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Señores
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re.: Código 02-01-538
Expediente No. 01023846
Solicitud de Patente
SMITHKLINE BEECHAM
CORPORATION

En relación con el Expediente de la referencia por medio del presente escrito muy respetuosamente me permito solicitarles se sirvan proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Para tal efecto acompaño el comprobante de pago por concepto de \$ 335.000.00, recibo No. 03 - 69794

De Ustedes Atentamente,

GERMAN CASTILLO GRAU
T.P. # 2978 del C.S.J.

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Radicalcion : 01023846 00000003 Folios: 2
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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 69,794
FECHA : SEPTIEMBRE 24 DE 2003

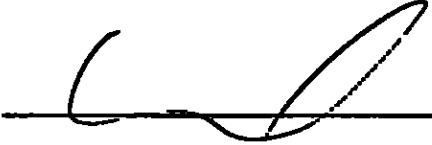
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	17000750	24/09/2003	1,418,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	85 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. 01-23846

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 caiga 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** ☒ _____

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

D₁

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/17		A1	(11) International Publication Number: WO 97/29743
			(43) International Publication Date: 21 August 1997 (21.08.97)
(21) International Application Number: PCT/US96/13632		ford, PA 19468 (US). RUTLEDGE, Melvin, Clarence, Jr. [US/US]; 2148 Schmitz Road, Lansdale, PA 19446 (US). HERTZBERG, Robert, Philip [US/US]; 121 Longfields Way, Downingtown, PA 19335 (US).	
(22) International Filing Date: 21 August 1996 (21.08.96)			
(30) Priority Data: PCT/US96/02260 16 February 1996 (16.02.96) WO (34) Countries for which the regional or international application was filed: US et al.		(74) Agents: DINNER, Dora, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).	
(60) Parent Application or Grant (63) Related by Continuation US Filed on PCT/US96/02260 (CIP) 16 February 1996 (16.02.96)		(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), 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).	
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(54) Title: IL-8 RECEPTOR ANTAGONISTS			
(57) Abstract This invention relates to novel compounds and a novel use of phenyl ureas in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8).			

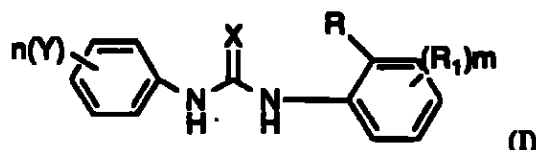
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D₁ de requerimiento No. 1738.

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1. A method of treating a chemokine mediated disease state, wherein the chemokine binds to an IL-8 a or b receptor in a mammal, which comprises administering to said mammal an effective amount of a compound of the formula:

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wherein

X is oxygen or sulfur;

R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

- 10 R₁ is independently selected from hydrogen; halogen; nitro; cyano; C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; S(O)_tR₄; (CR_gR_g)_q S(O)_tR₄; hydroxy; hydroxy substituted C₁₋₄ alkyl; aryl; aryl C₁₋₄ alkyl; aryl C₂₋₁₀ alkenyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₂₋₁₀ alkenyl; heteroaryl C₁₋₄ alkyloxy;
- 15 heterocyclic, heterocyclic C₁₋₄ alkyl; heterocyclic C₁₋₄ alkyloxy; heterocyclic C₂₋₁₀ alkenyl; (CR_gR_g)_q NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R_g; (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; (CR_gR_g)_q C(O)OR₁₁; (CR_gR_g)_q OC(O)R₁₁; (CR_gR_g)_q NR₄C(O)R₁₁; (CR_gR_g)_q C(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁;
- 20 (CR_gR_g)_q NHS(O)₂R₁₃; (CR_gR_g)_q S(O)₂NR₄R₅, or two R₁ moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heterocyclic moieties may be optionally substituted;

t is 0, or an integer having a value of 1 or 2;

s is an integer having a value of 1 to 3;

- 25 R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄ alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom
- 30 selected from O/N/S;

Y is hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR_gR_g)_q S(O)_tR₄; (CR_gR_g)_q OR₄; hydroxy; hydroxy substituted C₁₋₄ alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; aryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl; heteroarylalkyl;

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- heteroaryl C₁₋₄ alkyloxy; heteroaryl C₂₋₁₀ alkenyl; heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclicC₂₋₁₀ alkenyl; (CR_gR_g)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_qC(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_qC(O)R₁₁; C₂₋₁₀ alkenylC(O)R₁₁; (CR_gR_g)_qC(O)OR₁₁; C₂₋₁₀alkenylC(O)OR₁₁; (CR_gR_g)_qOC(O)R₁₁; (CR_gR_g)_qNR₄C(O)R₁₁; (CR_gR_g)_qNHS(O)₂R_b; (CR_gR_g)_qS(O)₂NR₄R₅; (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; or two Y moieties together may form O-(CH₂)₅O- or a 5 to 6 membered unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;
- q is 0 or an integer having a value of 1 to 10;
m is an integer having a value of 1 to 3;
R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;
R_g is hydrogen or C₁₋₄ alkyl;
R₁₀ is C₁₋₁₀ alkyl C(O)₂R_g;
R₁₁ is hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
R₁₃ is suitably C₁₋₄ alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl;
R_b is NR₆R₇, alkyl, aryl, aryl C₁₋₄ alkyl, aryl C₂₋₄ alkenyl, heteroaryl, heteroaryl C₁₋₄ alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, heterocyclic C₁₋₄ alkyl, heterocyclic C₂₋₄ alkenyl, or camphor, all of which groups may be optionally substituted;
- or a pharmaceutically acceptably salt thereof.

2. The method according to Claim 1 wherein the ionizable hydrogen has a pK_a of 3 to 10.

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3. The method according to Claim 2 wherein R is hydroxy, carboxylic acid, thiol, -SR₂ -OR₂, -NH-C(O)R_a, -C(O)NR₆R₇, -NHS(O)₂R_b, -S(O)₂NHR_c, NHC(X)NHR_b, or tetrazolyl;

wherein R₂ is a substituted aryl, heteroaryl, or heterocyclic moiety which ring
5 has the functional moiety providing the ionizable hydrogen having a pK_a of 10 or less;
R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

10 R_a is an alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroaryl C₁₋₄alkyl, heterocyclic, or a heterocyclic C₁₋₄alkyl moiety, all of which may be optionally substituted;

R_b is a NR₆R₇, alkyl, aryl, arylC₁₋₄alkyl, arylC₂₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₂₋₄alkenyl, heterocyclic, heterocyclic C₁₋₄alkyl,
15 heterocyclic C₂₋₄alkenyl moiety, camphor, all of which may be optionally substituted one to three times independently by halogen; nitro; cyano, halosubstituted C₁₋₄ alkyl; C₁₋₄ alkyl; C₁₋₄ alkoxy; C₁₋₄ amino, NR₉C(O)R_a; C(O)NR₆R₇, S(O)₃H, or S(O)_mR_a (wherein m' is 0, 1, or 2) or C(O)OC₁₋₄ alkyl;

R₉ is hydrogen or a C₁₋₄ alkyl;

20 R_c is alkyl, aryl, arylC₁₋₄alkyl, arylC₂₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₂₋₄alkenyl, heterocyclic, heterocyclic C₁₋₄alkyl, or a heterocyclic C₂₋₄alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro, cyano, halosubstituted C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ amino, NR₉C(O)R_a, C(O)NR₆R₇, S(O)₃H, or C(O)OC₁₋₄ alkyl.

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4. The method according to Claim 3 wherein the R₂ is optionally substituted one to three times by halogen, nitro, halosubstituted C₁₋₁₀ alkyl, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, SH, -C(O)NR₆R₇, -NH-C(O)R_a, -NHS(O)R_b, S(O)NR₆R₇, C(O)OR₈, or a tetrazolyl ring.

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5. The method according to Claim 3 wherein R is OH, -NHS(O)₂R_b or C(O)OH.

6. The method according to Claim 1 wherein R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O)R₄R₁₀, alkenyl C(O)OR₁₂, heteroaryl,
35 heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅.

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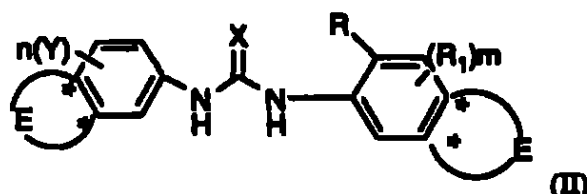
7. The method according to Claim 1 wherein Y is halogen, C₁₋₄ alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, methylene dioxy, NR₄R₅, thioC₁₋₄alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C₁₋₄alkyl, hydroxy alkyl.
- 5 8. The method according to Claim 1 wherein R is OH, SH, or NHS(O)_nR₁ and R₁ is substituted in the 3-position, the 4- position or di substituted in the 3,4- position by an electron withdrawing moiety.
- 10 9. The compound according to Claims 1 or 8 wherein Y is mono-substituted in the 2'-position or 3'- position, or is disubstituted in the 2'- or 3'- position of a monocyclic ring.
- 15 10. The compound according to Claims 1, 8 or 9 wherein n and m are each equal to 1 or more.
11. The method according to Claim 1 wherein R is a carboxylic acid, and R₁ is hydrogen, or R₁ is substituted in the 4-position.
- 20 12. The method according to Claim 1 wherein the mammal is afflicted with a chemokine mediated disease selected from psoriasis, or atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal
- 25 reperfusion injury, glomerulo-nephritis, or thrombosis, alzheimers disease, graft vs. host reaction, or allograft rejections.
13. The method according to Claim 1 wherein the compound, or a pharmaceutically acceptable salt is:
- 30 N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyphenyl)urea
N-(2-Hydroxy-4-nitrophenyl)-N'-(2-bromophenyl)urea
N-(2-Hydroxy-4-nitrophenyl)-N'-(2-phenylphenyl)urea
N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methylthiophenyl)urea
N-(2-Hydroxy-4-nitrophenyl)-N'-(2,3-dichlorophenyl)urea
- 35 N-(2-Hydroxy 4-nitro phenyl) N'-(2-chloro phenyl) urea
N-(2-Hydroxy-4-nitrophenyl)-N'-(2,3-methylenedioxyphenyl)urea
N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxy-3-chlorophenyl)urea

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- N-(2-hydroxy 4-nitro phenyl) N'-(2-phenyloxy phenyl) urea
 N-(3-Chloro-2-hydroxyphenyl)-N'-(bromophenyl)urea
 N-(2-Hydroxy-3-glycinemethylestercarbonylphenyl)-N'-(2-bromophenyl)urea
 N-(3-Nitro-2-hydroxyphenyl)-N'-(2-bromophenyl)urea
 5 N-(2-Hydroxy-4-cyanophenyl)-N'-(2-bromophenyl)urea
 N-(2-Hydroxy-3,4-dichlorophenyl)-N'-(2-bromophenyl)urea
 N-(3-Cyano-2-hydroxyphenyl)-N'-(2-bromophenyl)urea
 N-(2-Hydroxy-4-cyanophenyl)-N'-(2-methoxyphenyl)urea
 N-(2-Hydroxy-4-cyanophenyl)-N'-(2-phenylphenyl)urea
 10 N-(2-Hydroxy-4-cyanophenyl)-N'-(2,3-dichlorophenyl)urea
 N-(2-Hydroxy-4-cyanophenyl)-N'-(2-methylphenyl)urea
 N-(2-Hydroxy-3-cyano-4-methylphenyl)-N'-(2-bromophenyl)urea
 N-(4-Cyano-2-hydroxyphenyl)-N'-(2-trifluoromethylphenyl)urea
 N-(3-Trifluoromethyl-2-hydroxyphenyl)-N'-(2-bromophenyl)urea
 15 N-(3-Phenylaminocarbonyl-2-hydroxyphenyl)-N'-(2-bromophenyl)urea
 N-(2-hydroxy 4-nitro phenyl) N'-(2-iodo phenyl) urea
 N-(2-hydroxy 4-nitro phenyl) N'-(2-bromo phenyl) thiourea
 N-(2-phenylsulfonamido)-4-cyanophenyl-N'-(2-bromo phenyl)urea
 (E)-N-[3-[(2-Aminocarbonyl)ethenyl]-2-hydroxyphenyl]-N'-(2-bromophenyl)urea
 20 N-(2-Hydroxy-3,4-dichlorophenyl)-N'-(2-methoxyphenyl)urea
 N-(2-Hydroxy-3,4-dichlorophenyl)-N'-(2-phenylphenyl)urea
 N-(2-Hydroxy-3,4-dichlorophenyl)-N'-(2,3-dichlorophenyl)urea
 N-(2-Hydroxy-5-nitrophenyl)-N'-(2,3-dichlorophenyl)urea; or
 N-(2-Hydroxy-3-cyanophenyl)-N'-(2,3 dichlorophenyl)urea.

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14. A compound of the formula::



X is oxygen or sulfur;

R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

- 30 R₁ is independently selected from hydrogen; halogen; nitro; cyano; C₁-10 alkyl;
 halosubstituted C₁-10 alkyl; C₂-10 alkenyl; C₁-10 alkoxy; halosubstituted
 C₁-10 alkoxy; azide; S(O)_tR₄; (CR₈R₉)_q S(O)_tR₄; hydroxy; hydroxy substituted
 C₁-4 alkyl; aryl; aryl C₁-4 alkyl; aryl C₂-10 alkenyl; aryloxy; aryl C₁-4 alkyloxy;

- heteroaryl; heteroarylalkyl; heteroaryl C₂₋₁₀ alkenyl; heteroaryl C₁₋₄ alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclicC₁₋₄alkyloxy; heterocyclicC₂₋₁₀ alkenyl; (CR_gR_g)_q NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; (CR_gR_g)_q C(O)OR₁₁; (CR_gR_g)_q OC(O)R₁₁; (CR_gR_g)_qNR₄C(O)R₁₁; (CR_gR_g)_q C(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q NHS(O)₂R₁₃; (CR_gR_g)_q S(O)₂NR₄R₅, or two R₁ moieties together may form O-(CH₂)₃O- or a 5 to 6 membered unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heterocyclic moities may be optionally substituted;
- t is 0, or an integer having a value of 1 or 2;
- s is an integer having a value of 1 to 3;
- R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclicC₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;
- Y is hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR_gR_g)_qS(O)₁R₄; (CR_gR_g)_qOR₄; hydroxy; hydroxy substituted C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heteroaryl C₂₋₁₀ alkenyl; heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclicC₂₋₁₀ alkenyl; (CR_gR_g)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_qC(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_qC(O)R₁₁; C₂₋₁₀ alkenylC(O)R₁₁; (CR_gR_g)_qC(O)OR₁₁; C₂₋₁₀alkenylC(O)OR₁₁; (CR_gR_g)_qOC(O) R₁₁; (CR_gR_g)_qNR₄C(O)R₁₁; (CR_gR_g)_q NHS(O)₂R₅; (CR_gR_g)_q S(O)₂NR₄R₅; (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; or two Y moieties together may form O-(CH₂)₃O- or a 5 to 6 membered unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;
- q is 0 or an integer having a value of 1 to 10;
- n is an integer having a value of 1 to 3;
- m is an integer having a value of 1 to 3;
- R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring

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may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

R₈ is hydrogen or C₁₋₄ alkyl;

R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;

- 5 R₁₁ is hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;

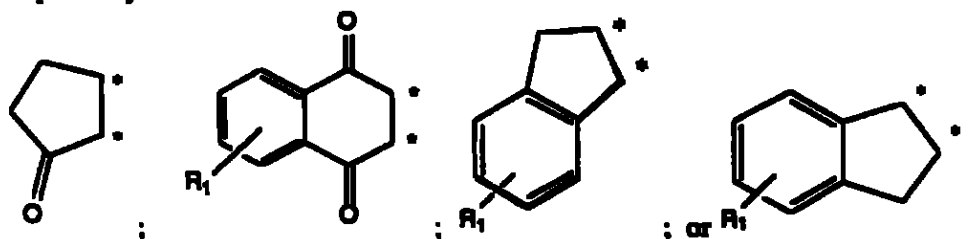
R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;

- 10 R₁₃ is suitably C₁₋₄ alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl;

R_b is NR₆R₇, alkyl, aryl, aryl C₁₋₄ alkyl, aryl C₂₋₄ alkenyl, heteroaryl, heteroaryl C₁₋₄ alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, heterocyclic C₁₋₄ alkyl,

- 15 heterocyclic C₂₋₄ alkenyl, or camphor, all of which groups may be optionally substituted;

E is optionally selected from



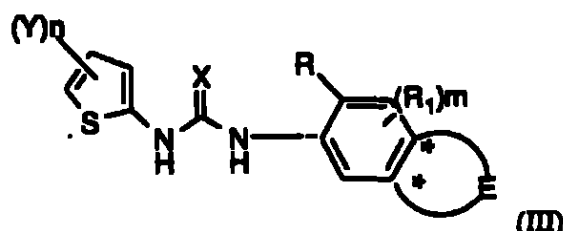
the asterisk * denoting point of attachment of the ring, with at least one E being present;

- 20 or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition comprising a compound according to Claim 14 and a pharmaceutically acceptable carrier or diluent.

- 25 16. A method of treating a chemokine mediated disease state, wherein the chemokine binds to an IL-8 a or b receptor in a mammal, which comprises administering to said mammal an effective amount of a compound of the formula according to Claim 14.

- 30 17. A compound of the formula:



wherein

X is oxygen or sulfur;

R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;

- 5 R₁ is independently selected from hydrogen; halogen; nitro; cyano; C₁₋₁₀ alkyl; halosubstituted C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; S(O)_tR₄; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy substituted C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryl C₂₋₁₀ alkenyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₂₋₁₀ alkenyl; heteroaryl C₁₋₄ alkyloxy;
- 10 heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclic C₁₋₄alkyloxy; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_q NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; (CR₈R₈)_q C(O)OR₁₁; (CR₈R₈)_q OC(O)R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁; (CR₈R₈)_q C(NR₄)NR₄R₅; (CR₈R₈)_q NR₄C(NR₅)R₁₁;
- 15 (CR₈R₈)_q NHS(O)₂R₁₃; (CR₈R₈)_q S(O)₂NR₄R₅, or two R₁ moieties together may form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heterocyclic moieties may be optionally substituted;

q is 0 or an integer having a value of 1 to 10;

t is 0, or an integer having a value of 1 or 2;

- 20 s is an integer having a value of 1 to 3;

R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are

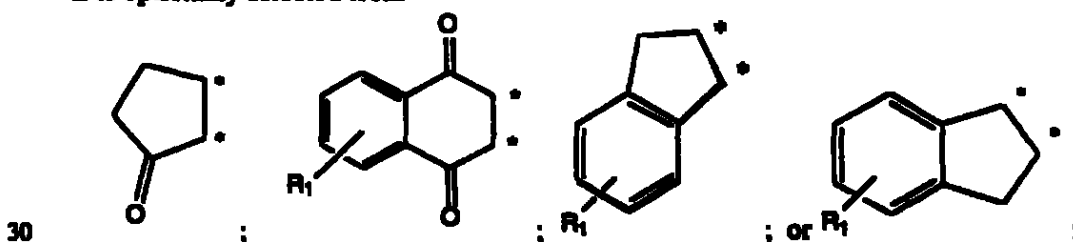
25 attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;

Y is hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_qS(O)_tR₄, (CR₈R₈)_qOR₄; hydroxy; hydroxy substituted C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl;

30 aryloxy; aryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heteroaryl C₂₋₁₀ alkenyl; heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl

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- $C(O)NR_4R_5$; $(CR_6R_7)qC(O)NR_4R_5$; $(CR_6R_7)qC(O)NR_4R_{10}$; $S(O)_3R_8$;
 $(CR_6R_7)qC(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; $(CR_6R_7)qC(O)OR_{11}$;
 C_{2-10} alkenyl $C(O)OR_{11}$; $(CR_6R_7)qOC(O)R_{11}$; $(CR_6R_7)qNR_4C(O)R_{11}$;
 $(CR_6R_7)qNHS(O)_2R_b$; $(CR_6R_7)qS(O)_2NR_4R_5$; $(CR_6R_7)qC(NR_4)NR_4R_5$;
 $(CR_6R_7)qNR_4C(NR_5)R_{11}$; or two Y moieties together may form $O-(CH_2)_5O-$ or a
 5 to 6 membered unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl,
 heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally
 substituted;
 n is an integer having a value of 1 to 3;
 m is an integer having a value of 1 to 3;
 R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together
 with the nitrogen to which they are attached form a 5 to 7 member ring which ring
 may optionally contain an additional heteroatom which heteroatom is selected from
 oxygen, nitrogen or sulfur;
 R₈ is hydrogen or C₁₋₄ alkyl;
 R₁₀ is C₁₋₁₀ alkyl $C(O)_2R_8$;
 R₁₁ is hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl,
 optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally
 substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally
 substituted heterocyclicC₁₋₄alkyl;
 R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted
 arylalkyl;
 R₁₃ is suitably C₁₋₄ alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroarylC₁₋₄alkyl,
 heterocyclic, or heterocyclicC₁₋₄alkyl;
 R_b is NR₆R₇, alkyl, aryl, aryl C₁₋₄ alkyl, aryl C₂₋₄ alkenyl, heteroaryl, heteroaryl
 C₁₋₄ alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, heterocyclic C₁₋₄ alkyl,
 heterocyclic C₂₋₄ alkenyl, or camphor, all of which groups may be optionally
 substituted;
 E is optionally selected from



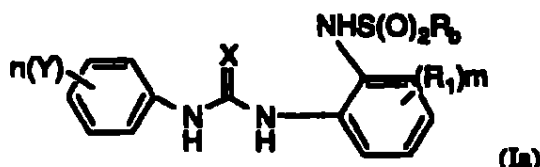
the asterix * denoting point of attachment of the ring;
 or a pharmaceutically acceptably salt thereof.

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18. A pharmaceutical composition comprising a compound according to Claim 17 and a pharmaceutically acceptable carrier or diluent.

5 19. A method of treating a chemokine mediated disease state, wherein the chemokine binds to an IL-8 a or b receptor in a mammal, which comprises administering to said mammal an effective amount of a compound of the formula according to Claim 17.

10 20. A compound of the formula:



wherein

X is oxygen or sulfur;

15 R_a is an alkyl, aryl, arylC₁₋₄alkyl, heteroaryl, heteroaryl C₁₋₄alkyl, heterocyclic, or a heterocyclic C₁₋₄alkyl moiety, all of which may be optionally substituted;

R_b is a NR₆R₇, alkyl, aryl, arylC₁₋₄alkyl, aryl C₂₋₄alkenyl, heteroaryl, heteroarylC₁₋₄alkyl, heteroarylC₂₋₄alkenyl, heterocyclic, or heterocyclic C₁₋₄alkyl, or a heterocyclic C₂₋₄alkenyl moiety, camphor, all of which may be
20 optionally substituted one to three times independently by halogen; nitro; halosubstituted C₁₋₄alkyl; C₁₋₄alkyl; C₁₋₄alkoxy; NR₉C(O) R_a ; S(O)_m R_a ; C(O)NR₆R₇; S(O)₃H, or C(O)OC₁₋₄alkyl;

R_6 and R_7 are independently hydrogen, or a C₁₋₄alkyl group, or R_6 and R_7 together with the nitrogen to which they are attached form a 5 to 7 member ring which ring
25 may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur, which ring may be optionally substituted;

R_9 is hydrogen or a C₁₋₄alkyl, preferably hydrogen;

R_1 is independently selected from hydrogen; halogen; nitro; cyano; C₁₋₁₀alkyl; halosubstituted C₁₋₁₀alkyl; C₂₋₁₀alkenyl; C₁₋₁₀alkoxy; halosubstituted
30 C₁₋₁₀alkoxy; azide; S(O)_t R_4 ; (CR₈R₈)_q S(O)_t R_4 ; hydroxy; hydroxy substituted C₁₋₄alkyl; aryl; aryl C₁₋₄alkyl; aryl C₂₋₁₀alkenyl; aryloxy; aryl C₁₋₄alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₂₋₁₀alkenyl; heteroaryl C₁₋₄alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclicC₁₋₄alkyloxy; heterocyclicC₂₋₁₀alkenyl; (CR₈R₈)_q NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; C₂₋₁₀alkenyl C(O)NR₄R₅;

- (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; (CR_gR_g)_q C(O)OR₁₁; (CR_gR_g)_q OC(O)R₁₁; (CR_gR_g)_q NR₄C(O)R₁₁; (CR_gR_g)_q C(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q NHS(O)₂R₁₃; (CR_gR_g)_q S(O)₂NR₄R₅, or two R₁ moieties together may form O-(CH₂)₅O- or a 5 to 6 membered unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heterocyclic moities may be optionally substituted;
- t is 0, or an integer having a value of 1 or 2;
- s is an integer having a value of 1 to 3;
- R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclicC₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;
- Y is hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR_gR_g)_qS(O)₂R₄; (CR_gR_g)_qOR₄; hydroxy; hydroxy substituted C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclicC₂₋₁₀ alkenyl; (CR_gR_g)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_qC(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_qC(O)R₁₁; C₂₋₁₀ alkenylC(O)R₁₁; (CR_gR_g)_qC(O)OR₁₁; C₂₋₁₀alkenylC(O)OR₁₁; (CR_gR_g)_qOC(O) R₁₁; (CR_gR_g)_qNR₄C(O)R₁₁; (CR_gR_g)_q NHS(O)₂R₆; (CR_gR_g)_q S(O)₂NR₄R₅; (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; or two Y moieties together may form O-(CH₂)₅O- or a 5 to 6 membered unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;
- q is 0 or an integer having a value of 1 to 10;
- n is an integer having a value of 1 to 3;
- m is an integer having a value of 1 to 3;
- R_g is hydrogen or C₁₋₄ alkyl;
- R₁₀ is C₁₋₁₀ alkyl C(O)₂R_g;
- R₁₁ is hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;

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R₁₂ is hydrogen, C₁-10 alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R₁₃ is suitably C₁-4 alkyl, aryl, aryl C₁-4alkyl, heteroaryl, heteroarylC₁-4alkyl, heterocyclic, or heterocyclicC₁-4alkyl;

5 or a pharmaceutically acceptably salt thereof.

21. The compound according to Claim 20 wherein R₁ is substituted in the 3-position, the 4- position or di substituted in the 3,4- position by an electron withdrawing moiety.

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22. The compound according to Claim 20 or 21 wherein Y is mono-substituted in the 2'-position or 3'- position, or is disubstituted in the 2'- or 3'- position of a monocyclic ring.

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23. The compound according to Claim 20 or 21 wherein n and m are each equal to 1 or more.

24. The compound according to Claim 20 which is

N-(4-Nitro 2-(phenylsulfonylamino)phenyl)-N'-phenyl urea

20 N-[(2-Phenylsulfamido) 4-cyanophenyl]- N'-(2-bromo phenyl) urea

N-(2-(Amino sulfonamido phenyl) phenyl) N'-(2-bromo phenyl) urea N-(2-(Amino sulfonyl styryl) phenyl) N'-(2-bromo phenyl) urea 2-[(3,4 Di-

methoxyphenylsulfonyl)amino] phenyl) N'-(2-bromo phenyl) urea N-(2-[(4-

Acetamidophenylsulfonyl)amino] phenyl) N'-(2-bromo phenyl) urea N-(2-(Amino

25 sulfonyl (2-thiophene) phenyl) N'-(2-bromo phenyl) urea N-(2-(Amino sulfonyl (3-

tolyl) phenyl) N'-(2-bromo phenyl) urea N-(2-(Amino sulfonyl (8-quinoliny)) phenyl)

N'-(2-bromo phenyl) urea N-(2-(Amino sulfonyl benzyl) phenyl) N'-(2-bromo phenyl) urea

N-[2-[[[2-(Trifluoromethyl)phenyl]sulfonyl]amino]phenyl]-N'-(2-bromophenyl)urea

30 N-(2-Bromophenyl)-N'-[2-dimethylaminosulfonylamino]phenyl]urea N-[2-

(Phenethylsulfonylamino)phenyl]-N'-(2-bromophenyl)urea N-[2-[(2-Acetamido-4-methylthiazol-5-yl)sulfonylamino]phenyl]-N'-(2-bromophenyl)urea N-[2-[(2,3-

Dichlorothien-5-yl)]sulfonylamino]phenyl]-N'-(2-bromophenyl)urea

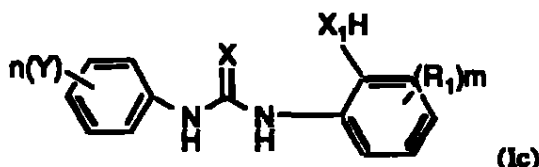
N-[2-[(3,5-Bis(trifluoromethyl)phenyl)sulfonylamino]phenyl]-N'-(2-bromophenyl)urea

35 N-[2-[(2-Benzyl)sulfonylamino]-(5-trifluoromethyl)phenyl]-N'-(2-bromophenyl)urea

N-[2-[2-(3-Nitrophenyl)sulfonylamino]phenyl]-N'-(2-bromophenyl)urea

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- N-[2-[2-(4-Phenoxyphenyl)sulfonylamino]phenyl]-N'-(2-bromophenyl)urea
 N-[[2-(1S)-10-Camphorsulfonylamino]phenyl]-N'-(2-bromophenyl)urea
 N-[[2-(1R)-10-Camphorsulfonylamino]phenyl]-N'-(2-bromophenyl)urea
 N-[2-[2-(2-Nitro-(4-trifluoromethyl)phenyl)sulfonylamino]phenyl]-N'-(2-bromophenyl)urea
 5 N-[2-(2-Amino-(4-trifluoromethyl)phenyl)sulfonylamino]phenyl]-N'-(2-bromophenyl)urea ; or N-[2-(aminosulfonylphenyl)-3-amino-phenyl]-N'-(2-bromophenyl)urea.
- 10 25. A pharmaceutical composition comprising a compound according to any of Claims 20 to 24 and a pharmaceutically acceptable carrier or diluent.
26. A compound of the formula:



15

wherein

X is oxygen or sulfur;

X₁ is oxygen or sulfur;

R₁ is independently selected from hydrogen; halogen; nitro; cyano; C₁-10 alkyl;

- 20 halosubstituted C₁-10 alkyl; C₂-10 alkenyl; C₁-10 alkoxy; halosubstituted C₁-10 alkoxy; azide; S(O)_tR₄; (CR_gR_g)_q S(O)_tR₄; hydroxy; hydroxy substituted C₁-4 alkyl; aryl; aryl C₁-4 alkyl; aryl C₂-10 alkenyl; aryloxy; aryl C₁-4 alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₂-10 alkenyl; heteroaryl C₁-4 alkyloxy; heterocyclic, heterocyclic C₁-4 alkyl; heterocyclic C₁-4 alkyloxy; heterocyclic C₂-10
- 25 alkenyl; (CR_gR_g)_q NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; C₂-10 alkenyl C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_q C(O)R₁₁; C₂-10 alkenyl C(O)R₁₁; C₂-10 alkenyl C(O)OR₁₁; (CR_gR_g)_q C(O)OR₁₁; (CR_gR_g)_q OC(O)R₁₁; (CR_gR_g)_q NR₄C(O)R₁₁; (CR_gR_g)_q C(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q NHS(O)₂R₁₃; (CR_gR_g)_q S(O)₂NR₄R₅, or two R₁ moieties together may
- 30 form O-(CH₂)_sO- or a 5 to 6 membered unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heterocyclic moieties may be optionally substituted;
- t is 0, or an integer having a value of 1 or 2;
- s is an integer having a value of 1 to 3;

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- R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄ alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;
- Y is hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR_gR_g)_qS(O)_tR₄, (CR_gR_g)_qOR₄; hydroxy; hydroxy substituted C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heteroaryl C₂₋₁₀ alkenyl; heterocyclic, heterocyclic C₁₋₄alkyl; heterocyclicC₂₋₁₀ alkenyl; (CR_gR_g)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_qC(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_qC(O)R₁₁; C₂₋₁₀ alkenylC(O)R₁₁; (CR_gR_g)_qC(O)OR₁₁; C₂₋₁₀alkenylC(O)OR₁₁; (CR_gR_g)_qOC(O) R₁₁; (CR_gR_g)_qNR₄C(O)R₁₁; (CR_gR_g)_q NHS(O)₂R_b; (CR_gR_g)_q S(O)₂NR₄R₅, (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; or two Y moieties together may form O-(CH₂)_nO- or a 5 to 6 membered unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;
- q is 0 or an integer having a value of 1 to 10;
- n is an integer having a value of 1 to 3;
- m is an integer having a value of 1 to 3;
- R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;
- R₈ is hydrogen or C₁₋₄ alkyl;
- R₁₀ is C₁₋₁₀ alkyl C(O)₂R_g;
- R₁₁ is hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
- R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
- R₁₃ is suitably C₁₋₄ alkyl, aryl, aryl C₁₋₄alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl;

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R_b is NR_6R_7 , alkyl, aryl, aryl C_{1-4} alkyl, aryl C_{2-4} alkenyl, heteroaryl, heteroaryl C_{1-4} alkyl, heteroaryl C_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4} alkyl, heterocyclic C_{2-4} alkenyl, or camphor, all of which groups may be optionally substituted; provided that

- 5 when $n = 1$ than Y is substituted in the 2- or 3- position;
 when $n = 2$ than Y is di-substituted in the 2'- 3'- position, the 2'-5'- position, the 2'-6' position, the 3'-5' or the 3'-6' position;
 when $n = 3$ than Y is trisubstituted in the 2'-3'-5' or the 2'-3'-6'- positions;
 further provided that
 10 when X_1 is O, $m=2$, R_1 is 2-t-butyl, 4-methyl, and $n=3$ than Y is not 2'-OH, 3'-t-butyl, 5'-methyl;
 when X_1 is O, $m=1$, R_1 is 4-methyl, and $n=2$ than Y is not 2'-OH, 5'-methyl;
 when X_1 is O, $m=1$, R_1 is hydrogen, and $n=2$ than Y is not 2'-6'-diethyl;
 when X_1 is O, $m=1$, R_1 is 6-OH, and $n=2$ than Y is not 2'-5'-methyl;
 15 when X_1 is S, $m=1$, R_1 is 4-ethyl, and $n=1$ than Y is not 2-methoxy;
 or a pharmaceutically acceptable salt thereof.

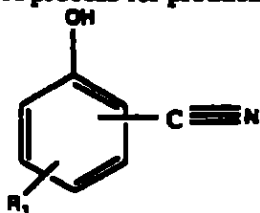
27. The compound according to Claim 26 wherein R_1 is substituted in the 3- position, the 4- position or di-substituted in the 3,4- position by an electron withdrawing moiety.
 20

28. The compound according to Claim 26 or 27 wherein Y is mono-substituted in the 2'-position or 3'- position, or is disubstituted in the 2' or 3' position of a monocyclic ring.
 25

29. The compound according to Claim 26 or 27 wherein n and m are each equal to 1 or more.

30. A pharmaceutical composition comprising a compound according to any of Claims 26 to 29 and a pharmaceutically acceptable carrier or diluent.
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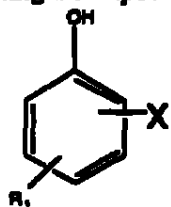
31. A process for producing a cyano phenol derivative of the formula:



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wherein R₁ is as defined for Formula (I) above, which method comprises

a) reacting a compound of the formula:



wherein X is halogen

with copper (I) cyanide, dimethylformamide, triethylamine and a catalytic amount of
5 dimethylamino pyridine.

32. The process according to Claim 31 wherein the temperature is about 60 to about
80° C, and X is bromine.

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

**Doctor
Germán Castillo Grau
Apoderado
SMITHKLINE BEECHAM CORPORATION**

Oficio N° 12921

REFERENCIA	Radicación	01 23846
	Trámite	002
	Evento	001
	Actuación	430
	Folios	007

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 01 23846, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

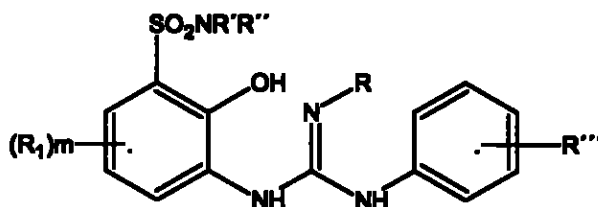
- El resumen y el capítulo descriptivo de la solicitud en los folios 109 y 4 a 22 respectivamente.
- Los ejemplos que ilustran la invención en los folios 23 a 102.
- Las cláusulas 1 a 14 relacionadas en el capítulo reivindicatorio de la solicitud que se encuentran en los folios 103 a 108.
- El primer examen de forma realizado a la solicitud de oficio No. 1349, que se encuentra en el folio 117.
- La respuesta al primer examen de forma, allegada mediante memorial de fecha 18/05/2001 que se encuentra en los folios 118 a 176 que contiene la copia de la solicitud mediante la cual se reivindica prioridad.
- La copia de la solicitud original mediante la cual se reivindica prioridad de Estados Unidos US60/192,132 de 24/03/2000 en los folios 123 a 176.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente, allegada mediante memorial de fecha 24/09/2003, que se encuentra en los folios 179 y 180.

2. OBJETO DE LA INVENCION:

La solicitud hace referencia a un **"Antagonistas de receptores de IL-8"**.

- **Reivindicaciones 1 a 11:**

Se reivindica un compuesto que responde a la fórmula (I):



En particular se reclama la siguiente serie de compuestos:

N-(2-bromofenil)-N'-[4-cloro-2-hidroxi-3-(N'',N''-dimetilamino-sulfonil)fenil]cianoguanidina

N-(2,3-diclorofenil)-N'-[4-cloro-2-hidroxi-3-[S-(+)-(2-metoxi-metil)pirrolidin-1-il]aminosulfonilfenil]cianoguanidina

N-(2-bromofenil)-N'-[4-cloro-2-hidroxi-3-[S-(+)-(2-carboxi)pirrolidin-1-il]aminosulfonilfenil]cianoguanidina

N-(2,3-diclorofenil)-N'-[4-cloro-2-hidroxi-3-[S-(+)-(2-carboxi)pirrolidin-1-il]aminosulfonilfenil]cianoguanidina

N-(2-benzoxifenil)-N'-[4-cloro-2-hidroxi-3-[S-(+)-(2-metoximetil)pirrolidin-1-il]sulfonilfenil]cianoguanidina

- **Reivindicación 12:**

Se reivindica una composición farmacéutica que comprende un compuesto según cualquiera de las reivindicaciones 1 a 11 y un excipiente o diluyente farmacéuticamente aceptable.

- **Reivindicaciones 13 y 14:**

Se reivindica un método de tratamiento de una enfermedad que cursa con mediación de una quimioquina, en el que la quimioquina se une a un receptor de IL-8 a o b en un mamífero, cuyo método comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la fórmula según una cualquiera de las reivindicaciones 1 a 11.

En particular se reivindica un método para tratar una enfermedad que se selecciona entre: psoriasis, dermatitis atópica, osteoartritis, artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, síndrome de insuficiencia respiratoria del adulto, enfermedad Intestinal Inflamatoria, enfermedad de Crohn, colitis ulcerosa, ataque fulminante, choque séptico, esclerosis múltiple, choque endotóxico, sepsis por gram-negativos, síndrome de choque tóxico, lesión por repercusión cardíaca y renal, glomerulonefritis, trombosis, reacción de injerto frente al huésped, enfermedad de Alzheimer, rechazos de aloinjertos, malaria,estenosis, anglogénesis, aterosclerosis, osteoporosis, gingivitis y liberación indeseada de células pluripotenciales hematopoyéticas y enfermedades causadas por virus respiratorios, herpes virus y virus de la hepatitis, meningitis, fibrosis quística, fatiga prematura, tos, prurito, disfunción multiorgánica, trauma, fatiga, torceduras, contusiones, artritis psoriásicas, herpes, encefalitis, vasculitis del SNC, lesión cerebral traumática, tumores del SNC, hemorragia subaracnoide, trauma posquirúrgico, neumonitis intersticial, hipersensibilidad, artritis inducida por cristales, pancreatitis aguda, enterocolitis necrosante, sinusitis crónica, uveítis, polimiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celíaca, esofagitis, glositis, obstrucción del flujo de aire, hipersensibilidad de las vías respiratorias, bronconeumonía obliterante, neumonía, bronquiectasia, bronconeumonía, bronconeumonía obliterante, bronquitis crónica, corazón pulmonar, disnea, enfisema, hipercapnia, hiperinflamación, hipoxemia, inflamaciones inducidas por hiperoxia, hipoxia, reducción quirúrgica del volumen pulmonar, hipertrofia ventricular derecha, sarcoidosis, enfermedades leves de las vías respiratorias, desequilibrio entre ventilación-perfusión, jadeo, catarrros y lupus.

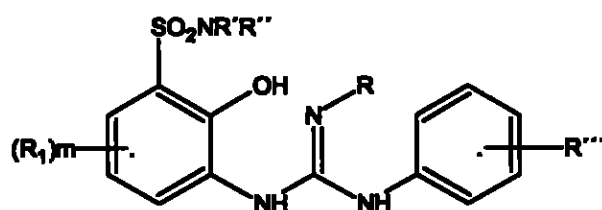
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Una vez catalogada la invención ésta se clasificó en la sección: A 61 K ³¹/17 de la Clasificación Internacional de Patentes.

3. CLARIDAD DE LA SOLICITUD:

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

- En atención al artículo 30 de la norma andina, esta Dependencia se permite señalar la falta de claridad que presenta el capítulo reivindicatorio, porque en atención a las diversas connotaciones que presentan los sustituyentes R', R'', R''', R₁, es posible obtener compuestos de mayor complejidad química y estructural que los definidos por la fórmula (I).



Si bien es cierto, todos los compuestos presentan la estructura central de la

guanidina , la complejidad de química de la estructura sustituida por fenol y fenilo no es la suficiente como para definir todos los compuestos que se obtienen una vez se efectúan las correspondientes sustituciones sobre los radicales R', R'', R''' y R₁.

Lo anterior se hace evidente cuando se evalúan las diferentes connotaciones químicas de los radicales citados y la diversidad química y estructural de los ejemplos que se presentan en la cláusula 11.

Por esta razón se remite al interesado a estudiar las connotaciones de los radicales primarios R', R'', R''' y R₁ en especial de aquellos que comprometen sustituciones heterocíclicas, teniendo en cuenta que los compuestos de carácter heterocíclico se clasifican en atención al número de átomos que componen los anillos y a los heteroátomos y al número y tipo de ellos que comprenden. Para ilustrar este hecho se dirige su atención a la bibliografía básica sobre compuestos heterocíclicos, en la que encontrará una de las clasificaciones empleadas para comprender la amplitud de dicha materia:

- 1) **Análogos heterocíclicos del ciclopropano:** azirinas, aziridina, oxirano, tiorano, diazireno y diazidirina, oxaziridina.
- 2) **Análogos heterocíclicos de ciclobutano:** azetidina, azetidinonas, oxeteno y oxetano, oxetanonas, tiete y tietano.
- 3) **Anillos heterocíclicos de cuatro miembros con dos heteroátomos:** dioxetano y ditetanos.

- 4) **Análogos heterocíclicos del ciclo pentadien con un heteroátomo:** pirrol, furano, tiofeno.
- 5) **Sistemas de anillos fusionados que incluyen a los anillos de pirrol, furano y tiofeno:** indol, isoindol, indolizina y ciclazina, benzofurano, dibenzofurano, isobenzofurano, benzo[b]tiofeno, benzo[c]tiofeno.
- 6) **Análogos heterocíclicos del benceno con un heteroátomo:** piridina, sales de pirilio, piranos, pironas.
- 7) **Análogos heterocíclicos del naftaleno con un heteroátomo:** quinolina, isoquinolina, quinolizina, acridina y fenantridina, sales de benzopirilio y benzopiranos.
- 8) **Compuestos con dos heteroátomos en un anillo de cinco miembros:** pirazol e imidazol, isoxazol y oxazol, isotiazol y tiazol, dioxol, dioxolano.
- 9) **Compuestos con dos heteroátomos en su anillo de seis miembros:** piridazina, pirimidina, pirazinas, oxazinas y tiazinas, dioxanos.
- 10) **Compuestos con más de dos heteroátomos:** purinas, pteridinas, triazinas, sidnonas, benzotriazoles.
- 11) **Compuestos heterocíclicos con anillos de siete o más miembros:** borepina, azepina, diazepina, oxepina, tiepina.
- 12) **Heterociclos con anillos mayores:** azocinas y azotinas.

En consecuencia, se recomienda al interesado manejar un lenguaje químico específico, de tal suerte que pueda determinarse el verdadero alcance de la invención reclamada porque tal como se presenta existe falta de claridad con respecto a la frontera que verdaderamente delimita si la invención es novedosa e inventiva frente a la materia comprendida en el estado de la técnica.

- Del estudio de los radicales primarios R' , R'' , R''' y R_1 , se encuentra que existe gran variedad de radicales secundarios que forman parte de las connotaciones señaladas para los sustituyentes en mención, sin embargo en ningún momento se definieron químicamente las connotaciones que toma cada uno de los radicales: R_{15} , R_{16} , R_{18} , R_{11} , R_{17} , R_8 , R_7 , R_a , R_9 , R_b , R_6 , R_4 , $R_{5,}$, es por ello que se insta al interesado para que determine con claridad el alcance real de su invención, teniendo en cuenta que el límite entre la materia novedosa e inventiva y aquella contemplada en el estado del arte lo determinan las cláusulas reivindicatorias.
- La cláusula 3 determina que el radical R_1 puede sustituirse en la posición 4 principalmente por un resto que retira electrones, expresión esta que no precisa un grupo en particular y que genera ambigüedad frente al alcance de la invención.
- Ahora bien, si se efectuaran las combinaciones de todas las posibles sustituciones contempladas a lo largo de las cláusulas 1 a 10 se obtendrían diversos compuestos que no encuentran representatividad única bajo el núcleo básico de la fórmula (I), dada la menor complejidad química que presenta la misma.

4. EXCEPCIONES A LA PATENTABILIDAD:

El artículo 20 en su literal (d) contempla: *"No serán patentables 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 cláusulas 13 y 14 que reclama un método para el tratamiento de enfermedades asociadas a la actividad de la quimioguina, en el que la quimioguina se une a un receptor de IL-8, tal es el caso de psoriasis, dermatitis atópica, osteoartritis, artritis reumatoide, asma, enfermedad pulmonar obstructiva crónica, síndrome de insuficiencia respiratoria del adulto, enfermedad intestinal inflamatoria, enfermedad de Crohn, colitis ulcerosa, ataque fulminante, choque séptico, esclerosis múltiple, choque endotóxico, sepsis por gram-negativos, síndrome de choque tóxico, lesión por repercusión cardíaca y renal, glomerulonefritis, trombosis, reacción de injerto frente al huésped, enfermedad de Alzheimer, rechazos de aloinjertos, malaria, restenosis, angiogénesis, aterosclerosis, osteoporosis, gingivitis y liberación indeseada de células pluripotenciales hematopoyéticas y enfermedades causadas por virus respiratorios, herpes virus y virus de la hepatitis, meningitis, fibrosis quística, fatiga prematura, tos, prurito, disfunción multiorgánica, trauma, fatiga, torceduras, contusiones, artritis psoriásicas, herpes, encefalitis, vasculitis del SNC, lesión cerebral traumática, tumores del SNC, hemorragia subaracnoide, trauma posquirúrgico, neumonitis intersticial, hipersensibilidad, artritis inducida por cristales, pancreatitis aguda, enterocolitis necrosante, sinusitis crónica, uveitis, polmiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celiaca, esofagitis, glositis, obstrucción del flujo de aire, hipersensibilidad de las vías respiratorias, bronconeumonía obliterante, neumonía, bronquiectasia, bronconeumonía, bronconeumonía obliterante, bronquitis crónica, corazón pulmonar, disnea, enfisema, hipercapnia, hiperinflamación, hipoxemia, inflamaciones inducidas por hiperoxia, hipoxia, reducción quirúrgica del volumen pulmonar, hipertrofia ventricular derecha, sarcoidosis, enfermedades leves de las vías respiratorias, desequilibrio entre ventilación-perfusión, jadeo, catarros y lupus; se encuentran contempladas dentro de las exclusiones legales a la patentabilidad, de acuerdo con el artículo 20 de la Decisión 486.

En consecuencia, se recomienda al interesado eliminar del alcance de su invención las cláusulas señaladas, teniendo en cuenta que no pueden ser objeto de protección por patente de invención.

5. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de Información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 24.03.2000-, relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	WO9729743	"IL-8 receptor antagonists"	21/08/1997

Anterioridad D1 en los folios 182 a 198.

6. 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*

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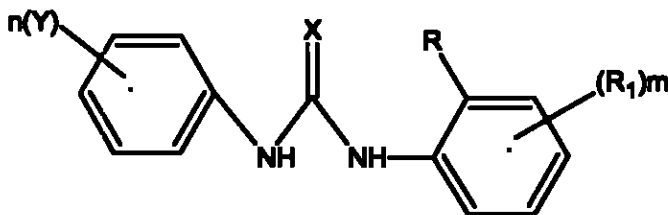
producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar 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.

7. Evaluación del NIVEL INVENTIVO:

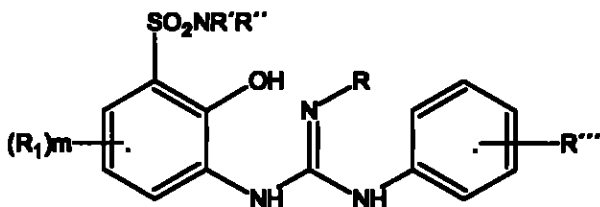
El artículo 18 de la decisión 486 dispone "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".

El documento D1 hace referencia a compuestos que presentan el núcleo estructural:



Donde X es oxígeno o nitrógeno
n(Y) puede ser (CR₃R₃)_qNHS(O)₂Rb en donde q puede ser cero y Rb es alquilo, arilo., alquenilo.
(R₁)m se selecciona entre hidrógeno, halógeno, nitro, ciano, alquilo C₁-C₁₀, alquenilo C₁-C₁₀, entre otros.

Al efectuar la comparación correspondiente elemento por elemento en cada una de las fórmulas, se encuentra que es posible a partir de la materia divulgada en la anterioridad D1 derivar los compuestos reclamados por la solicitud en estudio.



Si bien es cierto existen algunas diferencias en cuanto a las sustituciones que presenta el radical fenilo y el fenol, la mayor parte de las características esenciales de la fórmula química se encuentran reveladas en la anterioridad en cuestión. Así las cosas esta Dependencia observa que la altura inventiva de la materia reclamada se ve afectada al tenor de la divulgación hecha por el documento D1.

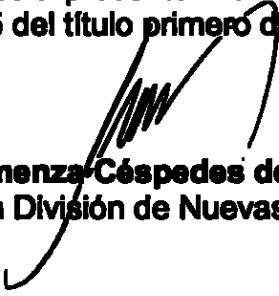
En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9729743	1 a 12	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad

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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 5 del título primero de la Circular Única N° 10 de 2001.


Álix Carmona Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

09 NOV. 2006

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO Número 01738	EXAMINADOR TÉCNICO Código 202044
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