SUPERINDUSTRIA Y COMERCIO
Radicacion : 00043844 00000003 Folios: 2
Fecha (AMD): 2003-01-30 09:33:58
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

...dos

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

Re.: Código 02-01-538
Expediente No. 00-43.844
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.oo, recibo No. 03-6001

De Ustedes Atentamente,

GERMAN CASTILLO GRAU
T.P. # 2.978 del C.S.J.

SUPERINTENDENCIA Y COMERCIO
Radicacion : 00043844 00000003 Folios: 2
Fecha (AMD): 2003-01-30 09:33:58
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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 6,001
FECHA : ENERO 30 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	8771306	30/01/2003	1,965,000.00

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

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._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
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Bogotá, D.C., Colombia

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300
2005-08-0
375

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Germán Castillo Grau
Apoderado

Oficio Nº 06545

REFERENCIA	**Radicación**	**00 43844**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**012**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 00 43844, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

. Descripción: folios 4-46
. Ejemplos: folios 46-136
. Capítulo reivindicatorio estudiado: 284-288
. Se reivindica prioridad presentada en Estados Unidos, el 16.06.99, bajo el número 60/139675

Objeto de la invención

Según las reivindicaciones 1 a 12 de la presente solicitud, se refiere compuestos antagonistas del receptor IL-8 de fórmula (I) que son útiles en el tratamiento de enfermedades mediadas por citoquinas.

Clasificación internacional de patentes A 61 K 31/17; 31/17

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 prioridad de la presente solicitud –16.06.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	WO 9729743	"Antagonistas del receptor IL-8"	21.08.97

Evaluación de los requisitos de patentabilidad:

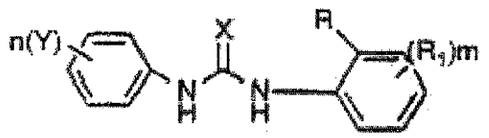
El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*"

En cumplimiento del artículo 14 de la decisión 486 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.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 contempla que *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación WO 9729743 se relaciona con compuestos antagonistas de IL-8 de fórmula (I):



Cuyos sustituyentes se revelan en la descripción. Tales compuestos son útiles en el tratamiento de enfermedades mediadas por citoquinas, especialmente la interleucina-8.

Comparando elemento por elemento, los compuestos de la presente solicitud son iguales a los de la anterioridad citada y pueden afectar la novedad de la presente solicitud.

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

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9729743	1-12	Novedad

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

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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 Nº 10 de 2001

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

04 AGO. 2005

El anterior requerimiento fue notificado por fijación en lista, de fecha_____

CONCEPTO TÉCNICO Número 1050	**EXAMINADOR TÉCNICO** Código 202024

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(11) International Publication Number: **WO 97/29743**

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(21) International Application Number: PCT/US96/13632

(22) International Filing Date: 21 August 1996 (21.08.96)

(30) Priority Data:
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(60) Parent Application or Grant
(63) Related by Continuation
US PCT/US96/02260 (CIP)
Filed on 16 February 1996 (16.02.96)

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(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).

Published
With international search report.

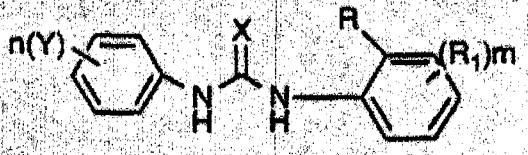
(54) Title: IL-8 RECEPTOR ANTAGONISTS

(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).

This invention also relates to a method of inhibiting the binding of IL-8 to its receptors in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

Compounds of Formula (I) useful in the present invention are represented by the structure:



(I)

wherein

X is oxygen or sulfur;

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

R_1 is independently selected from hydrogen; halogen; nitro; cyano; C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10}alkoxy; azide; $S(O)_tR_4$; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxy substituted C_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryl C_{2-10} alkenyl; aryloxy; aryl C_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{2-10} alkenyl; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; heterocyclicC_{1-4}alkyloxy; heterocyclicC_{2-10} alkenyl; $(CR_8R_8)q\ NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3H$; $S(O)_3R_8$; $(CR_8R_8)q\ C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $(CR_8R_8)q\ C(O)OR_{11}$; $(CR_8R_8)q\ OC(O)R_{11}$; $(CR_8R_8)qNR_4C(O)R_{11}$; $(CR_8R_8)q\ C(NR_4)NR_4R_5$; $(CR_8R_8)q\ NR_4C(NR_5)R_{11}$; $(CR_8R_8)q\ NHS(O)_2R_{13}$; $(CR_8R_8)q\ S(O)_2NR_4R_5$, or two R_1 moieties together may form $O\text{-}(CH_2)_sO$- 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;

R_4 and R_5 are independently hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, or R_4 and R_5 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 C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $(CR_8R_8)qS(O)_tR_4$, $(CR_8R_8)qOR_4$; hydroxy; hydroxy substituted C_{1-4}alkyl; aryl; aryl C_{1-4} alkyl;

aryloxy; arylC_{1-4} alkyloxy; aryl C_{2-10} alkenyl; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4} alkyloxy; heteroaryl C_{2-10} alkenyl; heterocyclic, heterocyclic C_{1-4}alkyl; heterocyclicC_{2-10} alkenyl; $(CR_8R_8)_qNR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)_qC(O)NR_4R_5$; $(CR_8R_8)_q$ $C(O)NR_4R_{10}$; $S(O)_3R_8$; $(CR_8R_8)_qC(O)R_{11}$; C_{2-10} alkenyl$C(O)R_{11}$; $(CR_8R_8)_qOC(O)R_{11}$; $(CR_8R_8)_qNR_4C(O)R_{11}$; $(CR_8R_8)_qNHS(O)_2R_b$; $(CR_8R_8)_qS(O)_2NR_4R_5$; $(CR_8R_8)_qC(NR_4)NR_4R_5$; $(CR_8R_8)_q$ $NR_4C(NR_5)R_{11}$; or two Y moieties together may form $O-(CH_2)_sO-$ 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;

R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl 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 may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

R_8 is hydrogen or C_{1-4} alkyl;

R_{10} is C_{1-10} alkyl $C(O)_2R_8$;

R_{11} is hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4}alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC_{1-4}alkyl;

R_{12} is hydrogen, C_{1-10} alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R_{13} is suitably C_{1-4} alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl;

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

or a pharmaceutically acceptably salt thereof.

Another aspect of the present invention is to a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 a or b receptor and which method comprises administering an effective amount of a compound of Formula (II) or a pharmaceutically acceptable salt thereof, as defined herein.

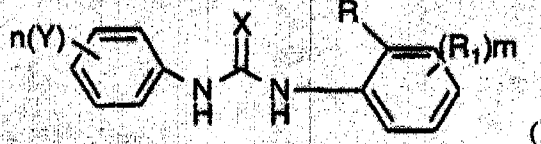
Accordingly, the present invention provides a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 a or b receptor and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. In particular, the chemokines ars IL-8, GROα, GROβ, GROγ or NAP-2.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine function, in particular IL-8, GROα, GROβ, GROγ or NAP-2 , such that they are biologically regulated down to normal levels of physiological function, or in some case to subnormal levels, so as to ameliorate the disease state. Abnormal levels of IL-8, GROα, GROβ, GROγ or NAP-2 for instance in the context of the present invention, constitute: (i) levels of free IL-8 greater than or equal to 1 picogram per mL; (ii) any cell associated IL-8, GROα, GROβ, GROγ or NAP-2 above normal physiological levels; or (iii)the presence of IL-8, GROα, GROβ, GROγ or NAP-2 above basal levels in cells or tissues in which IL-8, GROα, GROβ, GROγ or NAP-2respectively, is produced.

There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. Chemokine mediated diseases include psoriasis, atopic dermatitis, arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft vs. host reaction, alzheimers disease, allograft rejections, malaria, restinosis, angiogenesis or undesired hematopoietic stem cells release.

These diseases are primarily characterized by massive neutrophil infiltration, T-cell infiltration, or neovascular growth, and are associated with increased IL-8 GROα, GROβ, GROγ or NAP-2 production which is responsible for the chemotaxis of neutrophils into the inflammatory site or the directional growth of endothelial cells. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 GROα, GROβ, GROγ or NAP-2 has the unique property of promoting neutrophil chemotaxis, enzyme release including but not limited to elastase release as well as superoxide production and activation. The a-chemokines but particularly, GROα, GROβ, GROγ or NAP-2, working through the IL-8 type I or II receptor can promote the neovascularization of tumors by promoting the directional growth of endothelial cells. Therefore, the

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:



(I)

wherein

X is oxygen or sulfur;

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

R_1 is independently selected from hydrogen; halogen; nitro; cyano; C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10}alkoxy; azide; $S(O)_tR_4$; $(CR_8R_8)q\ S(O)_tR_4$; hydroxy; hydroxy substituted C_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryl C_{2-10} alkenyl; aryloxy; aryl C_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{2-10} alkenyl; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; heterocyclicC_{1-4}alkyloxy; heterocyclicC_{2-10} alkenyl; $(CR_8R_8)q\ NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)q\ C(O)NR_4R_{10}$; $S(O)_3H$; $S(O)_3R_8$; $(CR_8R_8)q\ C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $(CR_8R_8)q\ C(O)OR_{11}$; $(CR_8R_8)q\ OC(O)R_{11}$; $(CR_8R_8)qNR_4C(O)R_{11}$; $(CR_8R_8)q\ C(NR_4)NR_4R_5$; $(CR_8R_8)q\ NR_4C(NR_5)R_{11}$, $(CR_8R_8)q\ NHS(O)_2R_{13}$; $(CR_8R_8)q\ S(O)_2NR_4R_5$, or two R_1 moieties together may form $O\text{-}(CH_2)_sO$- 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;

R_4 and R_5 are independently hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C_{1-4}alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, or R_4 and R_5 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 C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $(CR_8R_8)qS(O)_tR_4$, $(CR_8R_8)qOR_4$; hydroxy; hydroxy substituted C_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; arylC_{1-4} alkyloxy; aryl C_{2-10} alkenyl; heteroaryl; heteroarylalkyl;

heteroaryl C_{1-4} alkyloxy; heteroaryl C_{2-10} alkenyl; heterocyclic, heterocyclic C_{1-4}alkyl; heterocyclicC_{2-10} alkenyl; $(CR_8R_8)qNR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)qC(O)NR_4R_5$; $(CR_8R_8)q$ $C(O)NR_4R_{10}$; $S(O)_3R_8$; $(CR_8R_8)qC(O)R_{11}$; C_{2-10} alkenyl$C(O)R_{11}$; $(CR_8R_8)qC(O)OR_{11}$; C_{2-10}alkenyl$C(O)OR_{11}$; $(CR_8R_8)qOC(O)R_{11}$; $(CR_8R_8)qNR_4C(O)R_{11}$; $(CR_8R_8)qNHS(O)_2R_b$; $(CR_8R_8)qS(O)_2NR_4R_5$; $(CR_8R_8)qC(NR_4)NR_4R_5$; $(CR_8R_8)q$ $NR_4C(NR_5)R_{11}$; or two Y moieties together may form O-$(CH_2)_5$O- 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;

R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl 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 may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

R_8 is hydrogen or C_{1-4} alkyl;

R_{10} is C_{1-10} alkyl $C(O)_2R_8$;

R_{11} is hydrogen, optionally substituted C_{1-4} alkyl, optionally substituted aryl, optionally substituted aryl C_{1-4}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-4}alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC_{1-4}alkyl;

R_{12} is hydrogen, C_{1-10} alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R_{13} is suitably C_{1-4} alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl;

R_b is NR_6R_7, alkyl, aryl, aryl C_{1-4} alkyl, aryl C_{2-4} alkenyl, heteroaryl, heteroaryl C_{1-4} alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4} alkyl, heterocyclic C_{2-4} 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 pKa of 3 to 10.

3. The method according to Claim 2 wherein R is hydroxy, carboxylic acid, thiol, -SR_2 -OR_2, -NH-C(O)R_a, -C(O)NR_6R_7, -$NHS(O)_2R_b$, -$S(O)_2NHR_c$, NHC(X)NHR_b, or tetrazolyl;

wherein R_2 is a substituted aryl, heteroaryl, or heterocyclic moiety which ring has the functional moiety providing the ionizable hydrogen having a pKa of 10 or less;

R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl 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 may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

R_a is an alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, or a heterocyclic C_{1-4}alkyl moiety, all of which may be optionally substituted;

R_b is a NR_6R_7, alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, heterocyclic C_{2-4}alkenyl moiety, camphor, all of which may be optionally substituted one to three times independently by halogen; nitro; cyano, halosubstituted C_{1-4} alkyl; C_{1-4} alkyl; C_{1-4} alkoxy; C1-4 amino, $NR_9C(O)R_a$; $C(O)NR_6R_7$, $S(O)_3H$, or $S(O)_{m'}R_a$ (wherein m' is 0, 1, or 2) or $C(O)OC_{1-4}$ alkyl;

R_9 is hydrogen or a C_{1-4} alkyl;

R_c is alkyl, aryl, arylC_{1-4}alkyl, arylC_{2-4}alkenyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4}alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, or a heterocyclic C_{2-4}alkenyl moiety, all of which may be optionally substituted one to three times independently by halogen, nitro,cyano, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} alkoxy, C1-4 amino , $NR_9C(O)R_a$, $C(O)NR_6R_7$, $S(O)_3H$, or $C(O)OC_{1-4}$ alkyl.

4. The method according to Claim 3 wherein the R_2 is optionally substituted one to three times by halogen, nitro, halosubstituted C_{1-10} alkyl, C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, SH, -$C(O)NR_6R_7$, -NH-C(O)R_a, -$NHS(O)R_b$, $S(O)NR_6R_7$, $C(O)OR_8$, or a tetrazolyl ring.

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 R_1 is halogen, cyano, nitro, CF_3, $C(O)NR_4R_5$, alkenyl $C(O)NR_4R_5$, $C(O)R_4R_{10}$, alkenyl $C(O)OR_{12}$, heteroaryl, heteroarylalkyl , heteroaryl alkenyl, or $S(O)NR_4R_5$.

7. The method according to Claim 1 wherein Y is halogen, C_{1-4} alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, methylene dioxy, NR_4R_5, thioC_{1-4}alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C_{1-4}alkyl, hydroxy alkyl.

8. The method according to Claim 1 wherein R is OH, SH, or $NHS(O)_sR_b$ and R_1 is substituted in the 3-position, the 4- position or di substituted in the 3,4- position by an electron withdrawing moiety.

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.

10. The compound according to Claims 1, 8 or 9 wherein n amd m are each equal to 1 or more.

11. The method according to Claim 1 wherein R is a carboxylic acid, and R_1 is hydrogen, or R_1 is substituted in the 4-position.

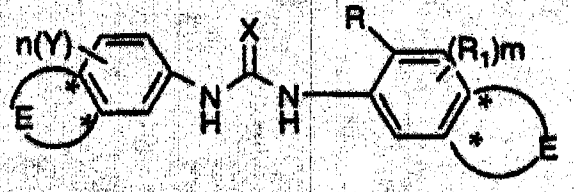
12. The method according to Claim 1 wherein the mammal is afflicted with a chemokine mediated disease selected from psoriasis, or atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal 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 accepatable salt is:

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
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

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
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
N-(2-Hydorxy-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
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
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.

14. A compound of the formula::



(II)

X is oxygen or sulfur;
R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less;
R_1 is independently selected from hydrogen; halogen; nitro; cyano; C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10}alkoxy; azide; $S(O)_tR_4$; $(CR_8R_8)_q$ $S(O)_tR_4$; hydroxy; hydroxy substituted C_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryl C_{2-10} alkenyl; aryloxy; aryl C_{1-4} alkyloxy;

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: **0-43844** EDICTO No. **18000**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución** No. **31669** de **28-NOV-2005**. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "DERIVADOS NOVEDOSOS DE FENIL-UREA COMO ANTAGONISTAS DEL RECEPTOR IL-8".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Germán Castillo Grau, o a quien haga sus veces, en su calidad de apoderado de Smithkline Beecham Corporation., entregándole copia de la misma, advirtiéndole que contra ella procede 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 28 NOV. 2005

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO RUBIO 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 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **14-DIC-2005** Este edicto se desfija hoy **27-DIC-2005** a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. **18000**