

RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

AVENIDA 82 N° 10 - 82, Piso 6
TELÉFONO: (57-1) 6341500
BOGOTÁ, D.C. COLOMBIA
WWW.BAKERINFO.COM
OFFICE.BOGOTA@BAKERNET.COM

205 186

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO

Radicación : 01007000 00000003 Folios: 3
Fecha (SIS): 2003-07-23 12:53:36
Trámite : 002 PATENTES D 1 REGISTRO/ 530 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. 01.007.880

Solicitud de Patente de Invención Titulada:

"NUEVOS DERIVADOS DE AMIDAS
HETEROCICLICAS".

Solicitante: PFIZER PRODUCTS INC.

**SOLICITUD DE EXAMEN DE FONDO SEGÚN EL ARTICULO 44 DE LA
DECISION 486, GACETA No. 527**

ALVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá, D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado sustituto, de la sociedad Pfizer Products Inc., respetuosamente me permito solicitar, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Adjunto recibo por el monto de \$ 335.000 pesos para cubrir la tasa correspondiente, según la Resolución 41687 del año 2002.

Atentamente,

ALVARO CORREA ORDONEZ
C.C. No. 79.143.366 de Usaquén
T.P. 20.281

Anexos: • Sustitución de Poder
Recibo por \$ 335.000 pesos

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circulo de Santafé de Bogotá, compareció

Quién exhibió la C.C. No. 7710330

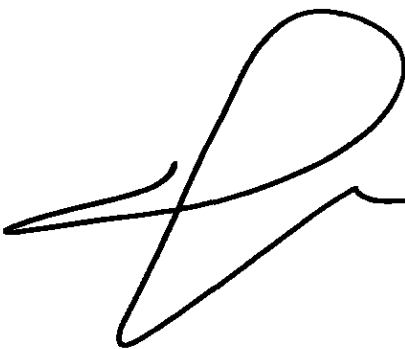
expedida en Uzgen Y.P. 1026

y declaró que la firma y huella que aparecen en el presente memorial son suyas y que el contenido del mismo es cierto

Memorial dirigido a interesado

Santafé de Bogotá, D.C.

23 JUL 2003


Firma del Declarante


HUELLA

Autorizó la anterior Diligencia



NOTARIO ONCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ, D.C. COLOMBIA
NOTARIO DE CIRCULO DE
SANTAFÉ DE BOGOTÁ, D.C.


MANVARRORE BAUTISTA
NOTARIO ONCE

RAISBECK, LARA, RODRÍGUEZ & RUEDA
MIEMBROS DE LA FIRMA
BAKER & MCKENZIE

AVENIDA 82 No. 10-82, 6° Piso
TELÉFONO: (57-1) 634-1500
BOGOTÁ, D.C. COLOMBIA
WWW.BAKERNET.COM
OFFICE.BOGOTA@BAKERNET.COM

206 187

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Solicitud colombiana de patente No. **01.007.880**

Solicitante: **PFIZER PRODUCTS INC.**

**"NUEVOS DERIVADOS DE AMIDAS
HETEROCICLICAS".**

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor y vecino de Bogotá. D.C., identificado como aparece al pie de mi firma, actuando en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad en el doctor **ALVARO CORREA ORDÓÑEZ**, identificado con la Cédula de Ciudadanía número 79.143.366 de Usaquén y con la Tarjeta Profesional número 20.281, para que sea él quien en adelante, asuma el trámite de la presente solicitud.

El apoderado sustituto queda con las mismas facultades del principal.

Atentamente,



CARLOS R OLARTE
C.C. No. 79.782.747 de Bogotá
T. P. No. 74.295 del Consejo Superior de la Judicatura

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Círculo de Santa Fe de Bogotá, compareció

Quién exhibió la C.C. No. 74225

expedida en

T.P.

y declaró que la firma y huella que aparecen en el presente memorial son autas y que el contenido del mismo es cierto.

Memorial dirigido a

interesado

Sancti de Bogotá, D.C.

15 JUL 2003

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTA FE DE BOGOTA

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTA FE DE BOGOTA, D.C.

MONICA Z. BAUTISTA N
NOTARIA ONCE(E)

207
188

SUPERINDUSTRIA Y COMERCIO
Radicacion : 81007000 00000003 Folios: 3
Fecha (MM): 2003-07-23 12:53:56
Tramite : 002 PATENTES D 1 REGISTRO/ 530 PETICION
Dependencia: ENDO DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 43,891
FECHA : JUNIO 24 DE 2003

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	13228244	24/06/2003	18,050,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	05 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
		TOTAL :	\$ 335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 01-7880

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 527, DE

FECHA 30 DE ABRIL DE 2003, EL TERMINO HABIL SEÑALADO POR LA LEY

EXPIRA EL 29 DE JULIO DE 2003.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud calga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X _____



209-
D1
190

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

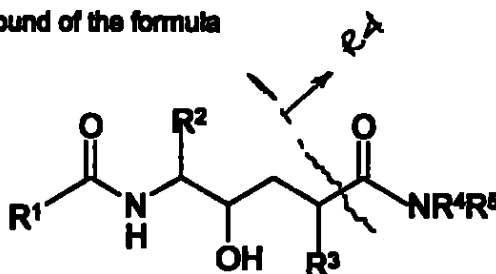
(51) International Patent Classification ⁶ : C07D 215/34, A61K 31/47, C07D 241/44, A61K 31/50, C07D 213/82, A61K 31/455, C07D 217/26, 237/28, A61K 31/495, C07D 307/85, A61K 31/34, C07D 333/70, A61K 31/38, C07D 235/24, A61K 31/415, C07D 241/24, 209/42, A61K 31/40, C07D 277/68, A61K 31/425, C07D 221/04, 213/81, 405/12, 401/12, 409/12, 417/12, 403/12, 471/04 // (C07D 471/04, 231:00, 221:00)	A1	(11) International Publication Number: WO 98/38167 (43) International Publication Date: 3 September 1998 (03.09.98)
(21) International Application Number: PCT/US98/01568 (22) International Filing Date: 5 February 1998 (05.02.98) (30) Priority Data: 60/039,169 26 February 1997 (26.02.97) US (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): BROWN, Matthew, Frank [US/US]; 66 Greenhaven Road, Pawcatuck, CT 06379 (US). KATH, John, Charles [US/US]; 252 Shore Road, Waterford, CT 06385 (US). POSS, Christopher, Stanley [US/US]; 10 Hermitage Drive, Gales Ferry, CT 06335 (US).	(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: HETEROARYL-HEXANOIC ACID AMIDE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS SELECTIVE INHIBITORS OF MIP-1-ALPHA BINDING TO ITS CCR1 RECEPTOR (57) Abstract Compounds of formula (I) wherein R¹ is optionally substituted (C₂-C₉)heteroaryl; R² is optionally substituted phenyl-(CH₂)_m, naphthyl-(CH₂)_m, (C₃-C₁₀)cycloalkyl-(CH₂)_m, (C₁-C₆)alkyl or (C₂-C₉)heteroaryl-(CH₂)_m, m is an integer from zero to four; R³ is hydrogen, or optionally substituted (C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl-(CH₂)_n, (C₂-C₉)heterocycloalkyl-(CH₂)_n, (C₂-C₉)heteroaryl-(CH₂)_n or aryl-(CH₂)_n, n is an integer from zero to six; or R³ and the carbon to which it is attached form an optionally substituted and/or fused five to seven membered carbocyclic ring; R⁴ is hydrogen, (C₁-C₆)alkyl, hydroxy, (C₁-C₆)alkoxy, hydroxy (C₁-C₆)alkyl, (C₁-C₆)alkoxyCO, (C₃-C₁₀)cycloalkyl-(CH₂)_p, or optionally substituted (C₂-C₉)heterocycloalkyl-(CH₂)_p, (C₂-C₉)heteroaryl-(CH₂)_p, phenyl-(CH₂)_p or naphthyl-(CH₂)_p, p is an integer from zero to four; or R⁴ and R⁵ together with the nitrogen atom to which they are attached form an optionally substituted (C₂-C₉)heterocycloalkyl group; R⁵ is hydrogen, (C₁-C₆)alkyl or amino. The present compounds are potent and selective inhibitors of MIP-1-alpha binding to its receptor CCR1, and are thus useful to treat inflammation and other immune disorders. (I)		

210
191

5

CLAIMS

1. A compound of the formula



I

10 wherein R^1 is (C_2-C_6) heteroaryl optionally substituted with one or more substituents independently selected from the group consisting of hydrogen, halo, CN, (C_1-C_6) alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy- (C_1-C_6) alkyl, (C_1-C_6) alkoxy optionally substituted with one or more fluorine atoms, (C_1-C_6) alkoxy- (C_1-C_6) alkyl, HO-(C=O)-, (C_1-C_6) alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C_1-C_6) alkyl-O-(C=O)-(C₁-C₆)alkyl, (C_1-C_6) alkyl-

15 (C=O)-O-, (C_1-C_6) alkyl-(C=O)-O-(C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C_1-C_6) alkyl(O=C)-, (C_1-C_6) alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C_1-C_6) alkylamino, $[(C_1-C_6)alkyl]_2$ amino, amino- (C_1-C_6) alkyl, (C_1-C_6) alkylamino- (C_1-C_6) alkyl, $[(C_1-C_6)alkyl]_2$ amino- (C_1-C_6) alkyl, H₂N-(C=O)-, $(C_1-C_6)alkyl-NH-(C=O)-$, $[(C_1-C_6)alkyl]_2N-(C=O)-$, H₂N(C=O)-(C₁-C₆)alkyl, $(C_1-C_6)alkyl-HN(C=O)-(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]_2N-(C=O)-(C_1-C_6)alkyl$, H(O=C)-NH-, $(C_1-C_6)alkyl(C=O)-NH$, $(C_1-C_6)alkyl(C=O)-[NH](C_1-C_6)alkyl$, $(C_1-C_6)alkyl(C=O)-[N(C_1-C_6)alkyl](C_1-C_6)alkyl$, $(C_1-C_6)alkyl-S$, $(C_1-C_6)alkyl-(S=O)-$, $(C_1-C_6)alkyl-SO_2$, $(C_1-C_6)alkyl-SO_2-NH$, H₂N-SO₂, H₂N-SO₂-(C₁-C₆)alkyl, $(C_1-C_6)alkylHN-SO_2-(C_1-C_6)alkyl$, $[(C_1-C_6)alkyl]_2N-SO_2-(C_1-C_6)alkyl$, CF₃SO₂, $(C_1-C_6)alkyl-SO_2$, phenyl, (C_3-C_{10}) cycloalkyl, (C_2-C_6) heterocycloalkyl, and (C_2-C_6) heteroaryl;

25 R^2 is phenyl-(CH₂)_m-, naphthyl-(CH₂)_m-, (C_3-C_{10}) cycloalkyl-(CH₂)_m-, (C_1-C_6) alkyl or (C_2-C_6) heteroaryl-(CH₂)_m-, wherein m is an integer from zero to four, wherein each of said phenyl, naphthyl, (C_3-C_{10}) cycloalkyl or (C_2-C_6) heteroaryl moieties of said phenyl-(CH₂)_m-, naphthyl-(CH₂)_m-, (C_3-C_{10}) cycloalkyl-(CH₂)_m- or (C_2-C_6) heteroaryl-(CH₂)_m- groups may optionally be substituted with one or more substituents independently selected from

30 hydrogen, halo, CN, (C_1-C_6) alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy- (C_1-C_6) alkyl, (C_1-C_6) alkoxy optionally substituted with one or more fluorine atoms, (C_1-C_6) alkoxy- (C_1-C_6) alkyl, HO-(C=O)-, (C_1-C_6) alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C_1-C_6) alkyl-O-(C=O)-(C₁-C₆)alkyl, (C_1-C_6) alkyl-(C=O)-O-, (C_1-C_6) alkyl-(C=O)-O-(C₁-C₆)alkyl,

- 5 H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-C₆)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-
- 10 [NH](C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂-, (C₁-C₆)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₂-, (C₁-C₆)alkyl-SO₂-, phenyl, phenoxy, benzyloxy, (C₃-C₁₀)cycloalkyl, (C₂-C₆)heterocycloalkyl, and (C₂-C₆)heteroaryl;
- 15 R³ is hydrogen, (C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl-(CH₂)_n-, (C₂-C₆)heterocycloalkyl-(CH₂)_n-, (C₂-C₆)heteroaryl-(CH₂)_n- or aryl-(CH₂)_n-; wherein n is an interger from zero to six; wherein said R³ (C₁-C₁₀)alkyl group may optionally be substituted with one or more substituents, independently selected from hydrogen, halo, CN, (C₁-C₆)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally substituted with one or more fluorine atoms, (C₁-C₆)alkoxy(C₁-C₆)alkyl, HO-(C=O)-,
- 20 (C₁-C₆)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl-(C=O)-O-(C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl,
- 25 [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-C₆)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-[NH](C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂-, (C₁-C₆)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₂-, (C₁-C₆)alkyl-SO₂-, phenyl,
- 30 (C₃-C₁₀)cycloalkyl, (C₂-C₆)heterocycloalkyl, and (C₂-C₆)heteroaryl; and wherein any of the carbon-carbon single bonds of said (C₁-C₁₀)alkyl may optionally be replaced by a carbon-carbon double bond;

- wherein the (C₃-C₁₀)cycloalkyl moiety of said R³ (C₃-C₁₀)cycloalkyl-(CH₂)_n- group
- 35 may optionally be substituted by one to three substituents independently selected from the group consisting of hydrogen, halo, CN, (C₁-C₆)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally substituted with one or more fluorine atoms, (C₁-C₆)alkoxy(C₁-C₆)alkyl, HO-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl-(C=O)-O-

- 5 (C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-
(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂amino, amino(C₁-C₆)alkyl,
(C₁-C₆)alkylamino(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-
(C=O)-, [(C₁-C₆)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)-(C₁-C₆)alkyl,
10 [(C₁-C₆)alkyl]₂N-(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-
[NH](C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-
(S=O)-, (C₁-C₆)alkyl-SO₂-, (C₁-C₆)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₆)alkyl,
(C₁-C₆)alkylHN-SO₂-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₂-, (C₁-C₆)alkyl-
SO₂-, phenyl, (C₃-C₁₀)cycloalkyl, (C₂-C₆)heterocycloalkyl, and (C₂-C₆)heteroaryl;

- wherein the (C₂-C₆)heterocycloalkyl moiety of said R³ (C₂-C₆)heterocycloalkyl-
15 (CH₂)_n- group may contain from one to three heteroatoms independently selected from
nitrogen, sulfur, oxygen, >S(=O), >SO₂ or >NR⁸, wherein said (C₂-C₆)heterocycloalkyl moiety
of said (C₂-C₆)heterocycloalkyl-(CH₂)_n- group may optionally be substituted on any of the
ring carbon atoms capable of forming an additional bond with a substituent independently
20 selected from the group consisting of hydrogen, halo, CN, (C₁-C₆)alkyl optionally substituted
with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally
substituted with one or more fluorine atoms, (C₁-C₆)alkoxy(C₁-C₆)alkyl, HO-(C=O)-,
(C₁-C₆)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-
(C=O)-O-, (C₁-C₆)alkyl-(C=O)-O-(C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl,
(C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino,
25 [(C₁-C₆)alkyl]₂amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl,
[(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-C₆)alkyl]₂N-(C=O)-,
H₂N(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-(C=O)-
(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-[NH](C₁-C₆)alkyl,
(C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-
30 SO₂-, (C₁-C₆)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-
(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₂-, (C₁-C₆)alkyl-SO₂-, phenyl,
(C₃-C₁₀)cycloalkyl, (C₂-C₆)heterocycloalkyl, and (C₂-C₆)heteroaryl;

- wherein the (C₂-C₆)heteroaryl moiety of said R³ (C₂-C₆)heteroaryl-(CH₂)_n- group may
contain from one to three heteroatoms independently selected from nitrogen, sulfur or
35 oxygen wherein said (C₂-C₆)heteroaryl moiety of said (C₂-C₆)heteroaryl-(CH₂)_n- group may
optionally be substituted on any of the ring carbon atoms capable of forming an additional
bond with a substituent selected from the group consisting of hydrogen, halo, CN,
(C₁-C₆)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-
(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally substituted with one or more fluorine atoms,

- 5 (C₁-C₈)alkoxy(C₁-C₈)alkyl, HO-(C=O)-, (C₁-C₈)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-O-(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-(C=O)-O-, (C₁-C₈)alkyl-(C=O)-O-(C₁-C₈)alkyl, H(O=C)-, H(O=C)-(C₁-C₈)alkyl, (C₁-C₈)alkyl(O=C)-, (C₁-C₈)alkyl(O=C)-(C₁-C₈)alkyl, NO₂, amino, (C₁-C₈)alkylamino, [(C₁-C₈)alkyl]₂amino, amino(C₁-C₈)alkyl, (C₁-C₈)alkylamino(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂amino(C₁-C₈)alkyl, H₂N-(C=O)-, (C₁-C₈)alkyl-NH-
- 10 (C=O)-, [(C₁-C₈)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-HN(C=O)-(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂N-(C=O)-(C₁-C₈)alkyl, H(O=C)-NH-, (C₁-C₈)alkyl(C=O)-NH-, (C₁-C₈)alkyl(C=O)-[NH](C₁-C₈)alkyl, (C₁-C₈)alkyl(C=O)-N(C₁-C₈)alkyl[(C₁-C₈)alkyl, (C₁-C₈)alkyl-S-, (C₁-C₈)alkyl-(S=O)-, (C₁-C₈)alkyl-SO₂-, (C₁-C₈)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₈)alkyl, (C₁-C₈)alkylHN-SO₂-(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂N-SO₂-(C₁-C₈)alkyl, CF₃SO₂-, (C₁-C₈)alkyl-SO₂-, phenyl, (C₃-C₁₀)cycloalkyl, (C₂-C₉)heterocycloalkyl, and (C₂-C₉)heteroaryl; and

- wherein said aryl moiety of said R³ aryl-(CH₂)_n- group is optionally substituted phenyl or naphthyl, wherein said phenyl and naphthyl may optionally be substituted with from one to three substituents independently selected from the group consisting of hydrogen, halo, CN, (C₁-C₈)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-
- 20 (C₁-C₈)alkyl, (C₁-C₈)alkoxy optionally substituted with one or more fluorine atoms, (C₁-C₈)alkoxy(C₁-C₈)alkyl, HO-(C=O)-, (C₁-C₈)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-O-(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-(C=O)-O-, (C₁-C₈)alkyl-(C=O)-O-(C₁-C₈)alkyl, H(O=C)-, H(O=C)-(C₁-C₈)alkyl, (C₁-C₈)alkyl(O=C)-, (C₁-C₈)alkyl(O=C)-(C₁-C₈)alkyl, NO₂, amino, (C₁-C₈)alkylamino, [(C₁-C₈)alkyl]₂amino, amino(C₁-C₈)alkyl,
- 25 (C₁-C₈)alkylamino(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂amino(C₁-C₈)alkyl, H₂N-(C=O)-, (C₁-C₈)alkyl-NH-(C=O)-, [(C₁-C₈)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-HN(C=O)-(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂N-(C=O)-(C₁-C₈)alkyl, H(O=C)-NH-, (C₁-C₈)alkyl(C=O)-NH-, (C₁-C₈)alkyl(C=O)-[NH](C₁-C₈)alkyl, (C₁-C₈)alkyl(C=O)-N(C₁-C₈)alkyl[(C₁-C₈)alkyl, (C₁-C₈)alkyl-S-, (C₁-C₈)alkyl-(S=O)-, (C₁-C₈)alkyl-SO₂-, (C₁-C₈)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₈)alkyl,
- 30 (C₁-C₈)alkylHN-SO₂-(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂N-SO₂-(C₁-C₈)alkyl, CF₃SO₂-, (C₁-C₈)alkyl-SO₂-, phenyl, (C₃-C₁₀)cycloalkyl, (C₂-C₉)heterocycloalkyl, and (C₂-C₉)heteroaryl;

- or R³ and the carbon to which it is attached form a five to seven membered carbocyclic ring, wherein any of the carbon atoms of said five membered carbocyclic ring may optionally be substituted with a substituent selected from the group consisting of
- 35 hydrogen, halo, CN, (C₁-C₈)alkyl optionally substituted with one or more fluorine atoms (preferably one to three fluorine atoms), hydroxy, hydroxy-(C₁-C₈)alkyl, (C₁-C₈)alkoxy optionally substituted with one or more fluorine atoms (preferably one to three fluorine atoms), (C₁-C₈)alkoxy(C₁-C₈)alkyl, HO-(C=O)-, (C₁-C₈)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-O-(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-(C=O)-O-, (C₁-C₈)alkyl-(C=O)-O-(C₁-C₈)alkyl,

- 5 H(O=C)-, H(O=C)-(C₁-C₈)alkyl, (C₁-C₈)alkyl(O=C)-, (C₁-C₈)alkyl(O=C)-(C₁-C₈)alkyl, NO₂, amino, (C₁-C₈)alkylamino, [(C₁-C₈)alkyl]₂amino, amino(C₁-C₈)alkyl, (C₁-C₈)alkylamino(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂amino(C₁-C₈)alkyl, H₂N-(C=O)-, (C₁-C₈)alkyl-NH-(C=O)-, [(C₁-C₈)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-HN(C=O)-(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂N-(C=O)-(C₁-C₈)alkyl, H(O=C)-NH-, (C₁-C₈)alkyl(C=O)-NH-, (C₁-C₈)alkyl(C=O)-
- 10 [NH](C₁-C₈)alkyl, (C₁-C₈)alkyl(C=O)-[N(C₁-C₈)alkyl](C₁-C₈)alkyl, (C₁-C₈)alkyl-S-, (C₁-C₈)alkyl-(S=O)-, (C₁-C₈)alkyl-SO₂-, (C₁-C₈)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₈)alkyl, (C₁-C₈)alkylHN-SO₂-(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂N-SO₂-(C₁-C₈)alkyl, CF₃SO₂-, (C₁-C₈)alkyl-SO₂-, phenyl, (C₂-C₁₀)cycloalkyl, (C₂-C₈)heterocycloalkyl, and (C₂-C₈)heteroaryl, wherein one of the carbon-carbon bonds of said five to seven membered carbocyclic ring may optionally
- 15 be fused to an optionally substituted phenyl ring, wherein said substituents may be independently selected from hydrogen, halo, CN, (C₁-C₈)alkyl optionally substituted with one or more fluorine atoms (preferably one to three fluorine atoms), hydroxy, hydroxy-(C₁-C₈)alkyl, (C₁-C₈)alkoxy optionally substituted with one or more fluorine atoms (preferably one to three fluorine atoms), (C₁-C₈)alkoxy(C₁-C₈)alkyl, HO-(C=O)-, (C₁-C₈)alkyl-O-(C=O)-, HO-(C=O)-
- 20 (C₁-C₈)alkyl, (C₁-C₈)alkyl-O-(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-(C=O)-O-, (C₁-C₈)alkyl-(C=O)-O-(C₁-C₈)alkyl, H(O=C)-, H(O=C)-(C₁-C₈)alkyl, (C₁-C₈)alkyl(O=C)-, (C₁-C₈)alkyl(O=C)-(C₁-C₈)alkyl, NO₂, amino, (C₁-C₈)alkylamino, [(C₁-C₈)alkyl]₂amino, amino(C₁-C₈)alkyl, (C₁-C₈)alkylamino(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂amino(C₁-C₈)alkyl, H₂N-(C=O)-, (C₁-C₈)alkyl-NH-(C=O)-, [(C₁-C₈)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₈)alkyl, (C₁-C₈)alkyl-HN(C=O)-(C₁-C₈)alkyl,
- 25 [(C₁-C₈)alkyl]₂N-(C=O)-(C₁-C₈)alkyl, H(O=C)-NH-, (C₁-C₈)alkyl(C=O)-NH-, (C₁-C₈)alkyl(C=O)-[NH](C₁-C₈)alkyl, (C₁-C₈)alkyl(C=O)-[N(C₁-C₈)alkyl](C₁-C₈)alkyl, (C₁-C₈)alkyl-S-, (C₁-C₈)alkyl-(S=O)-, (C₁-C₈)alkyl-SO₂-, (C₁-C₈)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₈)alkyl, (C₁-C₈)alkylHN-SO₂-(C₁-C₈)alkyl, [(C₁-C₈)alkyl]₂N-SO₂-(C₁-C₈)alkyl, CF₃SO₂-, (C₁-C₈)alkyl-SO₂-, phenyl, (C₂-C₁₀)cycloalkyl, (C₂-C₈)heterocycloalkyl, and (C₂-C₈)heteroaryl
- 30 R⁴ is hydrogen, (C₁-C₈)alkyl, hydroxy, (C₁-C₈)alkoxy, hydroxy(C₁-C₈)alkyl, (C₁-C₈)alkoxy(C=O)-, (C₂-C₁₀)cycloalkyl-(CH₂)_p-, (C₂-C₈)heterocycloalkyl-(CH₂)_p-, (C₂-C₈)heteroaryl-(CH₂)_p-, phenyl-(CH₂)_p-, or naphthyl-(CH₂)_p-, wherein p is an integer from zero to four, wherein said (C₂-C₈)heterocycloalkyl, (C₂-C₈)heteroaryl, phenyl and naphthyl groups of said (C₂-C₈)heterocycloalkyl-(CH₂)_p-, (C₂-C₈)heteroaryl-(CH₂)_p-, phenyl-(CH₂)_p-, or naphthyl-(CH₂)_p- may be optionally substituted on any of the ring atoms capable of supporting an additional bond with a substituent selected from the group consisting of hydrogen, halo, CN, (C₁-C₈)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₈)alkyl, (C₁-C₈)alkoxy optionally substituted with one or more fluorine atoms, (C₁-C₈)alkoxy(C₁-C₈)alkyl, HO-(C=O)-, (C₁-C₈)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₈)alkyl,
- 35

215
196

- 5 (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl-(C=O)-O-(C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂ amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino (C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-, [(C₁-C₆)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)-(C₁-C₆)alkyl,
- 10 [(C₁-C₆)alkyl]₂N-(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-[NH](C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂-, (C₁-C₆)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₂-, (C₁-C₆)alkyl-SO₂-, phenyl, (C₃-C₁₀)cycloalkyl, (C₂-C₉)heterocycloalkyl, and (C₂-C₉)heteroaryl;
- 15 or R⁴ and R⁵ together with the nitrogen atom to which they are attached form a (C₂-C₉)heterocycloalkyl group wherein any of the ring atoms of said (C₂-C₉)heterocycloalkyl group may optionally be substituted with a substituent selected from the group consisting of hydrogen, halo, CN, (C₁-C₆)alkyl optionally substituted with one or more fluorine atoms, hydroxy, hydroxy-(C₁-C₆)alkyl, (C₁-C₆)alkoxy optionally substituted with one or more fluorine
- 20 atoms, (C₁-C₆)alkoxy(C₁-C₆)alkyl, HO-(C=O)-, (C₁-C₆)alkyl-O-(C=O)-, HO-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-O-(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-(C=O)-O-, (C₁-C₆)alkyl-(C=O)-O-(C₁-C₆)alkyl, H(O=C)-, H(O=C)-(C₁-C₆)alkyl, (C₁-C₆)alkyl(O=C)-, (C₁-C₆)alkyl(O=C)-(C₁-C₆)alkyl, NO₂, amino, (C₁-C₆)alkylamino, [(C₁-C₆)alkyl]₂ amino, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino (C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂amino(C₁-C₆)alkyl, H₂N-(C=O)-, (C₁-C₆)alkyl-NH-(C=O)-,
- 25 [(C₁-C₆)alkyl]₂N-(C=O)-, H₂N(C=O)-(C₁-C₆)alkyl, (C₁-C₆)alkyl-HN(C=O)-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-(C=O)-(C₁-C₆)alkyl, H(O=C)-NH-, (C₁-C₆)alkyl(C=O)-NH-, (C₁-C₆)alkyl(C=O)-[NH](C₁-C₆)alkyl, (C₁-C₆)alkyl(C=O)-[N(C₁-C₆)alkyl](C₁-C₆)alkyl, (C₁-C₆)alkyl-S-, (C₁-C₆)alkyl-(S=O)-, (C₁-C₆)alkyl-SO₂-, (C₁-C₆)alkyl-SO₂-NH-, H₂N-SO₂-, H₂N-SO₂-(C₁-C₆)alkyl, (C₁-C₆)alkylHN-SO₂-(C₁-C₆)alkyl, [(C₁-C₆)alkyl]₂N-SO₂-(C₁-C₆)alkyl, CF₃SO₂-, (C₁-C₆)alkyl-
- 30 SO₂-, phenyl, (C₃-C₁₀)cycloalkyl, (C₂-C₉)heterocycloalkyl, and (C₂-C₉)heteroaryl;

R⁶ is hydrogen, (C₁-C₆)alkyl or amino;

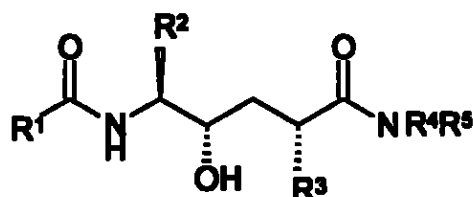
R⁶ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy-(CH₂)_g-, (C₁-C₆)alkoxy(C=O)-(CH₂)_g-, (C₁-C₆)alkyl-(SO₂)-(CH₂)_g-, (C₆-C₁₀)aryloxy-(CH₂)_g-, (C₆-C₁₀)aryloxy(C=O)-(CH₂)_g-, and (C₆-C₁₀)aryl-(SO₂)-(CH₂)_g-, wherein g is an integer from 1 to four;

- 35 with the proviso that when either R⁴ or R⁵ is hydrogen, and the other of R⁴ or R⁵ is (C₁-C₆)alkyl, R² is (C₃-C₁₀)cycloalkyl or isopropyl and R³ is (C₃-C₆)alkyl, phenyl, methylvinyl, dimethylvinyl, halovinyl, hydroxy(C₁-C₃)alkyl or amino(C₁-C₄)alkyl then R¹ must be other than indol-5-yl, 6-azaindol-2-yl, 2,3-dichloro-pyrol-5-yl, 4-hydroxyquinolin-3-yl, 2-hydroxyquinoxalin-3-yl, 6-azaindolin-3-yl, or optionally substituted indol-2 or 3-yl;

216
197

5 and the pharmaceutically acceptable salts of such compounds.

2. A compound according to claim 1, wherein said compound of formula I has the exact stereochemistry depicted in formula



Ia

wherein R¹, R², R³, R⁴ and R⁵ are as described in claim 1.

10 3. A compound according to claim 1, wherein R¹ is optionally substituted pyrazolo[3,4-b]pyridinyl, cinnolinyl, pyridinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzothiazolyl, indolyl, pyrazinyl, benzimidazolyl, benzofuranyl, benzo[b]thiophenyl, naphthalenyl, quinoxalinyl, isoquinolinyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl or quinolinyl.

15 4. A compound according to claim 2, wherein R¹ is optionally substituted pyrazolo[3,4-b]pyridinyl, cinnolinyl, pyridinyl, 6,7-dihydro-5H-[1]pyrindinyl, benzothiazolyl, indolyl, pyrazinyl, benzimidazolyl, benzofuranyl, benzo[b]thiophenyl, naphthalenyl, quinoxalinyl, isoquinolinyl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl or quinolinyl.

20 5. A compound according to claim 1, wherein R¹ is optionally substituted pyrazolo[3,4-b]pyridin-5-yl, cinnolin-4-yl, pyridin-2-yl, 6,7-dihydro-5H-[1]pyrindin-3-yl, benzothiazol-2-yl, indol-2-yl, pyrazin-2-yl, benzimidazol-2-yl, benzofuran-2-yl, benzo[b]thiophen-2-yl, naphthalen-2-yl, quinoxalin-2-yl, quinoxalin-6-yl, isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl or quinolin-6-yl.

25 6. A compound according to claim 2, wherein R¹ is optionally substituted pyrazolo[3,4-b]pyridin-5-yl, cinnolin-4-yl, pyridin-2-yl, 6,7-dihydro-5H-[1]pyrindin-3-yl, benzothiazol-2-yl, indol-2-yl, pyrazin-2-yl, benzimidazol-2-yl, benzofuran-2-yl, benzo[b]thiophen-2-yl, naphthalen-2-yl, quinoxalin-2-yl, quinoxalin-6-yl, isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, 5, 6, 7, 8-tetrahydro-quinolin-3-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl or quinolin-6-yl.

30 7. A compound according to claim 1, wherein R¹ is optionally substituted quinoxalin-2-yl, quinoxalin-6-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl or quinolin-6-yl.

8. A compound according to claim 2, wherein R¹ is optionally substituted quinoxalin-2-yl, quinoxalin-6-yl, quinolin-2-yl, quinolin-3-yl, quinolin-4-yl or quinolin-6-yl.

9. A compound according to claim 1, wherein R² is optionally substituted benzyl.

217
198

5 amount of a compound according to claim 1 that is effective in treating or preventing such disorder or condition and a pharmaceutically acceptable carrier.

42. A pharmaceutical composition for treating or preventing a disorder or condition that can be treated or prevented by inhibiting MIP-1 α binding to the receptor CCR1 in a mammal, comprising an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and a
10 pharmaceutically acceptable carrier.

43. A method for treating or preventing a disorder or condition selected from autoimmune diseases, acute and chronic inflammatory conditions, allergic conditions, infection associated with inflammation, viral, transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity, and granulomatous in a mammal, comprising administering to a
15 mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder or condition.

44. A method for treating or preventing a disorder or condition that can be treated or prevented by antagonizing the CCR1 receptor in a mammal, comprising administering to a
20 mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder or condition.

45. A pharmaceutical composition for treating or preventing a disorder or condition selected from autoimmune diseases, acute and chronic inflammatory conditions, allergic conditions, infection associated with inflammation, viral, transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity, and granulomatous in a mammal, comprising a CCR1 receptor antagonizing effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
25

46. A pharmaceutical composition for treating or preventing a disorder or condition that can be treated or prevented by antagonizing the CCR1 receptor in a mammal, comprising a CCR1 receptor antagonizing effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
30

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

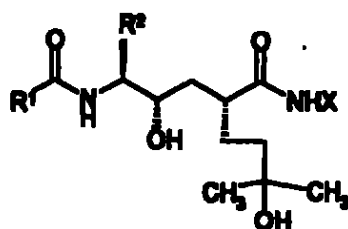
D2

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

218
199

(51) International Patent Classification 6: C07C 231/00	A2	(11) International Publication Number: WO 99/40061 (43) International Publication Date: 12 August 1999 (12.08.99)
(21) International Application Number: PCT/US99/00067 (22) International Filing Date: 18 January 1999 (18.01.99) (30) Priority Data: 60/073,801 5 February 1998 (05.02.98) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): KATH, John, Charles [US/US]; 252 Shore Road, Waterford, CT 06385 (US). BROWN, Matthew, Frank [US/US]; 66 Greenhaven Road, Pawcatuck, CT 06379 (US). POSS, Christopher, Stanley [US/US]; 231 Wyannup Road, North Stonington, CT 06359 (US). (74) Agents: SPIEGEL, Allen, J.; c/o Simpson, Allison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB) et al.	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UA, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>	

(54) Title: NOVEL DIHYDROXYHEXANOIC ACID DERIVATIVES



(I)

(57) Abstract

Dihydroxyhexanoic acid derivatives of general formula (I) are useful to treat inflammation and other immune disorders.

5

NOVEL DIHYDROXYHEXANOIC ACID DERIVATIVES**Background of the Invention**

The present invention relates to novel dihydroxyhexanoic acid derivatives, methods of use and pharmaceutical compositions containing them.

The compounds of the invention are potent and selective inhibitors of MIP-1 α binding to its receptor CCR1 found on inflammatory and immunomodulatory cells (preferably leukocytes and lymphocytes). The CCR1 receptor is also sometimes referred to as the CC-CKR1 receptor. These compounds also inhibit MIP-1 α (and the related chemokine shown to interact with CCR1 (e.g., RANTES and MCP-3)) induced chemotaxis of THP-1 cells and human leukocytes and are potentially useful for the treatment or prevention of autoimmune diseases (such as rheumatoid arthritis, type I diabetes (recent onset), inflammatory bowel disease, optic neuritis, psoriasis, multiple sclerosis, polymyalgia rheumatica, uveitis, and vasculitis), acute and chronic inflammatory conditions (such as osteoarthritis, adult Respiratory Distress Syndrome, Respiratory Distress Syndrome of infancy, ischemia reperfusion injury, and glomerulonephritis), allergic conditions (such as asthma and atopic dermatitis), infection associated with inflammation (such as viral inflammation (including influenza and hepatitis) and Guillian-Barre), transplantation tissue rejection (chronic and acute), organ rejection (chronic and acute), atherosclerosis, restenosis, HIV infectivity (co-receptor usage), and granulomatous diseases (including sarcoidosis, leprosy and tuberculosis).

MIP-1 α and RANTES are soluble chemotactic peptides (chemokines) which are produced by inflammatory cells, in particular CD8 $^{+}$ lymphocytes, polymorphonuclear leukocytes (PMNs) and macrophages, J.Biol. Chem., 270 (30) 29671-29675 (1995). These chemokines act by inducing the migration and activation of key inflammatory and immunomodulatory cells. Elevated levels of chemokines have been found in the synovial fluid of rheumatoid arthritis patients, chronic and rejecting tissue transplant patients and in the nasal secretions of allergic rhinitis patients following allergen exposure (Teran, et al., J. Immunol., 1806-1812 (1996), and Kuna et al., J. Allergy Clin. Immunol. 321 (1994)). Antibodies which interfere with the chemokine/receptor interaction by neutralizing MIP-1 α or gene disruption have provided direct evidence for the role of MIP-1 α and RANTES in disease by limiting the recruitment of monocytes and CD8 $^{+}$ lymphocytes (Smith et al., J. Immunol. 153, 4704 (1994) and Cook et al., Science, 269, 1583 (1995)). Together this data demonstrates that CCR1 antagonists would be an effective treatment of several immune based diseases. The compounds described within are highly soluble, potent and selective antagonists of CCR1.

201
220

5 United States Patent 4,923,864, issued May 8, 1990, refers to certain heterocyclic hexanamides that are useful for treating hypertension.

PCT publication WO 88/01488, published February 23, 1988, refers to renin inhibiting peptides which possess nonpeptide linkages.

10 PCT publication WO 93/ 025057, published February 4, 1993, refers to dipeptide analogs which are claimed to inhibit retroviral proteases.

PCT publication WO 93/17003, published September 2, 1993 refers to other dipeptide analogs which are claimed to inhibit retroviral proteases.

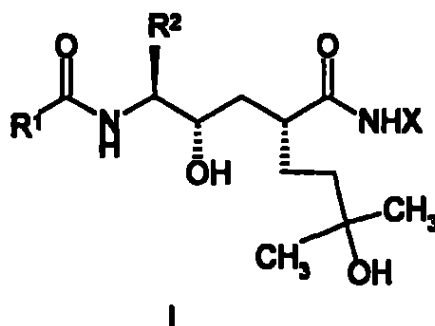
15 PCT publication WO 92/17490, published October 15, 1992, refers to peptides containing at least one O-phosphate monoester or diester. The compounds are claimed to possess activity for inhibiting retroviruses.

European Patent Publication 708,085, published April 24, 1996, refers to antiviral ethers of aspartate protease inhibitors.

20 United States Provisional Patent Application 80/039189, filed February 28, 1997, refers to other hexanoic acid derivatives which are also antagonists of the MIP-1 α /RANTES interaction with CCR1.

Summary of the Invention

The present invention relates to compounds of the formula I



wherein said compound is:

25 quinoxaline-2-carboxylic acid 4(R)-carbamoyl-1(S)-(3-chloro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;

7,8-difluoro-quinoline-3-carboxylic acid (1S)-benzyl-4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-octyl]-amide;

30 6,7,8-trifluoro-quinoline-3-carboxylic acid (1(S)-benzyl-4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-octyl)-amide;

quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(3-fluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;

221202

5 quinoxaline-2-carboxylic acid (1(S)-benzyl-2(S),7-dihydroxy-4(R)-hydroxycarbamoyl-7-methyl-octyl)-amide;

quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(2-chloro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;

10 quinoxaline-2-carboxylic acid [1(S)-(2-fluoro-benzyl)-2(S),7-dihydroxy-4(R)-hydroxycarbamoyl-7-methyl-octyl]-amide; (b)

quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(2-fluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;

quinoxaline-2-carboxylic acid [1(S)-(3,4-difluoro-benzyl)-2(S),7-dihydroxy-4(R)-hydroxycarbamoyl-7-methyl-octyl]-amide; (c)

15 quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(3,4-difluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide; or

quinoxaline-2-carboxylic acid (4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-1(S)-naphthalen-1-ylmethyl-octyl)-amide;

and pharmaceutically acceptable salts thereof.

20 The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, 25 phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The invention also relates to base addition salts of formula I. The chemical bases that 30 may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water- 35 soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder or condition selected from autoimmune diseases (such as rheumatoid arthritis, type I diabetes (recent onset), inflammatory bowel disease, optic neuritis, psoriasis,

5 multiple sclerosis, polymyalgia rheumatica, uveitis, and vasculitis), acute and chronic inflammatory conditions (such as osteoarthritis, adult respiratory distress syndrome, Respiratory Distress Syndrome of Infancy, ischemia reperfusion injury, and glomerulonephritis), allergic conditions (such as asthma and atopic dermatitis), infection associated with inflammation (such as viral inflammation (including influenza and hepatitis)
10 and Guillain-Barre), transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity (co-receptor usage), and granulomatous diseases (including sarcoidosis, leprosy and tuberculosis). In a mammal, preferably a human, comprising an amount of a compound of the formula I or a pharmaceutically acceptable salt thereof effective in treating or preventing such disorder or condition and a pharmaceutically acceptable carrier.

15 The present invention also relates to a pharmaceutical composition for treating or preventing a disorder or condition that can be treated or prevented by inhibiting MIP-1 α binding to the receptor CCR1 in a mammal, preferably a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and a pharmaceutically acceptable carrier. Examples of such
20 disorders and conditions are those enumerated in the preceding paragraph.

The present invention also relates to a method for treating or preventing a disorder or condition selected from autoimmune diseases (such as rheumatoid arthritis, type I diabetes (recent onset), inflammatory bowel disease, optic neuritis, psoriasis, multiple sclerosis, polymyalgia rheumatica, uveitis, and vasculitis), acute and chronic inflammatory conditions
25 (such as osteoarthritis, adult respiratory distress syndrome, Respiratory Distress Syndrome of Infancy, ischemia reperfusion injury, and glomerulonephritis), allergic conditions (such as asthma and atopic dermatitis), infection associated with inflammation (such as viral inflammation (including influenza and hepatitis) and Guillain-Barre), transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity (co-receptor usage), and granulomatous diseases (including sarcoidosis, leprosy and tuberculosis) in a mammal, preferably a human,
30 comprising administering to a mammal in need of such treatment or prevention an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder or condition.

The present invention also relates to a method for treating or preventing a disorder or
35 condition that can be treated or prevented by antagonizing the CCR1 receptor in a mammal, preferably a human, comprising administering to a mammal in need of such treatment or prevention an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder or condition.

223
204

5 The present invention also relates to a pharmaceutical composition for treating or preventing a disorder or condition selected from autoimmune diseases (such as rheumatoid arthritis, type I diabetes (recent onset), inflammatory bowel disease, optic neuritis, psoriasis, multiple sclerosis, polymyalgia rheumatica, uveitis, and vasculitis), acute and chronic inflammatory conditions (such as osteoarthritis, adult respiratory distress syndrome, Respiratory Distress Syndrome of infancy, ischemia reperfusion injury, and glomerulonephritis), allergic conditions (such as asthma and atopic dermatitis), infection associated with inflammation (such as viral inflammation (including influenza and hepatitis) and Guillain-Barre), transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity (co-receptor usage), and granulomatous diseases (including sarcoidosis, leprosy and tuberculosis) in a mammal, preferably a human, comprising a CCR1 receptor antagonizing effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

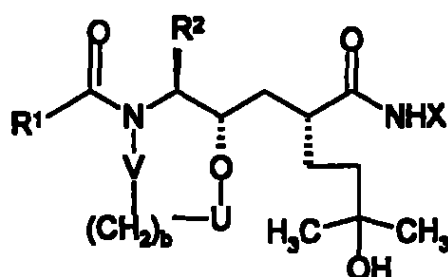
20 The present invention also relates to a pharmaceutical composition for treating or preventing a disorder or condition that can be treated or prevented by antagonizing the CCR1 receptor in a mammal, preferably a human, comprising a CCR1 receptor antagonizing effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25 The present invention also relates to a method for treating or preventing a disorder or condition selected from autoimmune diseases (such as rheumatoid arthritis, type I diabetes (recent onset), inflammatory bowel disease, optic neuritis, psoriasis, multiple sclerosis, polymyalgia rheumatica, uveitis, and vasculitis), acute and chronic inflammatory conditions (such as osteoarthritis, adult respiratory distress syndrome, Respiratory Distress Syndrome of infancy, ischemia reperfusion injury, and glomerulonephritis), allergic conditions (such as asthma and atopic dermatitis), infection associated with inflammation (such as viral inflammation (including influenza and hepatitis) and Guillain-Barre), transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity (co-receptor usage), and granulomatous diseases (including sarcoidosis, leprosy and tuberculosis) in a mammal, preferably a human, comprising administering to a mammal in need of such treatment or prevention a CCR1 receptor antagonizing effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

This invention also encompasses pharmaceutical compositions containing and methods of treating or preventing comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a

224/05

5 polypeptide chain of two or more (e.g., two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy or carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, 10 citrulline homocysteine, homoserine, ornithine and methionine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include compounds of formula I in which an amide nitrogen and a hydroxy group when taken together form a cyclic group such as the following formula



14

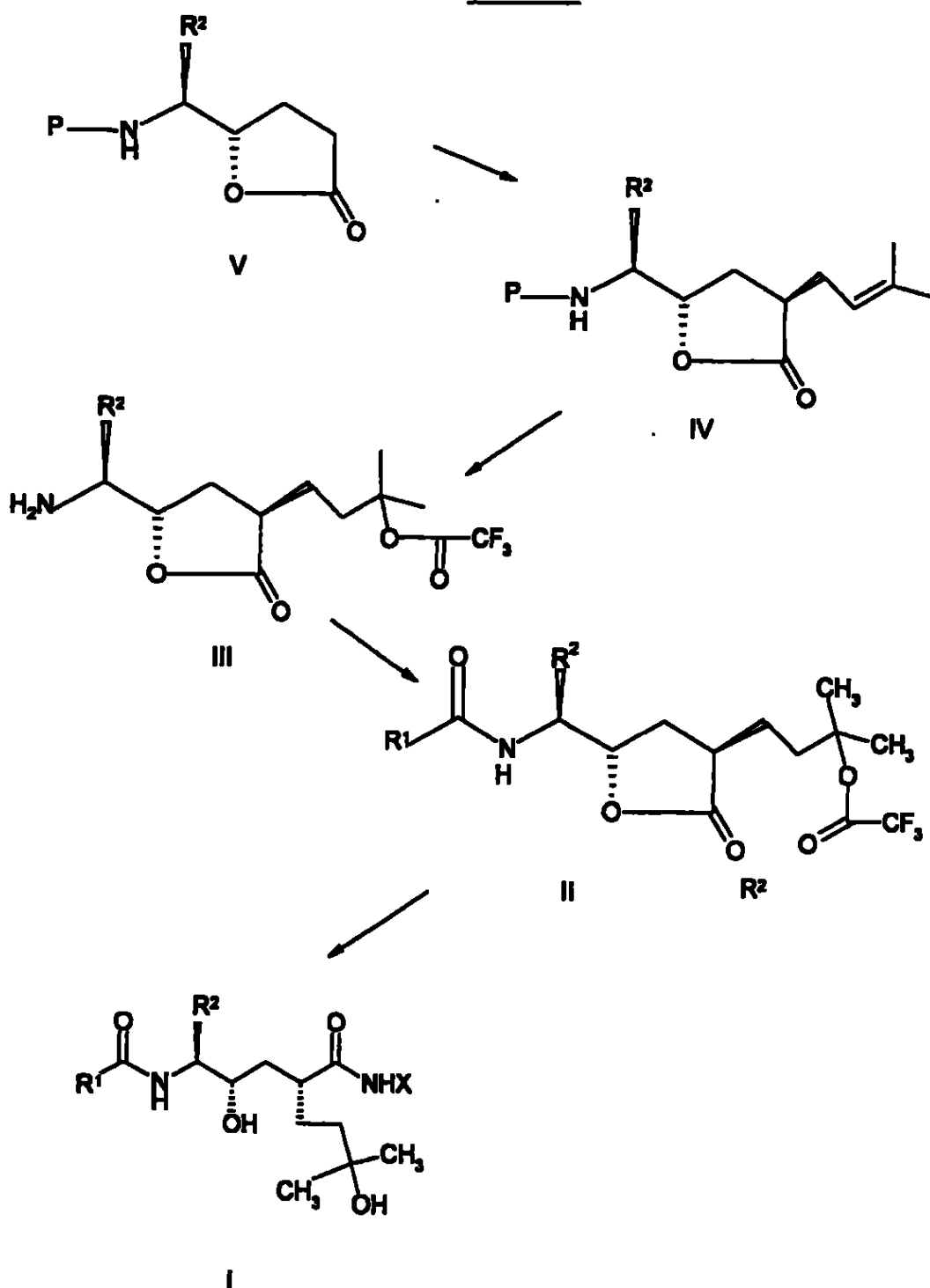
15 wherein R¹ and R² are as defined in formula I and U and V are independently carbonyl, methylene, SO₂ or SO₃, and b is an integer from one to three wherein each methylene group is optionally substituted with hydroxy.

Detailed Description of the Invention

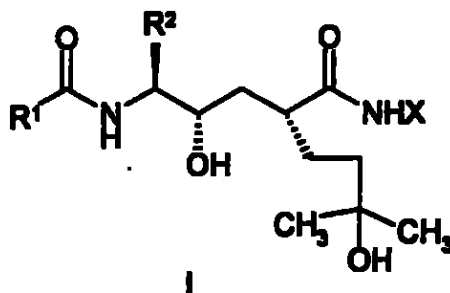
20 Compounds of the formula I may be prepared according to the following reaction Scheme and discussion.

5

SCHEME 1



- 5 Scheme 1 refers to the preparation of compounds of the formula I having the exact stereochemistry



- Compounds of the formula I, or any of the intermediates thereof, can be separated by column chromatography according to methods well known to those of ordinary skill in the art, to yield pure compounds of the formula I.

- Referring to Scheme 1, compounds of the formula I, can be prepared from compounds of formula II by reaction with ammonia or another volatile low molecular weight amine in a polar solvent at a temperature from about -10°C to about 35°C, preferably at about 30°C. Suitable solvents include, alcohols, such as methanol, ethanol, or butanol; or ethers such as glyme or dioxane (an acid catalyst may be used with an ether solvent). Preferably the solvent is methanol.

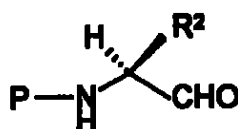
- Compounds of formula II are prepared by coupling a compound of formula III with an acid of the formula R^1CO_2H (or an acid chloride thereof wherein R^1 is quinoxaline-2-carboxylic acid, 7,8 difluoro-quinoline-3-carboxylic acid or 6,7,8-trifluoroquinoline-3-carboxylic acid). Such a coupling reaction is generally conducted at a temperature of about -30°C to about 80°C, preferably about 0°C to about 25°C. Examples of suitable coupling reagents which activate the carboxylic acid functionality are dicyclohexylcarbodiimide/hydroxybenzotriazole (DCC/HBT), N-3-dimethylaminopropyl-N'-ethylcarbodiimide (EDC)/HBT, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), carbonyl diimidazole (CDI)/dimethylaminopyridine (DMAP), and diethylphosphorylcyanide. The coupling is conducted in an inert solvent, preferably an aprotic solvent, such as acetonitrile, dichloromethane, chloroform, and dimethylformamide. The preferred solvent is dichloromethane.

- For a discussion of other conditions used for amide coupling see Houben-Weyl, Vol. XV, part II, E. Wunsch, Ed., George Thieme Verlag, 1974, Stuttgart, and those described in M. Bodanszky, Principles of Peptide Synthesis, Springer-Verlag, Berlin (1984) and The Peptides, Analysis, Synthesis and Biology (ed. E. Gross and J. Melenhofer), Vols 1-5. (Academic Press, New York) 1979-1983.

- 5 The compounds of formula III, can be prepared by deprotection and alkene hydrolysis of compounds of the formula IV by reaction with trifluoro acetic acid. Suitable protecting groups, of the formula P, include t-butoxycarbonyl.

Compounds of the formula IV, can be prepared by reaction of a compound of formula V with 4-bromo-2-methyl-2-butene, in the presence of a strong base in an aprotic polar solvent. Suitable bases include lithium dialkyl amides such as lithium N-isopropyl-N-cyclohexylamide (DA) or potassium hydride. Suitable solvents include ethers (such as THF, glyme or dioxane) benzene or toluene, preferably THF. The aforesaid reaction is conducted at about -78°C to about 0°C, preferably at about -78°C.

- Compounds of the formula V can be prepared by methods well known to those of ordinary skill in the art or are commercially available. Specifically, compounds of the formula V can be prepared by the method of Fray *et al.*, (*J. Org. Chem.*, 51, 4828-4833 (1986)) using an (S)-aldehyde of the formula



VII

- Compounds of the formula VII are prepared by reducing amino acids or amino esters to alcohols (Stanfield *et al.*, *J. Org. Chem.* 46, 4799-4800 (1981), Soal *et al.*, *Bull. Chem. Soc. Jpn.*, 57, 2327 (1984)) followed by oxidation of the alcohols to aldehydes of the formula VII (Luly *et al.*, *J. Org. Chem.*, 53 (26), 6109-6112 (1988) and Denis *et al.*, *J. Org. Chem.*, 56 (24), 6939-6942 (1991)). Un-natural amino acids can be prepared according to the method of Myers *et al.*, *Tet. Lett.* 36, (1995) and Myers *et al.* *J. Am. Chem. Soc.*, 117, 8488-8489 (1995).

- Alternatively, compounds of the formula V can also be made by the method of DeCamp *et al.*, (*Tetrahedron Lett.*, 32, 1867 (1991)).

Unless indicated otherwise, the pressure of each of the above reactions is not critical. Generally, the reactions will be conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

- The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base

209
228

5 compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

10 The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-
15 naphthoate)] salts.

Those compounds of the formula I which are also acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical
20 bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an
25 aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of
30 reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

Compounds of the formula I and their pharmaceutically acceptable salts (hereinafter also referred to, collectively, as "the active compounds") are potent antagonists of the CCR1 receptors. The active compounds are useful in the treatment or prevention of autoimmune
35 diseases (such as rheumatoid arthritis, type I diabetes (recent onset), inflammatory bowel disease, optic neuritis, psoriasis, multiple sclerosis, polymyalgia rheumatica, uveitis, and vasculitis), acute and chronic inflammatory conditions (such as osteoarthritis, adult respiratory distress syndrome, Respiratory Distress Syndrome of infancy, ischemia reperfusion injury, and glomerulonephritis), allergic conditions (such as asthma and atopic dermatitis), infection

210
229

5 associated with inflammation (such as viral inflammation (including influenza and hepatitis) and Guillien-Barre), transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity (co-receptor usage), and granulomatous diseases (including sarcoidosis, leprosy and tuberculosis).

10 The activity of the compounds of the invention can be assessed according to procedures know to those of ordinary skill in the art. Examples of recognized methods for determining CCR1 induced migration can be found in Coligan, J. E., Kruisbeek, A.M., Margulies, D.H., Shevach, E.M., Strober, W. editors: Current Protocols In Immunology, 6.12.1- 6.12.3. (John Wiley and Sons, NY, 1991). One specific example of how to determine the activity of a compound for inhibiting migration is described in detail below.

15

Chemotaxis Assay:

The ability of compounds to inhibit the chemotaxis to various chemokines can be evaluated using standard 48 or 96 well Boyden Chambers with a 5 micron polycarbonate filter. All reagents and cells can be prepared in standard RPMI (BioWhittaker Inc.) tissue culture medium supplemented with 1 mg/ml of bovine serum albumin. Briefly, MIP-1 α (Peprotech, inc., P.O. Box 275, Rocky Hill NJ) or other test agonists, were placed into the 20 lower chambers of the Boyden chamber. A polycarbonate filter was then applied and the upper chamber fastened. The amount of agonist chosen is that determined to give the maximal amount of chemotaxis in this system (e.g., 1 nM for MIP-1 α should be adequate).

25 THP-1 cells (ATCC TIB-202), primary human monocytes, or primary lymphocytes, isolated by standard techniques can then be added to the upper chambers in triplicate together with various concentrations of the test compound. Compound dilutions can be prepared using standard serological techniques and are mixed with cells prior to adding to the chamber.

30 After a suitable incubation period at 37 degrees centigrade (e.g. 3.5 hours for THP-1 cells, 90 minutes for primary monocytes), the chamber is removed, the cells in the upper chamber aspirated, the upper part of the filter wiped and the number of cells migrating can be determined according to the following method.

35 For THP-1 cells, the chamber (a 96 well variety manufactured by Neuroprobe) can be centrifuged to push cells off the lower chamber and the number of cells can be quantitated against a standard curve by a color change of the dye fluorescein diacetate.

For primary human monocytes, or lymphocytes, the filter can be stained with Dif Quik® dye (American Scientific Products) and the number of cells migrating can be determined microscopically.

- 5 The number of cells migrating in the presence of the compound are divided by the number of cells migrating in control wells (without the compound). The quotient is the % inhibition for the compound which can then be plotted using standard graphics techniques against the concentration of compound used. The 50% inhibition point is then determined using a line fit analysis for all concentrations tested. The line fit for all data points must have
- 10 an coefficient of correlation (R squared) of > 90% to be considered a valid assay.

All of the compounds of the invention that were tested had IC₅₀ of less than 25µM, in the Chemotaxis assay.

- The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds
- 15 of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for administration by inhalation or insufflation. The active compounds of the invention may also be formulated for sustained delivery.

- For oral administration, the pharmaceutical compositions may take the form of, for
- 20 example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium
- 25 lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol
- 30 syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

- 35 The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain

212

~~231~~

5 formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

10 The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

15 For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be
20 formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

25 A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., rheumatoid arthritis) is 0.1 to 1000 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

30 Aerosol formulations for treatment of the conditions referred to above (e.g., rheumatoid arthritis) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 µg to 1000 µg of the compound of the invention. The overall daily dose with an aerosol will be within the range 0.1 mg to 1000 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

35 The active agents can be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,638,214, 4,080,598, 4,173,826, 3,119,742, and 3,492,397.

40 The compounds of the invention can also be utilized in combination therapy with other therapeutic agents such as with immunosuppressant agents such as cyclosporin A and FK-506, Cellcept®, rapamycin, leflunomide or with classical anti-inflammatory agents (e.g. cyclooxygenase/lipoxygenase inhibitors) such as tenidap, aspirin, acetaminophen, naproxen

213
232

- 5 and piroxicam, steroids including prednisone, azathioprine and biological agents such as OKT-3, anti IL-2 monoclonal antibodies (such as TAC),.

The compounds of the present invention possess unexpected solubility that could not be predicted based on United States Patent Application 60/039169, filed February 26, 1997. Specifically, all of the compounds of the present invention have at least 13 fold better solubility
10 than would be expected based on compounds from United States Provisional Application 60/039169. Specifically, quinoxaline-2-carboxylic acid (2(S)-hydroxy-6-methyl-4(R)-methylcarbamoyl-1(S)-naphthalen-2-ylmethyl-heptyl)-amide (Example 127), and N-1(S)-benzyl-4(R)-carbamoyl-7-fluoro-2(S)-hydroxy-7-methyl-octyl)-5,6-dichloro-nicotinamide (Example 247) both have solubilities of less than 5 µg/mL when assayed according to the
15 kinetic solubility assay described below.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification.
20 THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Low Resolution Mass Spectra (LRMS) were recorded on either a Hewlett Packard 59890, utilizing chemical ionization (ammonium), or a Fisons (or Micro Mass) Atmospheric Pressure Chemical Ionization (APCI) platform which
25 uses a 50/50 mixture of acetonitrile/water with 0.1% formic acid as the ionizing agent. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used. The names for the compounds of the invention were created by the Autonom 2.0 PC-batch version from Bellstein
30 Informationssysteme GmbH (ISBN 3-89536-976-4).

Solubility of the compounds was determined by a kinetic solubility assay such as described in Advanced Drug Delivery Review, 23, 3-25 (1997). One embodiment of the method described in Advanced Drug Delivery Review, 23, 3-25 (1997) is described below. One of ordinary skill in the art will appreciate that solubility can be determined by many
35 different methods.

Solubility of the compounds is determined at four fixed concentrations and is expressed as µg/mL. Solubility or insolubility is measured in phosphate buffer using a turbidometric plate reader by automated micro addition of a compound predissolved in DMSO. Solubilities at 50, 100, 200 and 250 or 100, 200, 400 and 500 micrograms/mL can be

214
233

- 5 determined by predissolving 1mg of compound in sufficient DMSO to reach an initial concentration of 20 or 40 µg/ uL.

A spectramax 250 UV transparent 96 well microplate is filled with 200 uL of Stock pH 7 phosphate buffer solution. A series of 25 absorption readings in a 5 by 5 matrix at a wavelength of 492nm are taken for each well in the microplate containing pH buffer alone.

- 10 This scan is to be used as a "blank", and the raw optical dispersion (OD) values are used as a baseline.

Compounds in DMSO solution are then added (column wise) down the microplate. Up to twenty four samples are assayed with each compound being placed in four contiguous wells column wise. Each column of the microplate contains four concentrations of compound

- 15 in ascending concentration and ascending row order (A-D), or row (E-H). The volume of DMSO stock added to each well ranges from 0.25 to 1.25% of the buffer well volume. The plate is then shaken for 20 minutes to allow for mixing.

Standard Dispense Procedure:

Row	µL Volume	µg compound in DMSO	%DMSO
A	0.5	20	0.25
B	1.0	20	0.50
C	2.0	20	1.00
D	2.5	20	1.25

Row	µL Volume	µg compound in DMSO	%DMSO
E	0.5	40	0.25
F	1.0	40	0.50
G	2.0	40	1.00
H	2.5	40	1.25

20

After compound addition, a second scan consisting of a series of 25 absorption readings in a 5 by 5 matrix are taken for each well in the microplate at the same wavelength as the first blank scan. The raw compound OD values for each reading in the 5 by 5 matrix are subtracted from the corresponding "blank" values in the 5 by 5 matrix to provide the raw solubility OD data.

25

Data obtained from the Tecan SLT Spectra Image Reader is then analyzed using a Visual Basic computer program (or can be calculated manually according to methods well known to those of ordinary skill in the art), so as to provide solubility data for each compound. The compound is considered to be out of solution when the absorbance value is greater than

- 5 three times the baseline value. All of the compounds of the invention had solubilities greater than 100 µg/mL.

PREPARATION 1

METHOD A

ALLYLIC ALKYLATION

10 (1(S)-[4(R)-[3-METHYL-BUT-2-ENYL]-5-OXO-TETRAHYDRO-FURAN-2(S)-YL]-2-PHENYL-ETHYL)-CARBAMIC ACID TERT-BUTYL ESTER

- To a flame dried round bottom flask under a nitrogen atmosphere was added tetrahydrofuran (40 mL) followed by 1,1,1,3,3,3-hexamethyldisilazane (8 mL, 37.8 mmol). The mixture was cooled to 0°C and n-butyl lithium (14.5 mL of a 2.5 M solution in hexanes, 15 38.0 mmol) was added. The mixture was stirred for 15 minutes, then cooled to -78 °C in dry ice / acetone bath. (1(S)-[5-Oxo-tetrahydro-furan-2(S)-yl]-2-phenyl-ethyl)-carbamic acid tert-butyl ester (5 g, 16.4 mmol) (prepared by the method of Fray, *J. Org. Chem.*, (51) 4828 (1986)) dissolved in tetrahydrofuran (50 mL) was added dropwise via syringe and stirring continued for 30 minutes. A solution of 4-bromo-2-methyl-2-butene (2.07 mL, 18.0 mmol) in 20 40 mL of THF was added dropwise via syringe. Stirring was continued for 3 hours during which time the temperature rose to -60°C. The mixture was quenched by slow addition of saturated, aqueous ammonium chloride (25 mL). Upon warming to room temperature, the solution was diluted with ether (300 mL) and transferred to a separatory funnel. The organic phase was washed with saturated aqueous citric acid (2x100mL), saturated aqueous sodium 25 bicarbonate (NaHCO₃)(2x100mL), and 100 mL brine. The organic layer was dried over magnesium sulfate (MgSO₄) and the solvent removed under reduced pressure. Thin layer chromatography in 1:2 hexanes/diethyl ether (Et₂O) revealed product with an R_f of 0.8. The resulting crude oil was chromatographed on silica gel (225g) eluting with 2:1 hexanes/diethyl ether to provide 4.73 g (77%) of the title compound. TLC: 1:2 Hexanes/Et₂O R_f: 0.8. ¹H NMR 30 (400 MHz, CDCl₃): δ 7.27 ppm (5H, m), 5.02 (1H, b), 4.52 (1H, d, J=9.3 Hz), 4.42 (1H, t, J=7.1 Hz), 3.98 (1H, dt, J= 8.5, 7.8 Hz), 2.93 (2H, m), 2.88 (1H, b), 2.68 (1H, m), 2.41 (1H, m), 2.24 (1H, m), 1.82 (1H, m), 1.65 (3H,s), 1.58 (3H,s), 1.37 (9H, s).

METHOD B

35 QUINOXALINE-2-CARBOXYLIC ACID 1(S)-BENZYL-4(R)-CARBAMOYL-2(S), 7-DIHYDROXY-7-METHYLOCTYL)-AMIDE

- To the lactone from method A (100 mg, 0.27 mmol) was added neat trifluoroacetic acid (1 mL). The resulting solution was stirred for 1 h and the trifluoroacetic acid removed in vacuo. The remaining residue was solvated in methylene chloride (10 mL) and triethylamine (0.15 mL, 1.07 mmol). Quinoxalyl chloride (58 mg, 0.3 mmol) was added as a solid and the 40 mixture stirred for 18 h. The mixture was transferred to a separatory funnel and washed with

5 citric acid (2x10 mL), NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried (MgSO₄) and the solvents filtered. The filtrate was concentrated in vacuo and the resulting residue was chromatographed on silica gel (10 g) eluting with 2:1 hexanes:ethyl acetate to provide 99 mg of the quinoxaline amide. This material was solvated in MeOH and ammonia gas was bubbled in for 5 min. The resulting solution was stirred for 16 h and the solvent removed in vacuo. The remaining residue was recrystallized (methylene chloride/methanol/Hexanes) to provide the title compound (90 mg, 72%). ¹H NMR (400 MHz, CD₃OD): δ 9.38 (1H, s), 8.21 (1H, dd, J=4.4, 2.5 Hz), 8.14 (1H, dd, J=4.4, 2.5 Hz), 7.93 (2H, m), 7.26 (2H, d, J=6.9 Hz), 7.17 (2H, t, J=7.1 Hz), 7.09 (1H, t, J=7.3 Hz), 4.30 (1H, m), 3.75 (1H, m), 3.03-2.98 (2H, m), 2.47 (1H, m), 1.77 (1H, m), 1.56 (2H, m), 1.4 (2H, m), 1.07 (6H, s).

15

EXAMPLE 1**QUINOXALINE-2-CARBOXYLIC ACID (4(R)-CARBAMOYL-2(S),7-DIHYDROXY-7-METHYL-1(S)-THIOPHEN-2-YLMETHYL-OCTYL)-AMIDE**

To a flame dried round bottom flask under a nitrogen atmosphere was added tetrahydrofuran (5 mL) followed by 1,1,1,3,3,3-hexamethyldisilazane (0.78 mL, 3.7 mmol). The mixture was cooled to 0°C and n-butyl lithium (1.4 mL of a 2.5 M solution in hexanes, 3.38 mmol) was added. The mixture was stirred for 15 minutes, then cooled to -78 °C in dry ice / acetone bath. (1(S)-[5-Oxo-tetrahydro-furan-2(S)-yl]-2-thienyl-ethyl)-carbamic acid tert-butyl ester (500 mg, 1.61 mmol) (prepared by the method of Fray, *J. Org. Chem.*, (51) 4828 (1986) using BOC-L-2-thienylalanine as a starting material) dissolved in tetrahydrofuran (6 mL) was added dropwise via syringe and stirring continued for 30 minutes. A solution of 4-bromo-2-methyl-2-butene (0.21 mL, 1.77 mmol) in 5 mL of THF was added dropwise via syringe. Stirring was continued for 3 hours during which time the temperature rose to -60°C. The mixture was quenched by slow addition of saturated, aqueous ammonium chloride. Upon warming to room temperature, the solution was diluted with ether and transferred to a separatory funnel. The organic phase was washed with saturated aqueous citric acid, saturated aqueous sodium bicarbonate (NaHCO₃), and brine. The organic layer was dried over magnesium sulfate (MgSO₄) and the solvent removed under reduced pressure. Thin layer chromatography in 2:1 hexane/diethyl ether (Et₂O) revealed product with an R_f of 0.25. The resulting crude oil was chromatographed on silica gel eluting with 2:1 hexanes/diethyl ether to provide 450 mg (74%) of the lactone.

To the lactone from above (450 mg, 1.19 mmol) was added neat trifluoroacetic acid (4.5 mL). The resulting solution was stirred for 1 hour and the trifluoroacetic acid removed in vacuo. The resulting amine salt (100mg, 0.34mmol) was solvated in methylene chloride (15 mL) and triethylamine (0.2 mL, 1.34 mmol). Quinoxalyl chloride (71 mg, 0.37 mmol) was added as a solid and the mixture stirred for 18 hours. The mixture was transferred to a

217
236

- 5 separatory funnel and washed with citric acid, NaHCO₃ and brine. The organic layer was dried (MgSO₄) and the solvents filtered. The filtrate was concentrated in vacuo and the resulting residue was chromatographed on silica gel eluting with 2:1 hexanes:ethyl acetate to provide 108 mg (71%) of the quinoxaline amide. This material was solvated in MeOH and ammonia gas was bubbled in for 5 minutes. The resulting solution was stirred for 16 hour and
- 10 the solvent removed in vacuo. The remaining residue was recrystallized (methylene chloride/methanol/Hexanes) to provide the title compound (60 mg, 53%). Melting point (MP) 158-159. Low Resolution Mass Spectrum (LRMS) 471, 453, 436. Solubility greater than 250 mg/mL.

- Table 1 refers to the preparation of compounds of the formula I by methods
- 15 analogous to the methods of Preparation 1 and Example 1.

TABLE 1

Example.	IUPAC Name	Melting Point	LRMS	Solubility
2	Quinoxaline-2-carboxylic acid 4(R)-carbamoyl-1(S)-(3-chloro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide	161-163	499, 481, 464	>100µg/ml
3	7,8-Difluoro-quinoline-3-carboxylic acid (1S)-benzyl-4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-octyl]-amide	171-173	501, 484	>250µg/ml
4	Quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(3-fluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide	153-155	483., 465., 448	>250µg/ml
5	6,7,8-Trifluoro-quinoline-3-carboxylic acid (1(S)-benzyl-4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-octyl)-amide	185-188	519, 502	>250µg/ml
6	Quinoxaline-2-carboxylic acid (1(S)-benzyl-2(S),7-dihydroxy-4(R)-hydroxycarbamoyl-7-methyl-octyl)-amide	108-110	482, 464, 447	>250µg/ml
7	Quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(2-chloro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide		481, 464	>250µg/ml
8	Quinoxaline-2-carboxylic acid [1(S)-(2-fluoro-	130-131	499	>250µg/ml

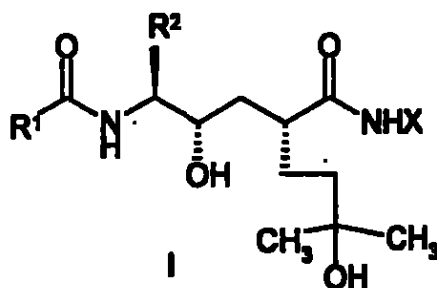
218
237

Example.	IUPAC Name	Melting Point	LRMS	Solubility
	benzyl)-2(S),7-dihydroxy-4(R)-hydroxycarbonyl-7-methyl-octyl)-amide			
9	Quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(2-fluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl)-amide	147-148	483	>250µg/ml
10	Quinoxaline-2-carboxylic acid [1(S)-(3,4-difluoro-benzyl)-2(S),7-dihydroxy-4(R)-hydroxycarbonyl-7-methyl-octyl)-amide	150-153	517, 499, 486	>200µg/ml
11	Quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(3,4-difluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl)-amide	110-120	501, 483, 486	>250µg/ml
12	Quinoxaline-2-carboxylic acid (4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-1(S)-naphthalen-1-ylmethyl-octyl)-amide	155-158	515, 497, 480	>250µg/ml

5

CLAIMS

1. A compound of the formula



wherein said compound is:

- 10 quinoxaline-2-carboxylic acid 4(R)-carbamoyl-1(S)-(3-chloro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;
- 7,8-difluoro-quinoline-3-carboxylic acid (1S)-benzyl-4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-octyl]-amide;
- 6,7,8-trifluoro-quinoline-3-carboxylic acid (1S)-benzyl-4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-octyl]-amide;
- 15 quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(3-fluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;
- quinoxaline-2-carboxylic acid (1(S)-benzyl-2(S),7-dihydroxy-4(R)-hydroxycarbamoyl-7-methyl-octyl)-amide;
- 20 quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(2-chloro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;
- quinoxaline-2-carboxylic acid [1(S)-(2-fluoro-benzyl)-2(S),7-dihydroxy-4(R)-hydroxycarbamoyl-7-methyl-octyl]-amide;
- quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(2-fluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide;
- 25 quinoxaline-2-carboxylic acid [1(S)-(3,4-difluoro-benzyl)-2(S),7-dihydroxy-4(R)-hydroxycarbamoyl-7-methyl-octyl]-amide;
- quinoxaline-2-carboxylic acid [4(R)-carbamoyl-1(S)-(3,4-difluoro-benzyl)-2(S),7-dihydroxy-7-methyl-octyl]-amide; or
- 30 quinoxaline-2-carboxylic acid (4(R)-carbamoyl-2(S),7-dihydroxy-7-methyl-1(S)-naphthalen-1-ylmethyl-octyl)-amide.

2. A pharmaceutical composition for treating or preventing a disorder or condition selected from autoimmune diseases, acute and chronic inflammatory conditions, allergic conditions, infection associated with inflammation, viral, transplantation tissue rejection,

220
239

5 atherosclerosis, restenosis, HIV infectivity, and granulomatous in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating or preventing such disorder or condition and a pharmaceutically acceptable carrier.

3. A pharmaceutical composition for treating or preventing a disorder or condition that can be treated or prevented by inhibiting MIP-1 α binding to the receptor CCR1 in a
10 mammal, comprising an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and a pharmaceutically acceptable carrier.

4. A method for treating or preventing a disorder or condition selected from autoimmune diseases, acute and chronic inflammatory conditions, allergic conditions,
15 infection associated with inflammation, viral, transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity, and granulomatous in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder or condition.

20 5. A method for treating or preventing a disorder or condition that can be treated or prevented by antagonizing the CCR1 receptor in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, that is effective in treating or preventing such disorder or condition.

25 6. A pharmaceutical composition for treating or preventing a disorder or condition selected from autoimmune diseases, acute and chronic inflammatory conditions, allergic conditions, infection associated with inflammation, viral, transplantation tissue rejection, atherosclerosis, restenosis, HIV infectivity, and granulomatous in a mammal, comprising a CCR1 receptor antagonizing effective amount of a compound according to claim 1, or a
30 pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition for treating or preventing a disorder or condition that can be treated or prevented by antagonizing the CCR1 receptor in a mammal, comprising a CCR1. receptor antagonizing effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

2020

Bogotá, D.C., Julio 11 de 2006

Abogado

ALVARO CORREA ORDÓÑEZ

ASUNTO	Radicación No.	01 007 880
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	8003
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

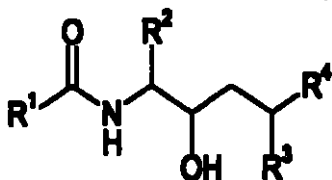
1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 105 - 166 y el capítulo reivindicatorio de los folios 168 - 180 de la solicitud.

2. Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 - 32 se refieren a compuestos derivados de ácido hexanóico de fórmula (I):



y sus sales farmacéuticamente aceptables.

Las reivindicaciones 33 - 34, 37 - 38 se refieren a composiciones farmacéuticas que contienen compuestos de la reivindicación 1.

Las reivindicaciones 35 - 36 se refieren a un método de tratamiento que consiste en administrar un compuesto.

El problema planteado en esta solicitud es la necesidad de compuestos inhibidores potentes y selectivos de la unión de MIP-1alfa a sus receptores CCR1 encontrados en células inflamatorias e inmunomoduladoras (preferiblemente leucocitos y linfocitos) para tratamiento de enfermedades inmunológicas.

Para resolver este problema técnico la solicitud en estudio proporciona derivados de ácido hexanóico.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/47 // 31/50; C 07 D 403/12.

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 60 180 159 de Febrero 4 de 2000, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Excepciones a la Patentabilidad

El artículo 20 de la Decisión 486 establece: *"No serán patentables: d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

Las reivindicaciones 35 – 36 se refieren a un método de tratamiento que consiste en administrar un compuesto.

Se observa que el método de tratamiento de las reivindicaciones 35 – 36 que comprende administrar un compuesto, no es patentable de acuerdo con la norma citada, que especifica que *los métodos terapéuticos para el tratamiento humano o animal* no son patentables.

En conclusión, el método de tratamiento de las reivindicaciones 35 – 36, que comprende administrar un compuesto, no es patentable de acuerdo con el Art 20, literal d), de la decisión 486.

Con respecto a los Art. 28 y 30 de la D 486

El artículo 28 de la Decisión 486 establece: *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información:*

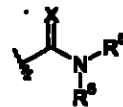
- a) el sector tecnológico al que se refiere o al cual se aplica la invención;*
- b) la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología;*
- c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior;*
- d) una reseña sobre los dibujos, cuando los hubiera;*
- e) una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes; y,*
- f) una indicación de la manera en que la invención satisface la condición de ser susceptible de aplicación industrial, si ello no fuese evidente de la descripción o de la naturaleza de la invención.*

El artículo 30 de la Decisión 486 establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.*

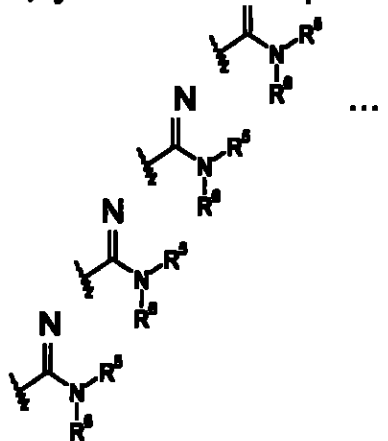
Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a

otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple".

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.



Pero en cuanto a la reivindicación 1 se observa que define R4 como en donde "X" es NR7; y R7 es R4. Así que la estructura final quedaría de la



siguiente manera: y sería un polímero infinito. De modo que el objeto de esta reivindicación no está bien definido y no es claro. Debe hacerse claridad al respecto.

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es Febrero 4 de 2000, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	WO 98 38167	Heteroaryl-Hexanoic Acid Amide Derivatives, Their Preparation And Their Use As Selective Inhibitors Of Mip-1-Alpha Binding To Its CCR1 Receptor	Sept 3, 1998
D2	WO 99 40081	Novel Dihydroxyhexanoic Acid Derivatives	Ago 12, 1999

5. Evaluación de los requisitos de Patentabilidad

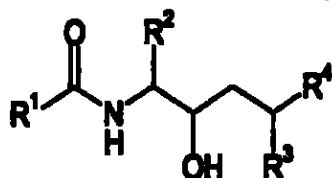
El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica*.

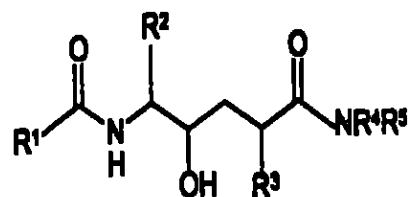
Las reivindicaciones 1 – 32 se refieren a compuestos derivados de ácido hexanóico de fórmula (I):



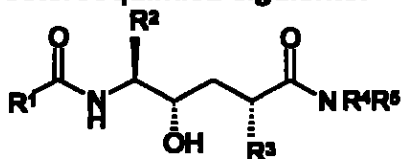
y sus sales farmacéuticamente aceptables.

Las reivindicaciones 33 – 34, 37 - 38 se refieren a composiciones farmacéuticas que contienen compuestos de la reivindicación 1.

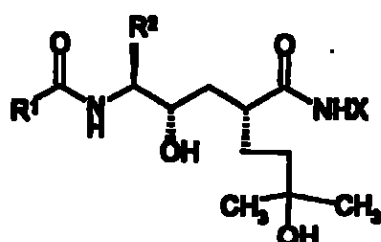
D1 enseña (ver folios 209 - 217) derivados de amida del ácido heteroaril hexanóico de fórmula:



y en la página 93 enseña (ver folio 216) los compuestos que tienen la estereoquímica siguiente:



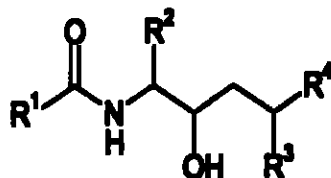
D2 enseña (ver folios 218 - 239) derivados del ácido dihidroxil hexanóico de fórmula:



Se observa:

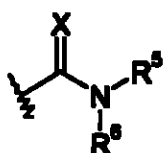
(a) debido a que:

- ♦ el elemento característico de los compuestos reivindicados, es decir la



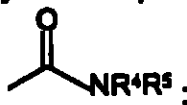
estructura: , del ácido hexanóico, ya era conocido en las anterioridades D1 y D2;

- ♦ los compuestos de esta solicitud tienen el grupo R4 que puede tener la

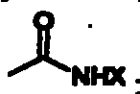


estructura: en la cual $X = S$ ó NR_7 ;

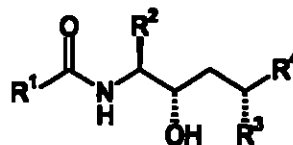
- ♦ y los compuestos de D1 tenían en esta misma posición el sustituyente



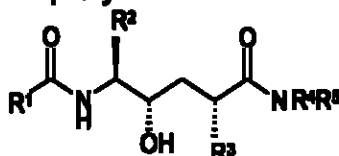
- ♦ de manera que lo nuevo en los compuestos reivindicados es que en lugar del átomo de oxígeno ($=O$) de las anterioridades, tienen un átomo de azufre ($=S$);
- ♦ y los compuestos de D2 tenían en esta misma posición el sustituyente



- ♦ de manera que lo nuevo en los compuestos reivindicados, con respecto a D1, es que en lugar del átomo de oxígeno ($=O$) de la anterioridad, tienen un átomo de azufre ($=S$); y con respecto a D2, es que R_5 y R_6 tienen otros significados además de H.
- ♦ con referencia a la estereoquímica característica de los compuestos



reivindicados que se representa como: ; se observa que es obvia porque ya se encontraba en la página 93 de D1 mediante



la estructura: , de manera que una persona de habilidades ordinarias en la técnica adaptará esta estructura para lograr la que se representa ahora en esta solicitud

- ♦ para una persona conocedora de la materia era evidente el obtener compuestos similares, teniendo en cuenta los conocidos.
- (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a los compuestos ni a las composiciones, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia
- (c) el problema planteado en esta solicitud que era la necesidad de compuestos inhibidores potentes y selectivos de la unión de MIP-1 alfa a sus receptores CCR1 encontrados en células inflamatorias e inmunomoduladoras (preferiblemente leucocitos y linfocitos) para tratamiento de enfermedades inmunológicas se resuelve proporcionando derivados de ácido hexanóico, es decir de la misma manera como se resolvía en las anterioridades; las

245
226

reivindicaciones son obvias y evidentes para una persona versada en la materia.

(d) el resultado obtenido: es decir derivados de ácido hexanóico no es inesperado.

(e) no parece haberse superado un prejuicio técnico anterior, con los compuestos ni con las composiciones propuestas

Por todo lo anterior, se considera que los compuestos reivindicados no tienen nivel inventivo. Y las composiciones tampoco tienen nivel inventivo porque los compuestos que las caracteriza no lo tienen.

6. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 98 38167	1 - 32, 33 - 34, 37 - 38	Nivel inventivo
D2	WO 98 40061	1 - 32, 33 - 34, 37 - 38	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
27 JUL 2006

CONCEPTO TÉCNICO No. 1102	EXAMINADOR TÉCNICO Código 202007
------------------------------	-------------------------------------

229

SUPERINTENDENCIA DE INDUSTRIA Y C MERO

RADICACIÓN: 1-7880

EDICTO No. 19149

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia proirió Resolución No. 30945 de 21-NOV-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

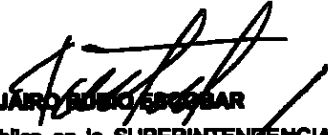
RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "NUEVOS DERIVADOS DE AMIDAS HETEROCICLICAS".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Álvaro Correa Ordoñez, o a quien haga sus veces, en su calidad de apoderado de Pfizer Products Inc., entregándole copia de la misma, advirtiéndole que contra ella proceda el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 21 NOV. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO BUSTOS ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaría General Ad-Hoc 06-DIC-2006
Secretaría General Ad-Hoc
EDICTO No. 19149

Este edicto se desfija hoy 20-DIC-2006 a las 4:30 p.m.