl methylether/cyclohexane 1:9→1:0). 4-Diphenylamino-[1,4']bipiperidiny-1'-carboxylic acid tert-butyl ester is isolated as a colorless solid. MS/ESI 436 (M+H)⁺

b) A mixture of 4-Diphenylamino-[1,4']bipiperidiny-1'-carboxylic acid tert-butyl ester (1.06 g; 2.4 mmol), TFA (2.5 ml), H₂O (0.25 ml) and methylene chloride (5 ml) is stirred at RT for 4 h. The mixture is added dropwise to ether and the precipitate formed is filtered off. The TFA salt of [1,4']bipiperidiny-4-yl-diphenyl-amine is isolated as a colorless solid. MS/ESI 336 (M+H)⁺

By following the procedure of Example 2 above and using as starting materials [1,4']bipiperidinyl-4-yl-diphenyl-amine the compounds of formula X₂

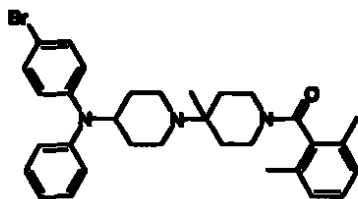


wherein R₂ has one of the significances given in Table 2, may be prepared

Table 2

Example	R ₂	MS/ESI
44		469
45		485
46		470
47		509
48		486
49		547
50		525

Example 51: 4-[(4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl)-(2,6-dimethyl-phenyl)-methanone



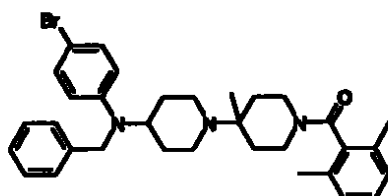
A mixture of [4-(4-bromo-phenylamino)-4'-methyl-[1,4']bipiperidinyl-1'-yl]-(2,6-dimethyl-phenyl)-methanone (97 mg; 0.20 mmol), iodobenzene (41 mg; 0.20 mmol), Pd (OAc)₂ (1.9 mg; 0.008 mmol), BINAP (5.7 mg; 0.009 mmol) and *t*-BuOK (0.23 ml of 1 M solution on THF) in toluene (3 ml) is heated at 110°C for 16h. The mixture is diluted with ethyl acetate and filtered. The resulting solution is extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (first SiO₂, *t*-butyl methylether/cyclohexane 1:4→1:0 and subsequently RP-18, methanol/H₂O 7:3). The title compound is isolated as a colorless solid. MS/ESI 560 (M+H)⁺.

[4-(4-bromo-phenylamino)-4'-methyl-[1,4']bipiperidinyl-1'-yl]-2,6-dimethylphenyl-methanone, used as starting material, may be prepared as follows:

- 8-(1-Benzyl-4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane is prepared from 1,4-dioxa-8-aza-spiro[4.5]decane and 1-benzyl-piperidin-4-one following a procedure as described in example 1c). MS/ESI 331 (M+H)⁺.
- A mixture of 8-(1-benzyl-4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane (2.0 g, 6.1 mmol) and Pd(OH)₂ (20%) on charcoal (1 g) in methanol (30 ml) is hydrogenated for 16h at RT. The catalyst is filtered off and the solvent removed. Crude 8-(4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane is isolated as a yellow oil. MS/ESI 241 (M+H)⁺.
- (2,6-Dimethyl-phenyl)-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-methyl-piperidin-1-yl]-methanone is obtained from crude 8-(4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane and 2,6-dimethyl-benzoyl acid by following a procedure as described in example 1. MS/ESI 373 (M+H)⁺.
- A solution of (2,6-dimethyl-phenyl)-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-methyl-piperidin-1-yl]-methanone (915 mg; 2.46 mmol) in dioxan (30 ml) and HCl (6N; 30ml) is stirred for 4h at 50°C. The mixture is diluted with ethyl acetate (50 ml), extracted with 2N NaOH and brine and dried with sodium sulfate. Removal of the solvent affords 1'-[2,6-dimethyl-benzoyl]-4'-methyl-[1,4']bipiperidinyl-4-one is isolated as a colorless solid. MS/ESI 329 (M+H)⁺.

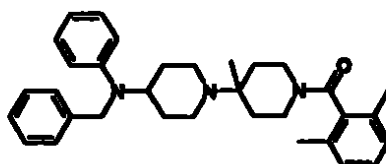
e) A mixture of 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidiny-4-one (49.3 mg; 0.15 mmol), 4-bromo-phenylamine (29 mg, 0.165 mmol), acetic acid (18 mg; 0.30 mmol) and $\text{NaBH}(\text{OAc})_3$ (35 mg; 0.165 mmol) in $(\text{CH}_2\text{Cl})_2$ (4 ml) is stirred for 16h at RT. The mixture is diluted with ethyl acetate, extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (RP-18, methanol/ H_2O 8:2→1:0). [4-(4-bromo-phenylamino)-4'-methyl-[1,4']bipiperidiny-1'-yl]-(2,6-dimethylphenyl)-methanone is isolated as a colorless solid. MS/ESI 484 (M+H)⁺.

Example 52: **{4-[Benzyl-(4-bromo-phenyl)-amino]-4'-methyl-[1,4']bipiperidiny-1'-yl}-(2,6-dimethyl-phenyl)-methanone**



A mixture of {4-[(4-bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidiny-1'-yl}-(2,6-dimethyl-phenyl)-methanone (97 mg; 0.20 mmol), bromomethyl-benzene (376 mg, 2.2 mmol) and K_2CO_3 (138 mg; 1.0 mmol) in DMF (3 ml) is stirred at 100°C for 16h. The mixture is diluted with ethyl acetate, extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (first SiO_2 , t-butyl methylether and subsequently RP-18, methanol/ H_2O 8:2). The title compound is isolated as a colorless solid. MS/ESI 574 (M+H)⁺.

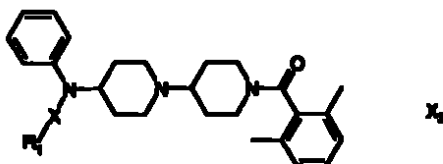
Example 53: **[4-(Benzyl-phenyl-amino)-4'-methyl-[1,4']bipiperidiny-1'-yl]-(2,6-dimethyl-phenyl)-methanone**



It is prepared from (2,6-dimethyl-phenyl)-(4'-methyl-4-phenylamino-[1,4']bipiperidiny-1'-yl)-methanone and benzyl bromide following a similar procedure as described in example 52. MS/ESI 498 (M+H)⁺. The starting material may be prepared from 1'-(2,6-dimethyl-benzoyl)-

4'-methyl-[1,4']bipiperidiny-4-one, by following a similar procedure as described in example 51e). MS/ESI 406 (M+H)⁺.

By following the procedure of Example 53 above and using the appropriate starting materials the compounds of formula X₃

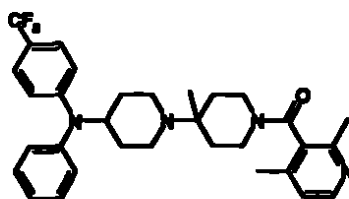


wherein -X-R₁ has the significances as indicated in Table 3 below, may be prepared.

Table 3

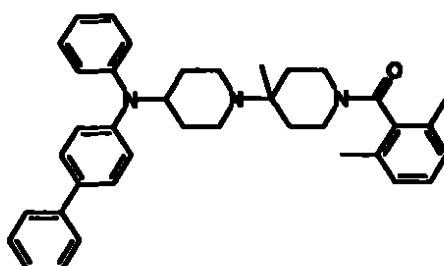
Example	-X-R ₁	MS/ESI (M+H) ⁺
54		517
55		497

Example 56: (2,4-Dimethyl-pyridin-3-yl)-(4'-methyl-4-[phenyl-(4-trifluoromethyl-phenyl)-amino]-[1,4']bipiperidiny-1'-yl)-methanone



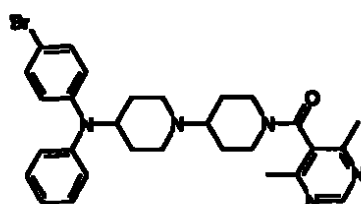
It is prepared from 4-(4-trifluoromethyl-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester by using a procedure as described in example 1. MS/ESI 551 (M+H)⁺. The starting material is prepared from 4-trifluoromethyl-phenylamine and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester following a procedure as described in example 51e). MS/ESI 345 (M+H)⁺.

Example 57: [4-(Biphenyl-4-yl-phenyl-amino)-4'-methyl-[1,4']bipiperidiny-1'-yl]-(2,6-dimethyl-phenyl)-methanone



It is prepared from 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester and 4-bromobiphenyl by using a procedure as described in example 1. MS/ESI 558 (M+H)⁺.

Example 58: **{4-[(4-Bromo-phenyl)-phenyl-amino]-[1,4']bipiperidinyl-1'-yl}-(4,6-dimethyl-pyrimidin-5-yl)-methanone**



It is prepared from [1,4']bipiperidinyl-4-yl-(4-bromo-phenyl)-phenyl-amine and 4,6-dimethylpyrimidine-5-carboxylic acid by following a procedure as described in example 1. MS/ESI 548 (M+H)⁺.

[1,4']bipiperidinyl-4-yl-(4-bromo-phenyl)-phenyl-amine used as starting materials may be prepared as follows:

a) 4-(4-Bromo-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester is prepared from 4-bromo-phenylamine and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester as described in example 51a). MS/ESI 355 (M+H)⁺.

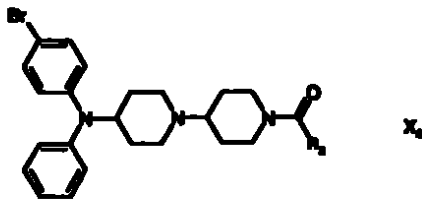
b) 4-[(4-Bromo-phenyl)-phenyl-amino]-piperidine-1-carboxylic acid tert-butyl ester is prepared from 4-(4-bromo-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester and iodo-benzene as described in example 51. MS/ESI 431 (M+H)⁺.

c) (4-Bromo-phenyl)-phenyl-piperidin-4-yl-amine is prepared from 4-[(4-bromo-phenyl)-phenyl-amino]-piperidine-1-carboxylic acid tert-butyl ester as described in example 1b). MS/ESI 331 (M+H)⁺.

d) 4-[(4-Bromo-phenyl)-phenyl-amino]-[1,4']bipiperidiny-1'-carboxylic acid tert-butyl ester is prepared from (4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester as described in example 43a). MS/ESI 514 (M+H)⁺.

e) [1,4']Bipiperidiny-4-yl-(4-bromo-phenyl)-phenyl-amine is prepared from 4-[(4-bromo-phenyl)-phenyl-amino]-[1,4']bipiperidiny-1'-carboxylic acid tert-butyl ester as described in example 1b). MS/ESI 414 (M+H)⁺.

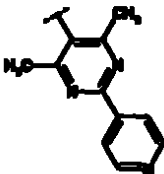
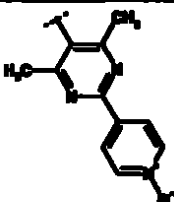
By using a procedure as disclosed above and the corresponding starting materials, the compounds of formula X₄



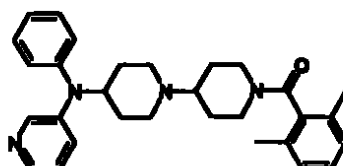
wherein R₂ is as defined in Table 4 below, may be prepared.

Table 4

Example	R ₂	MS/ESI (M+H) ⁺
59		546
60		587
61		603
62		583
63		584
64		548

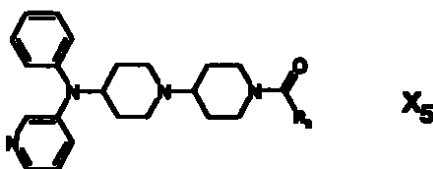
65		625
66		641

Example 67: (2,6-Dimethyl-phenyl)-[4-(phenyl-pyridin-3-yl-amino)-[1,4']bipiperidinyl-1'-yl]-methanone



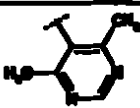
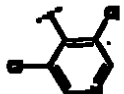
It is prepared from 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester and 3-bromo-pyridine by using a procedure as described in example 58 and 58b) to e). MS/ESI 469 (M+H)⁺.

By following a procedure as disclosed above, the compounds of formula X₅

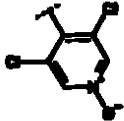
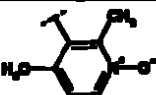
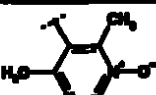


wherein R₂ is as given in Table 5 below, may be prepared.

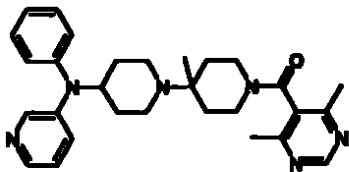
Table 5

Example	R ₂	MS/ESI (M+H) ⁺
68		471
69		510

134
135

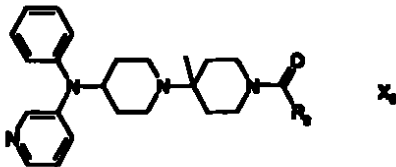
70		528
71		486
72		487

Example 73: (4,6-Dimethyl-pyrimidin-5-yl)-[4'-methyl-4-(phenyl-pyridin-3-yl-amino)-[1,4']bipiperidinyl-1'-yl]-methanone



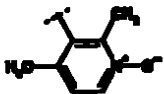
It is prepared from phenyl-piperidin-4-yl-pyridin-3-yl-amine and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d).
MS/ESI 485 (M+H)⁺.

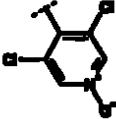
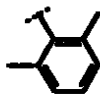
By following the procedure as disclosed in example 73, the compounds of formula X₆



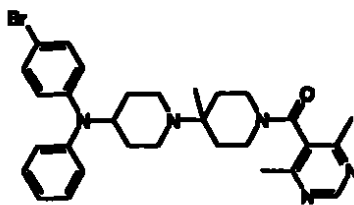
wherein R₂ has the significances as indicated in Table 6, may be prepared.

Table 6

Example	R ₂	MS/ESI (M+H) ⁺
74		500

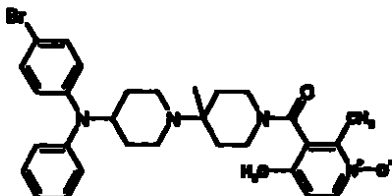
75		540
76		483

Example 77: **{4-[(4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl)-(4,6-dimethyl-pyrimidin-5-yl)-methanone**



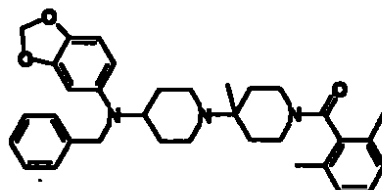
It is prepared from 4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 562 (M+H)⁺.

Example 78: **{4-[4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl)-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone**



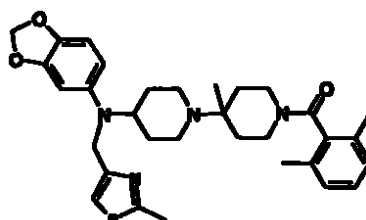
It is prepared from (4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 577 (M+H)⁺

Example 79: **[4-(Benzo[1,3]dioxol-5-yl-benzyl-amino)-4'-methyl-[1,4']bipiperidinyl-1'-yl)-(2,6-dimethyl-phenyl)-methanone**



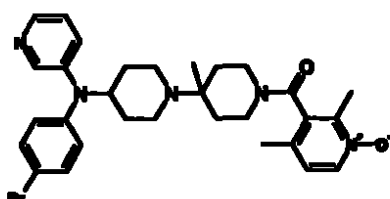
It is prepared from 1'-((2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidiny-4-one and benzo[1,3]dioxol-5-ylamine by following a procedure as described in examples 51 and 52. MS/ESI 540 (M+H)⁺.

Example 80: {4-[1,3-Benzodioxol-5-yl-(2-methyl-thiazol-4-ylmethyl)-amino]-4'-methyl-1,4'-bipiperidiny-1'-yl}-(2,6-dimethyl-phenyl)-methanone



It is prepared from 1'-((2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidiny-4-one and benzo[1,3]dioxol-5-ylamine by following a procedure as described in examples 51 and 52. MS(ESI) 561 (M+H)⁺

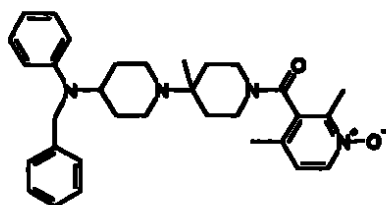
Example 81: {4-[(4-Bromo-phenyl)-pyridin-3-yl-amino]-4'-methyl-[1,4']bipiperidiny-1'-yl}-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone



It is prepared from 4-(pyridin-3-ylamino)-piperidine-1-carboxylic acid tert-butyl ester and 1,4-dibromo-benzene by following a procedure as described in example 1. MS/ESI 578 (M+H)⁺.

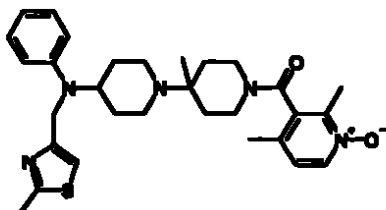
137
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Example 82: [4-(Benzyl-phenyl-amino)-4'-methyl-[1,4']bipiperidiny-1'-yl]-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone



It is prepared from phenyl-piperidin-4-yl-amine by following a procedure as described in examples 52 and 1. MS/ESI 513 (M+H)⁺.

Example 83: (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4'-methyl-4-[(2-methyl-thiazol-4-ylmethyl)-phenyl-amino]-[1,4']bipiperidiny-1'-yl)-methanone



It prepared from (4'-methyl-[1,4']bipiperidiny-4-yl)-(2-methyl-thiazol-4-ylmethyl)-phenyl-amine using a procedure as described in example 1. MS/ESI 534 (M+H)⁺.

(4'-methyl-[1,4']bipiperidiny-4-yl)-(2-methyl-thiazol-4-ylmethyl)-phenyl-amine, used as starting material, is obtained as follows: a mixture of 4-(benzyl-phenylamino)-4'-methyl-[1,4']bipiperidiny-1'-carboxylic acid tert.-butyl ester (1.0 g, 2.16 mmol), ammonium formate (0.5 g, 7.92 mmol) and Pd(OH)₂ (20%) on charcoal (0.25 g) in methanol (25 ml) is heated under reflux for 3 h. The catalyst is filtered off and washed with methanol. The solvent is removed and the residue dissolved in ethyl acetate. The organic solution is extracted with 1N NaOH and brine and dried with sodium sulfate. Removal of the solvent gives crude 4'-methyl-4-phenylamino-[1,4']bipiperidiny-1'-carboxylic acid tert.-butyl ester which is used in the next step without further purification. MS/ESI 374 (M+H)⁺.

4'-Methyl-4-phenylamino-[1,4']bipiperidiny-1'-carboxylic acid tert.-butyl ester is converted into (4'-methyl-[1,4']bipiperidiny-4-yl)-(2-methyl-thiazol-4-ylmethyl)-phenyl-amine using a procedure as described in examples 52 and 1d).

The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g. as CCR5 antagonists, e.g. as indicated in in vitro tests and therefore indicated for therapy.

a) CCR5 membrane binding assay

Human CCR5 is used to generate stable transfectants in CHO K1 cells. Membranes prepared from these CCR5 transfectants are used in a radioligand binding assay using ^{125} I MIP-1 α as a ligand and the compounds of formula I are tested for inhibitory activity. The data are reported as IC_{50} , i.e. the concentration of compound required to achieve 50% inhibition of [^{125} I]MIP-1 α binding. In this assay, compounds of formula I have an $IC_{50} \leq 1 \mu M$. Compounds of Examples 18, 53 and 83 have an IC_{50} of 2 to 3 nM, respectively.

b) CCR5 functional assay – Ca^{2+} mobilization

Human CCR5 is used to generate stable transfectants in CHO K1 cells. These CCR5 transfectants are used for assessing Ca^{2+} mobilization in response to stimulation by the CCR5 ligands MIP-1 α , MIP-1 β , HCC-1(9-74) or RANTES. For the assay the cells are loaded with a Ca^{2+} -sensitive fluorochrome (Fluo3 or Fluo4). Ligand concentrations between 0.01 - 100 nM are used to induce Ca^{2+} mobilization which is monitored in a fluorometer with appropriate settings.

To assess the activity of the compounds to be tested, a baseline fluorescence reading is taken after which the compounds at the desired concentration are added to the cells and fluorescence is further recorded for a certain time to assess whether compounds show agonistic effects. Next the agonist is added to the mixture and fluorescence monitored. The inhibition of Ca^{2+} flux in the presence of the compounds to be tested is calculated from the inhibition of maximal fluorescence induced by the agonist. IC_{50} values are calculated from dose-response curves obtained with the compounds. In this assay, compounds of formula I have an $IC_{50} \leq 1 \mu M$. For example, compounds of Example 1, 18 and 52 have an IC_{50} of 10, 9 and 4, respectively.

c) CCR5 functional assay – chemotaxis

CCR5 transfectants are generated in Jurkat T cells or the mouse pre B cell line L1.2. Migration of CCR5 transfectants is tested in transwell tissue chamber inserts system with the CCR5 agonist MIP-1 α at concentrations of 1-100 nM. Cells migrated in response to the agonist compared to a buffer control are quantified in a flow cytometer. The compounds to be tested are added to the cells and the agonist compartments. IC_{50} values are calculated

from concentration-response curves obtained with the compounds in the presence of MIP-1 α . In this assay, compounds of formula I have an $IC_{50} \leq 1 \mu M$.

d) Experiments performed in murine animal models show that vessel wall remodeling after experimental injury (e.g. induced by allotransplantation) is significantly inhibited in the absence of functional CCR5.

The compounds of formula I are, therefore, useful in the prevention and/or treatment of diseases or disorders mediated by interactions between chemokine receptors, e.g. CCR5, and their ligands, e.g. in transplantation, such as acute or chronic rejection of organ, tissue or cell allo- or xenografts or delayed graft function, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pernicious anemia, Sjogren syndrome, uveitis, psoriasis, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrheic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock and others, cancer, e.g. solid tumors or lymphatic cancer such as T cell lymphomas or T cell leukemias, metastasizing or angiogenesis, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock, adult respiratory distress syndrome or viral infections, e.g. AIDS. By transplantation is meant allo- or xeno grafts of e.g. cells, tissues or solid organs, for example pancreatic islets, stem cells, bone marrow, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus. Chronic rejection is also named graft vessel diseases.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to 10 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered,

for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 500 mg active ingredient.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The compounds of formula I may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

- 1.1 A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
- 1.2 A method for preventing or treating acute or chronic transplant rejection or inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
2. A compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 or 1.2 above.
3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 or 1.2 above comprising a compound of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier therefor.
4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 or 1.2 above.

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. in immunosuppressive or immunomodulating regimens or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, a chemotherapeutic agent or an anti-infective agent, e.g. an anti-viral agent such as e.g. an anti-retroviral agent or an antibiotic. For example, the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a macrocyclic lactone having immunosuppressive properties, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779 or ABT578; an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprine; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; an accelerating lymphocyte homing agent, e.g. FTY720; monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD11a/CD18, CD25, CD27, CD28, CD40, CD45, CD58, CD80, CD86, CD137, ICOS, CD150 (SLAM), OX40, 4-1BB or to their ligands, e.g. CD154, or antagonists thereof; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4lg (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or antichemokine antibodies or antichemokine receptor antibodies or low molecular weight chemokine receptor antagonists, e.g. anti MCP-1 antibodies.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory or chemotherapeutic therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I and at least a second drug substance, e.g. an immunosuppressant,

immunomodulatory, anti-inflammatory, anti-infective or chemotherapeutic drug, e.g. as indicated above.

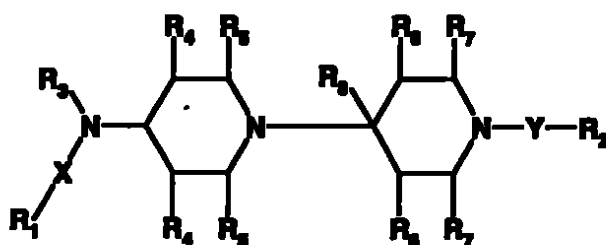
6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a CCR5 antagonist, e.g. a compound of formula I as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory, anti-infective or chemotherapeutic drug. The kit may comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Claims

1. A compound of formula I



wherein

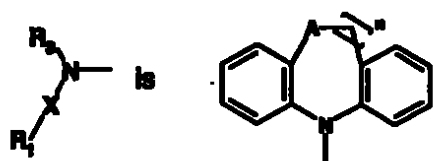
X is a direct bond; $-\text{CH}_2-$; $-\text{CH}_2\text{CH}_2-$; $-\text{CHR}_8-$; $-\text{C}(\text{O})-$; $-\text{O}-$; $-\text{NH}-$ or NR_9 ;

R_1 is optionally R_{10} and/or R_{11} -substituted phenyl; optionally R_{10} and/or R_{11} -substituted heteroaryl; optionally R_{10} and/or R_{11} -substituted heteroaryl N-oxide; or optionally R_{10} and/or R_{11} -substituted naphthyl;

R_2 has one of the significances given for R_1 ; or is optionally R_{10} and/or R_{11} -substituted fluorenyl; optionally R_{10} -substituted $\text{C}_1\text{-C}_8$ alkyl; optionally R_{10} -substituted $\text{C}_2\text{-C}_8$ alkenyl; optionally R_{10} -substituted $\text{C}_3\text{-C}_8$ cycloalkyl; optionally R_{10} -substituted adamantyl; or optionally R_{10} -substituted $\text{C}_4\text{-C}_8$ cycloalkenyl;

R_3 has one of the significances given for R_1 ; or is optionally R_{10} and/or R_{11} -substituted fluorenyl; R_{10} -substituted $\text{C}_1\text{-C}_8$ alkyl; optionally R_{10} -substituted $\text{C}_2\text{-C}_8$ alkenyl; optionally R_{10} -substituted $\text{C}_3\text{-C}_8$ cycloalkyl; optionally R_{10} -substituted adamantyl; or optionally R_{10} -substituted $\text{C}_4\text{-C}_8$ cycloalkenyl;

or



wherein A is $-\text{CH}_2-$, $-\text{NH}-$, $-\text{NR}_9-$, $-\text{S}-$, $-\text{SO}-$, SO_2- or $-\text{O}-$, n is 0, 1 or 2, and the aromatic rings are each, independently optionally R_{10} -substituted;

each of R_4 , independently, has one of the significances of R_5 ; or is CN; OH; OR_9 ; F; Cl; Br; or I;

each of R_5 , independently, is H; $\text{C}_1\text{-C}_8$ alkyl; $\text{C}_1\text{-C}_8$ hydroxyalkyl; $\text{C}_2\text{-C}_8$ alkoxyalkyl; $\text{C}_1\text{-C}_8$ halogenoalkyl; phenyl; benzyl; or heteroaryl;

each of R_6 , independently, has one of the significances given for R_4 ;

each of R_7 , independently, has one of the significances given for R_5 ;

R_8 is H; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; CN; CH_2NH_2 ; CH_2NHR_9 ; $CH_2NR_9R_9$; $CH_2NHC(O)R_9$; $CH_2NR_9C(O)R_9$; $CH_2NHC(O)NHR_9$; $CH_2NR_9C(O)NHR_9$; $CH_2NR_9C(O)NR_9R_9$; $CH_2NHC(O)OR_9$; $CH_2NR_9C(O)OR_9$; $CH_2NHSO_2R_9$; $CH_2N(SO_2R_9)_2$; or $CH_2NR_9SO_2R_9$;

each R_9 , independently, is C_1-C_6 alkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; heteroaryl; or CF_3 ;

R_{10} represents 1 to 4 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_9 ; $CONH_2$; $CONHR_9$; $CONR_9R_9$; $OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9 ; $COOH$; $COOR_9$; CF_3 ; CHF_2 ; CH_2F ; CN; NO_2 ; NH_2 ; NHR_9 ; NR_9R_9 ; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$; $NR_9C(O)OR_9$; $NHSO_2R_9$; $N(SO_2R_9)_2$; $NR_9SO_2R_9$; SR_9 ; $S(O)R_9$; SO_2R_9 ; $Si(CH_3)_3$ and $B(OC(CH_3)_2)_2$;

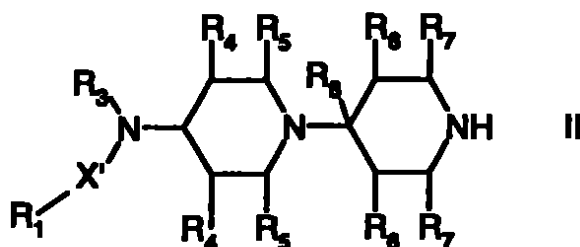
R_{11} represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; and

Y is a direct bond; $-C(O)-$; $-C(O)CH_2-$; $-S(O)-$; $-S(O)_2-$; $-C(S)-$; $-CH_2-$; $-C(-CH_2-CH_2)-$; $-CH(R_3)-$ or $-C(R_4)_2-$.

In free form or in salt form.

2. A compound according to claim 1, wherein R_1 is phenyl or heteroaryl, each being optionally substituted by R_{10} ; or phenyl optionally substituted by R_{11} ; wherein R_{10} represents 1 to 3 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_9 ; $CONH_2$; $CONHR_9$; $CONR_9R_9$; $OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9 ; $COOH$; $COOR_9$; CF_3 ; CHF_2 ; CH_2F ; CN; NO_2 ; NH_2 ; NHR_9 ; NR_9R_9 ; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$; $NR_9C(O)OR_9$; $NHSO_2R_9$; $N(SO_2R_9)_2$; $NR_9SO_2R_9$; SR_9 ; $S(O)R_9$; SO_2R_9 and $Si(CH_3)_3$ and R_{11} is an annulated 5 or 6 membered non aromatic ring optionally containing 1 or 2 oxygen atoms, and attached to 2 adjacent carbon atoms.

3. A compound according to claim 1, wherein each of R_4 , R_5 , R_6 or R_7 independently, is H; C_{1-6} alkyl; or benzyl.
4. A compound according to claim 1, wherein R_8 is H; C_{1-6} alkyl; or C_{2-6} alkenyl.
5. A compound according to claim 1 wherein X is a direct bond or $-CH_2-$ and / or Y is $-C(O)-$.
6. A process for the preparation of a compound of formula I according to claim 1, which process comprises
 - a) for the preparation of a compound of formula I wherein X is a direct bond, $-CH_2-$, $-CH_2CH_2-$ or $-CHR_2-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O_2)-$, amidating a compound of formula II

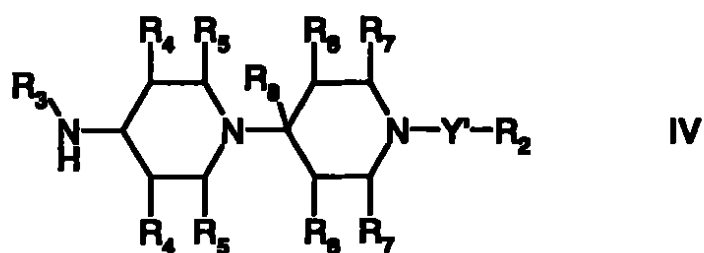


wherein R_1 and R_3 to R_8 are as indicated above and X' is a direct bond, $-CH_2-$, $-CH_2CH_2-$ or $-CHR_2-$
with a compound of formula III



wherein R_2 is as defined above, Y' is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O_2)-$ and A' is a leaving group, e.g. Cl, Br or OH,

- b) for the preparation of a compound of formula I wherein X is a direct bond and Y is $-CH_2-$, submitting a compound of formula II as defined above wherein X' is a direct bond, to a reductive amination; or
- c) for the preparation of a compound of formula I wherein X is CH_2- , $-CH_2CH_2-$ or $-CHR_2-$ and Y is $-CO-$, $-C(O)CH_2-$, $-S(O)-$ or $-S(O_2)-$, reacting a compound of formula IV



wherein R_2 to R_8 and Y' are as defined above, with a compound of formula V



wherein R_1 is as defined above and X'' is CH_2 or $-\text{CHR}_8$;

and, where required, converting the resulting compound of formula I obtained in free form into the desired salt form, or vice versa.

7. A compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.

8. A pharmaceutical composition comprising a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent a carrier therefor.

9. A pharmaceutical combination comprising

- a) a first agent which is a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and
- b) at least one co-agent.

10. A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, in a subject in need of such a treatment, which method comprises administering to said subject an effective amount of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof.

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Abstract

Piperidine derivatives of formula I as disclosed in the specification have interesting pharmaceutical properties e.g. as CCR5 inhibitors.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ☒ MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	☒	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	☒	()
- Descripción de la invención.	☒	()
- Dibujos de ser estos pertinentes.	☒	()
- Comprobante de Pago de las tasas establecidas.		()
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

Andrea Posse

Fecha:

03-090558

SUPERINDUSTRIA Y COMERCIO

SISTEMA DE REGISTRO I

Fecha 04/12/2003

MANTENIMIENTO DE PROTOCOLOS

Numero : 17398

Fecha : 16/04/1997

Conferido: NOVARTIS AG (NOVARTIS SA) (NOVARTIS INC.)

[Pais : CH SUITZA

Ciudad : 3 BASILEA

Represent: S Sustituir: S Desistir: S

Ino. Radicacion : 97 19953 Clase: 0 Scrv: 0 Scac: 0

Isencia Código Ctr

Nombre

1 5376 ESCOBAR URIBE JIMENA

1 2 267 ESCOBAR URIBE JIMENA

Encontrados (1/1) registro(s)

 $R^\# \leq R^\#x$



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Folio 150

2020
Bogotá DC

Doctor(a)
JIMENA ESCOBAR URIBE
Apoderado(a)
NOVARTIS AG.

REFERENCIA:	Radicación No.	03- 90558
	Solicitud Internacional	PCT/EP02/03871
	Fecha inicio fase nacional	09/11/2003
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	1480
	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,

7 8 DIC. 2003


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

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