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Señores

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá, D.C.

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re.: Expediente No. 00 - 84.288

En relación con la última providencia recaída en este expediente, le manifiesto lo siguiente:

1. Debidamente traducida, adjunto acompaño la copia oficial de la solicitud de patente básica estadounidense No. 60/164.350.

2. Se acompaña el arte final por triplicado.

3. Modifico el título de la invención en la siguiente forma:

   " COMPUESTOS DE DIFENILUREA SUSTITUIDOS CON SULFONAMIDA, COMPOSICIONES FARMACEUTICAS, PROCEDIMIENTO PARA SU PREPARACION Y ANTAGONISTAS DEL IL- 8 "

4. Por motivo de lo anterior, acompaño nueva carátula, extracto, tarjeta de archivo temático y tarjeta de propietario.

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5. Por exceso de palabras en el extracto y por la suma de $ 92.500.oo acompaño el comprobante de pago de tasas, recibo No.

Le solicito continuar con este trámite.

De Ustedes atentamente,

GERMAN CASTILLO GRAU

T.P. No. 2978 del C.S.J.

PA 333931

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 07, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/164,350***
FILING DATE: ***November 09, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

A/PROV

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JC743 U.S. PTO 11/09/99

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.	P51055P		

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
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TITLE OF THE INVENTION (280 characters max)
IL-8 RECEPTOR ANATGONISTS

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	36	☐ Small Entity Statement	
☐ Drawings	Number of Sheets		☐ Other (specify)	

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT ($)	$150.00

Respectfully submitted,
Signature:
Soma G. Simon
Date: November 9, 1999
Registration No.: 37,444

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

SEND TO: Assistant Commissioner for Patents, Box Provisional Application, Washington, D.C. 20231.
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____.

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IL-8 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to novel sulfonamide substituted diphenyl urea compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating IL-8, GROα, GROβ, GROγ, NAP-2, and ENA-78 mediated diseases.

BACKGROUND OF THE INVENTION

Many different names have been applied to Interleukin-8 (IL-8), such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor. Interleukin-8 is a chemoattractant for neutrophils, basophils, and a subset of T-cells. It is produced by a majority of nucleated cells including macrophages, fibroblasts, endothelial and epithelial cells exposed to TNF, IL-1α, IL-1β or LPS, and by neutrophils themselves when exposed to LPS or chemotactic factors such as FMLP. M. Baggiolini et al., J. Clin. Invest. *84*, 1045 (1989); J. Schroder et al, J. Immunol. *139*, 3474 (1987) and J. Immunol. *144*, 2223 (1990) ; Strieter, et al., Science *243*, 1467 (1989) and J. Biol. Chem. *264*, 10621 (1989); Casastella et al., J. Immunol. *148*, 3216 (1992).

GROα, GROβ, GROγ and NAP-2 also belong to the chemokine family. Like IL-8 these chemokines have also been referred to by different names. For instance GROα, β, γ have been referred to as MGSAα, β and γ respectively (Melanoma Growth Stimulating Activity), see Richmond et al., J. Cell Physiology 129, 375 (1986) and Chang et al., J. Immunol 148, 451 (1992). All of the chemokines of the α-family which possess the ELR motif directly preceding the CXC motif bind to the IL-8 B receptor (CXCR2).

IL-8, GROα, GROβ, GROγ, NAP-2, and ENA-78 stimulate a number of functions in vitro. They have all been shown to have chemoattractant properties for neutrophils, while IL-8 and GROα have demonstrated T-lymphocytes, and basophilic chemotactic activity. In addition IL-8 can induce histamine release from basophils from both normal and atopic individuals. GRO-α and IL-8 can in addition, induce lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis. This may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many known diseases are characterized by massive neutrophil infiltration. As IL-8, GROα, GROβ, GROγ and NAP-2 promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and

rheumatoid arthritis, Baggiolini et al., FEBS Lett. *307*, 97 (1992); Miller et al., Crit. Rev. Immunol. *12*, 17 (1992); Oppenheim et al., Annu. Rev. Immunol. *9*, 617 (1991); Seitz et al., J. Clin. Invest. *87*, 463 (1991); Miller et al., Am. Rev. Respir. Dis. *146*, 427 (1992); Donnely et al., Lancet *341*, 643 (1993). In addition the ELR chemokines (those containing the amino acids ELR motif just prior to the CXC motif) have also been implicated in angiostasis, Strieter et al., Science 258, 1798 (1992).

In vitro, IL-8, GROα, GROβ, GROγ and NAP-2 induce neutrophil shape change, chemotaxis, granule release, and respiratory burst, by binding to and activating receptors of the seven-transmembrane, G-protein-linked family, in particular by binding to IL-8 receptors, most notably the IL-8β receptor (CXCR2). Thomas et al., J. Biol. Chem. *266*, 14839 (1991); and Holmes et al., Science *253*, 1278 (1991). The development of non-peptide small molecule antagonists for members of this receptor family has precedent. For a review see R. Freidinger in: Progress in Drug Research, Vol. 40, pp. 33-98, Birkhauser Verlag, Basel 1993. Hence, the IL-8 receptor represents a promising target for the development of novel anti-inflammatory agents.

Two high affinity human IL-8 receptors (77% homology) have been characterized: IL-8Rα, which binds only IL-8 with high affinity, and IL-8Rβ, which has high affinity for IL-8 as well as for GROα, GROβ, GROγ and NAP-2. See Holmes et al., supra; Murphy et al., Science *253*, 1280 (1991); Lee et al., J. Biol. Chem. *267*, 16283 (1992); LaRosa et al., J. Biol. Chem. *267*, 25402 (1992); and Gayle et al., J. Biol. Chem. *268*, 7283 (1993).

There remains a need for treatment, in this field, for compounds, which are capable of binding to the IL-8 α or β receptor. Therefore, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cells subsets into the inflammatory site) would benefit by compounds, which are inhibitors of IL-8 receptor binding.

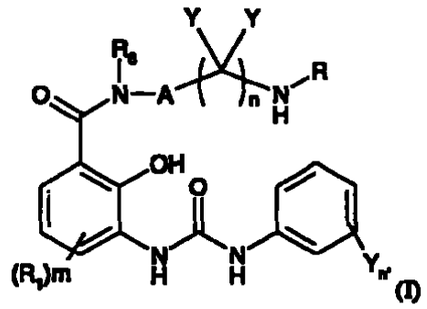
SUMMARY OF THE INVENTION

This invention provides for 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 chemokine is 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).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent.

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



(I)

wherein:

R represents R_6, $C(O)OR_8'$, COR_8', or $S(O)_2R_8'$;

A represents heteroaryl, heterocyclic, aryl or a covalent bond;

n represents an integer from 1 to 8;

R_8' is an alkyl, aryl, arylC$_{1-4}$alkyl, heteroaryl, heteroaryl C$_{1-4}$alkyl, heterocyclic or a heterocyclic C$_{1-4}$alkyl moiety, all of which moieties may be optionally substituted;

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

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

n' is an integer having a value of 1 to 3;

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;

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

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, $(CR_8R_8)_qC(O)NR_4R_5$, C$_{2-10}$ alkenyl $C(O)NR_4R_5$, $(CR_8R_8)_q$ $C(O)NR_4R_{10}$, $S(O)_3R_8$, $(CR_8R_8)_q$ $C(O)R_{11}$, C$_{2-10}$ alkenyl $C(O)R_{11}$, C$_{2-10}$ alkenyl $C(O)OR_{11}$, $(CR_8R_8)_q$ $C(O)OR_{11}$, $(CR_8R_8)_q$ $OC(O)R_{11}$, $(CR_8R_8)_qNR_4C(O)R_{11}$, $(CR_8R_8)_q$ $C(NR_4)NR_4R_5$, $(CR_8R_8)_q$ $NR_4C(NR_5)R_{11}$, $(CR_8R_8)_q$

$NHS(O)_tR_{13}$, $(CR_8R_8)q\ S(O)_tNR_4R_5$, or two R_1 moieties together may form $O-(CH_2)_2O$ or a 5 to 6 membered saturated or unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heterocyclic moieties may be optionally substituted;

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, heterocyclicC_{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 and S;

R_6 is selected from the group consisting of 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, and heterocyclicC_{1-4} alkyl;

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, $(CR_8R_8)qS(O)_tR_8$, $(CR_8R_8)qOR_8$, 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$C(O)OR_{11}$, $(CR_8R_8)qOC(O)R_{11}$, $(CR_8R_8)qNR_4C(O)R_{11}$, $(CR_8R_8)q\ NHS(O)_tR_{13}$, $(CR_8R_8)q\ S(O)_tNR_4R_5$, $(CR_8R_8)qC(NR_4)NR_4R_5$, $(CR_8R_8)q\ NR_4C(NR_5)R_{11}$, or two Y moieties together may form $O-(CH_2)_2-O$ or a 5 to 6 membered saturated or unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

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

R_9 is hydrogen or a 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_{13} is suitably C_{1-4} alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of Formula (I), may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of IL-8 or other chemokines which bind to the IL-8 α and β receptors. Chemokine mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section.

Suitably, R_1 is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl, such as CF_3, C_{1-10} alkyl, such as methyl, ethyl, isopropyl, or n-propyl, C_{2-10} alkenyl, C_{1-10} alkoxy, such as methoxy, or ethoxy; halosubstituted C_{1-10} alkoxy, such as trifluoromethoxy, azide, $(CR_8R_8)_q S(O)_tR_4$, wherein t is 0, 1 or 2, hydroxy, hydroxy C_{1-4}alkyl, such as methanol or ethanol, aryl, such as phenyl or naphthyl, aryl C_{1-4} alkyl, such as benzyl, aryloxy, such as phenoxy, aryl C_{1-4} alkyloxy, such as benzyloxy; heteroaryl, heteroarylalkyl, heteroaryl C_{1-4} alkyloxy; aryl C_{2-10} alkenyl, heteroaryl C_{2-10} alkenyl, heterocyclic C_{2-10} alkenyl, $(CR_8R_8)_qNR_4R_5$, C_{2-10} alkenyl $C(O)NR_4R_5$, $(CR_8R_8)_qC(O)NR_4R_5$, $(CR_8R_8)_qC(O)NR_4R_{10}$, $S(O)_3H$, $S(O)_3R_8$, $(CR_8R_8)_qC(O)R_{11}$, C_{2-10} alkenyl $C(O)R_{11}$, C_{2-10} alkenyl $C(O)OR_{11}$, $(CR_8R_8)_q C(O)R_{11}$, $(CR_8R_8)_qC(O)OR_{11}$, $(CR_8R_8)_q OC(O)R_{11}$, $(CR_8R_8)_qNR_4C(O)R_{11}$, $(CR_8R_8)_qC(NR_4)NR_4R_5$, $(CR_8R_8)_q NR_4C(NR_5)R_{11}$, $(CR_8R_8)_qNHS(O)_tR_{13}$, $(CR_8R_8)_qS(O)_tNR_4R_5$.

All of the aryl, heteroaryl, and heterocyclic-containing moieties may be optionally substituted as defined herein below.

For use herein the term "the aryl, heteroaryl, and heterocyclic containing moieties" refers to both the ring and the alkyl, or if included, the alkenyl rings, such as aryl, arylalkyl, and aryl alkenyl rings. The term "moieties" and "rings" may be interchangeably used throughout.

Suitably, 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, heterocyclicC_{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 and S.

Suitably, R_8 is independently hydrogen or C_{1-4} alkyl.

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

Suitably, q is 0 or an integer having a value of 1 to 10.

Suitably, R_{10} is C_{1-10} alkyl $C(O)_2R_8$, such as $CH_2C(O)_2H$ or $CH_2C(O)_2CH_3$.

Suitably, R_{11} is hydrogen, C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, or heterocyclic C_{1-4}alkyl.

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

Suitably, R_{13} is C_{1-4}alkyl, aryl, arylalkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl, wherein all of the aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted.

Suitably, Y is independently selected from 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; $(CR_8R_8)_q S(O)_t R_8$; hydroxy; hydroxyC_{1-4}alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; arylC_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4} alkyloxy; heterocyclic, heterocyclic C_{1-4}alkyl; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_8R_8)_q NR_4R_5$; C_{2-10} alkenyl $C(O)NR_4R_5$; $(CR_8R_8)_q C(O)NR_4R_5$; $(CR_8R_8)_q C(O)NR_4R_{10}$; $S(O)_3H$; $S(O)_3R_8$; $(CR_8R_8)_q C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$; $(CR_8R_8)_q C(O)OR_{12}$; $(CR_8R_8)_q OC(O) R_{11}$; $(CR_8R_8)_q C(NR_4)NR_4R_5$; $(CR_8R_8)_q NR_4C(NR_5)R_{11}$; $(CR_8R_8)_q NR_4C(O)R_{11}$; $(CR_8R_8)_q NHS(O)_tR_{13}$; or $(CR_8R_8)_q S(O)_tNR_4R_5$; or two Y moieties together may form $O-(CH_2)_s-O$ or a 5 to 6 membered saturated or unsaturated ring. The aryl, heteroaryl and heterocyclic containing moieties noted above may all be optionally substituted as defined herein.

Suitably s is an integer having a value of 1 to 3.

When Y forms a dioxybridge, s is preferably 1. When Y forms an additional unsaturated ring, it is preferably 6 membered resulting in a naphthylene ring system. These ring systems may be substituted 1 to 3 times by other Y moieties as defined above.

Y is preferably a halogen, C_{1-4} alkoxy, optionally substituted aryl, optionally substituted aryloxy or arylalkoxy, methylene dioxy, NR_4R_5, thio C_{1-4}alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C_{1-4} alkyl, or hydroxy alkyl. Y is more preferably mono-substituted halogen, disubstituted halogen, mono-substituted alkoxy, disubstituted alkoxy, methylenedioxy, aryl, or alkyl, more preferably these groups are mono or di-substituted in the 2'- position or 2'-, 3'-position.

While Y may be substituted in any of the ring positions, n is preferably one. While both R_1 and Y can both be hydrogen, it is preferred that at least one of the rings is substituted, preferably both rings are substituted.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine, hydroxy; hydroxy substituted

C_{1-10}alkyl, C_{1-10} alkoxy, such as methoxy or ethoxy, $S(O)_m$-C_{1-10} alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_4R_5 group, $NHC(O)R_4$, $C(O)NR_4R_5$, $COOR_4$, $S(O)_tNR_4R_5$, $NHS(O)_tR_{20}$, C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl, halosubstituted C_{1-10} alkyl, such CF_3, an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl, heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl, C_{1-10} alkoxy; $S(O)_m$-C_{1-10} alkyl; amino, mono & di-substituted alkyl amino, such as in the NR_4R_5 group; C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl, such as CF_3.

R_{20} is suitably C_{1-4} alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;

• "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.

• "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

• "wherein two R_1 moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of an aromatic ring system, such as naphthalene, or is a phenyl moiety having attached a 6 membered partially saturated or unsaturated ring such as a C_6 cycloalkenyl, i.e. hexene, or a C_5 cycloalkenyl moiety, such as cyclopentene.

Illustrative compounds of Formula (I) include:

3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide;

3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide;

N-[4-(2-aminoethyl)phenyl]-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide;

N-[4-(2-aminoethyl)phenyl]-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide;

3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide;

3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide;

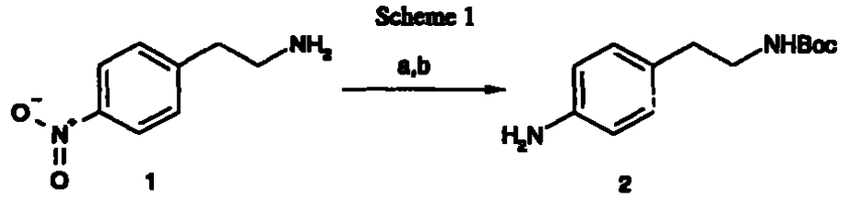
N-(6-aminohexyl)-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide; and
N-(6-aminohexyl)-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide;
or a pharmaceutically acceptable salt thereof.

METHODS OF PREPARATION

Methods of Preparation

If the desired Boc protected amine is not commercially available, the anilines for the amide formation can be obtained as outlined below in scheme 1. The commercially available ethyl amine 1 can be protected using tBoc anhydride. The resulting nitrobenzene can then be reduced using standard procedures like Pd/C and hydrogen gas, $SnCl_2$, or Zn to form the aniline 2.

Scheme 1

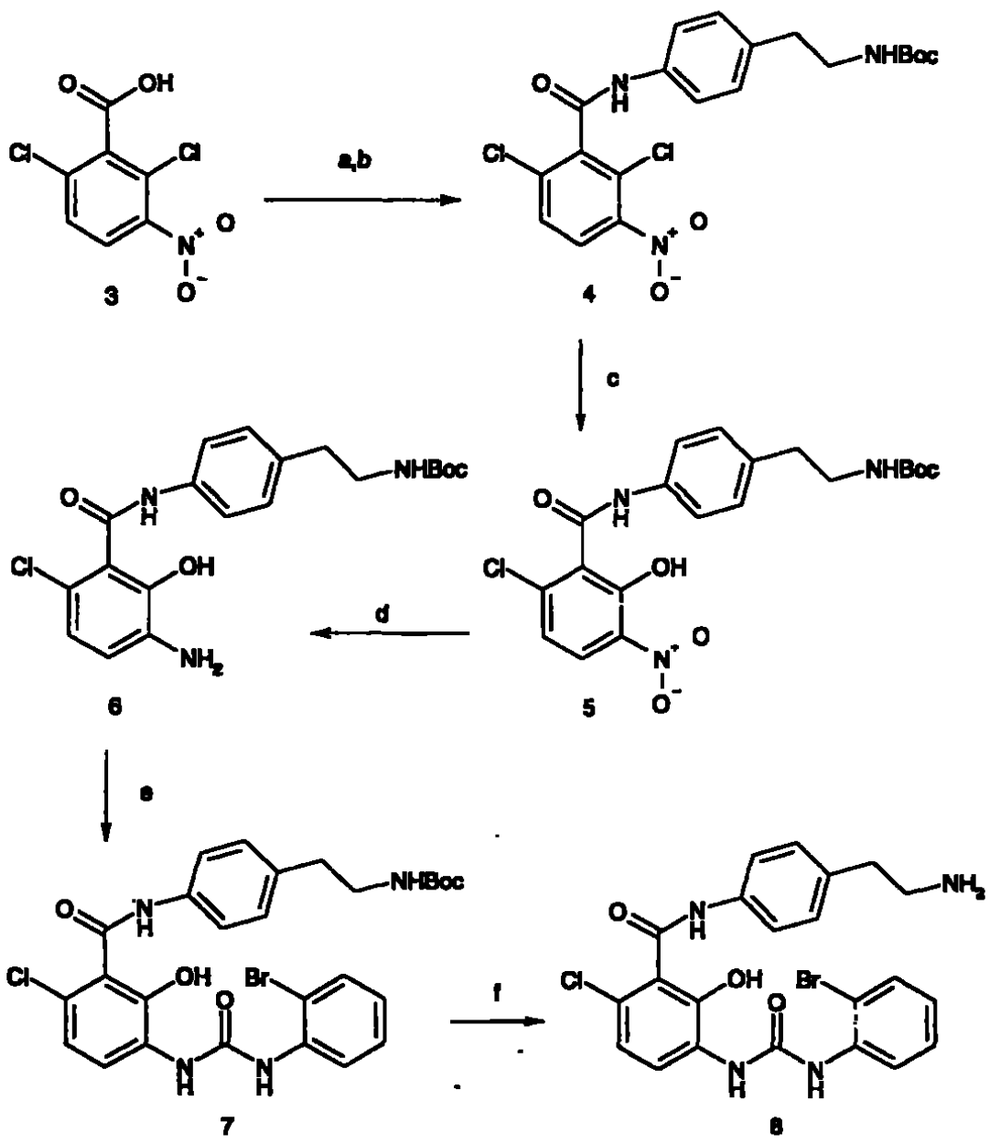


1 2

a) tBoc anhydride, Et_3N, CH_2Cl_2; b) H_2, Pd/C, EtOAc, 99.8%

The commercially available acid 3 is first converted to the acid chloride using standard procedures such as oxalyl chloride or thionyl chloride. The resulting acid chloride is then coupled with the amines from scheme 1 to generate the dichloroamide 4. Selective hydrolysis of the 2-Cl is accomplished with KOAc and 18-Crown-6 to yield the phenol 5. The nitro is then reduced using $SnCl_2$, and the resulting aniline is condensed with the desired isocyanate which can be purchased commercially. The protected amine can then be deprotected by standard conditions such as trifluoroacetic acid to form the urea 8.

Scheme 2

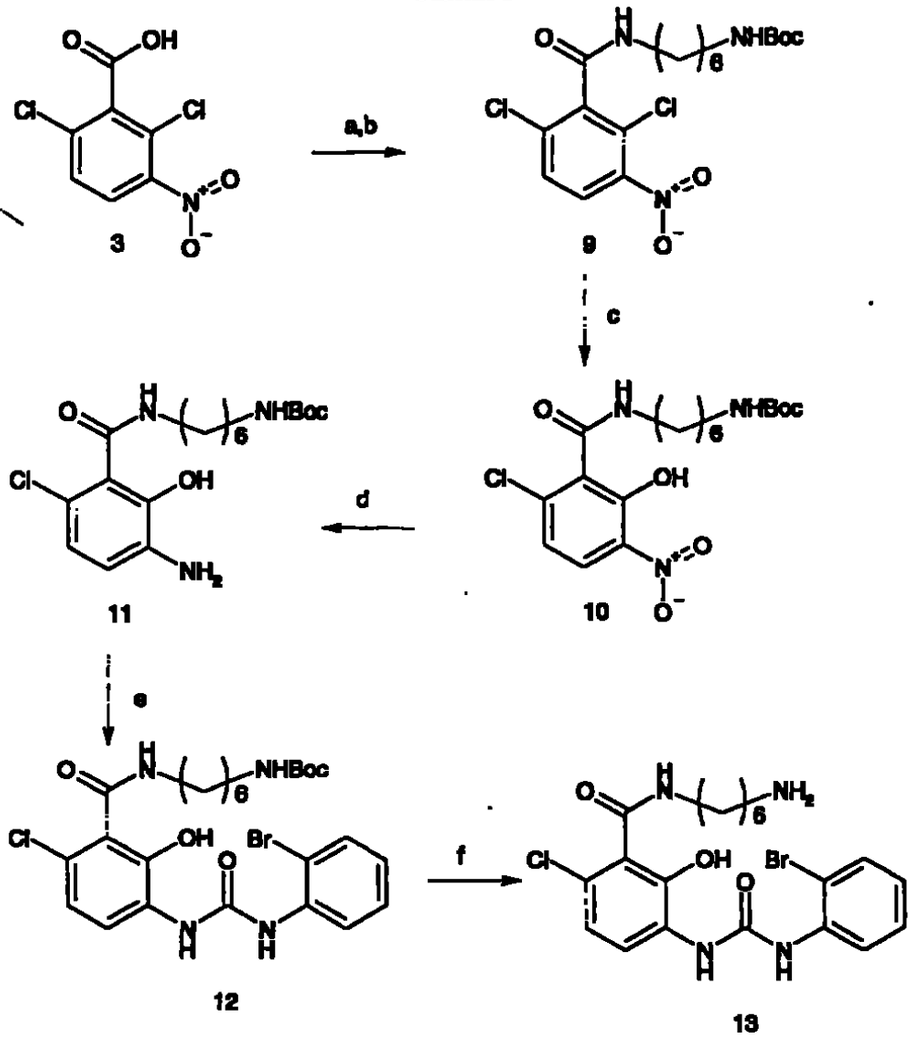


a) oxalyl chloride, CH_2Cl_2, DMF, 0°C; b) 2, Et_3N, DMF, 61%; c) KOAc, 18-Crown-6, DMSO, 100°C, 46%; d) $SnCl_2$, EtOH, 72% e) 2-bromophenyl isocyanate, DMF, 71%; f) TFA, 94%

To form the amine 13, the commercially available acid 3 is first converted to the acid chloride using standard procedures such as oxalyl chloride or thionyl chloride. The resulting acid chloride is then coupled with commercially available Boc protected amines to generate the

dichloro amide 9. If the amines are not commercially available they can be synthesized by coupling the desired diamine with 1 equiv. *t*-Boc anhydride. Selective hydrolysis of the 2-Cl is accomplished with KOAc and 18-Crown-6 to yield the phenol 10. The nitro is then reduced using $SnCl_2$, and the resulting aniline is condensed with the desired isocyanate which can be purchased commercially to form biaryl urea 12. The Boc-amine can then be deprotected by standard conditions such as triflouroacetic acid to form the urea 13.

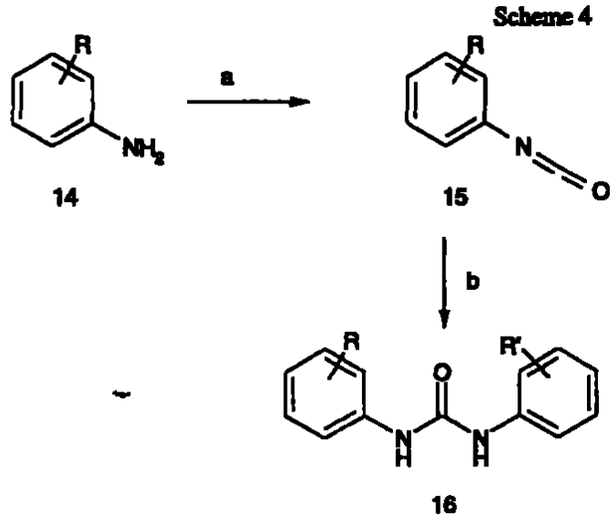
Scheme 3



a) oxalyl chloride, CH_2Cl_2, DMF, 0°C; b) tert-butyl N-(6-aminohexyl)-carbamate hydrochloride, Et_3N, DMF, 88%; c) KOAc, 18-Crown-6, DMSO, 100°C, 45%; d) H_2, Pd/C, EtOAc, 91%; e) 2-bromophenyl isocyanate, DMF, 60%; f) TFA, 100%

If the desired isocyanate is not commercially available, it can be prepared in a variety of ways as shown below in scheme 4 and 5. The aniline 14 can be reacted with a phosgene equivalent like triphosgene or carbonyl diimidazole in the presence of a base such as sodium bicarbonate to form the isocyanate 15 (or with thiophosgene to form the thioisocyanate). This isocyanate can then be condensed with the desired amine which can either be synthesized as above or purchased commercially to form the urea 16.

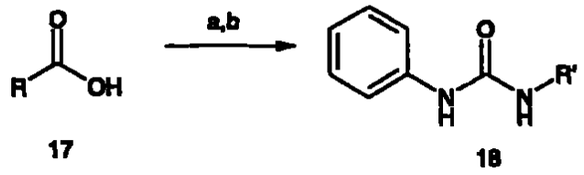
Scheme 4



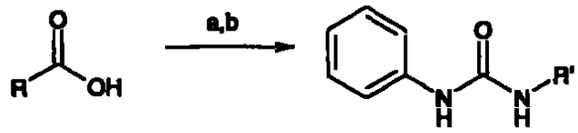
a) triphosgene, $NaHCO_3$; b)$R'NH_2$

Alternatively the isocyanate can be synthesized from the corresponding carboxylic acid using the Curtius rearrangement (dppa and triethyl amine, oxalyl chloride followed by sodium azide, scheme 5). This isocyanate can them be condensed with the desired amine to form the urea 18.

Scheme 5



a)DPPA, Et_3N; b)$R'NH_2$



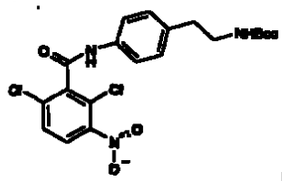
17 18

a)DPPA, Et_3N; b)$R'NH_2$

Pharmaceutically acceptable salts of compounds for Formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid or base in the presence of a suitable solvent.

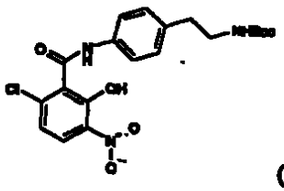
In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. ^{1}H-NMR (hereinafter "NMR") spectra were recorded at 250MHz or 400MHz using a Bruker AM 250 or Am 400 spectrometer, respetively. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated sloution, equiv. indicates the proportion of a molar equivalent of reagent relative to the principal reactant. Flash chromatography is run over Merck Silica get 60 (230-400mesh).

The present syntheses include the following novel intermediates represented by formulas (II), (III), (IV), (V), (VI) and (VII):



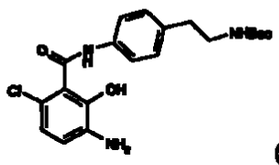
(II)

2,6-dichloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-3-nitrobenzamide;



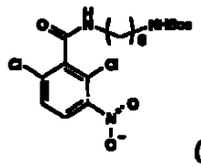
(III)

6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxy-3-nitrobenzamide;



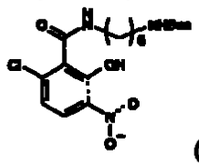
(IV)

3-amino-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide;



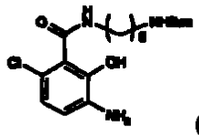
(V)

2,6-dichloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-3-nitrobenzamide;



(VI)

6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxy-3-nitrobenzamide;



(VII)

3-amino-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents used herein are of the highest available purity and all reactions are run under anhydrous conditions under an air atmosphere unless otherwise indicated.

In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated. ^{1}H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant. The purification, yields and spectral characteristics for each individual compound are listed below.

General Method A: Synthesis of N, N'-diphenyl urea To a solution of aniline (1.0 equiv.) in dimethyl formamide the corresponding phenyl isocyanate (1.0 equiv) was added. The reaction mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc, washed with water, and then the organic layer was dried with $MgSO_4$. The solvent was evaporated and recrystallization of the resulting mixture afforded the diphenyl urea. The purification, yields and spectral characteristics for each individual compound are listed below.

Preparation of *N*-[4-(2-aminoethyl)phenyl]-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide.

a) Preparation of 2: 4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]aniline

To a suspension of 4-nitrophenethylamine hydrochloride (11.00g, 54.28mmol) in CH_2Cl_2 (170mL) was added Et_3N (8.40mL, 60.27mmol). *t*-Boc anhydride (13.03g, 59.70mmol) was added in three portions, letting the bubbling of the reaction mixture stop between additions. Let the reaction stir at room temperature for 14 h, during which time all of the solid dissolves. Dilute the reaction mixture with 1N HCl, extract with CH_2Cl_2, and then dry the organic layer with $MgSO_4$. The solvent was evaporated resulting in a yellow solid, the Boc protected amine (14.45g, 100%). This solid (14.45g, 54.28mmol) was dissolved in EtOAc (400mL) and 10% Pd/C (5.4g) was added. The mixture was flushed with argon, then hydrogen was bubbled through the solution for 10 min. and a hydrogen atmosphere was maintained at balloon pressure overnight. The mixture was filtered through celite and the celite was washed with EtOAc. The solvent was evaporated to yield the desired product (12.80g, 100%). HI-MS m/z 237$(M-H)^+$.

b) Preparation of 4: 2,6-dichloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-3-nitrobenzamide

A suspension of 2,6-dichloro-3-nitrobenzoic acid (1.99g, 8.46mmol) in CH_2Cl_2 (33mL) was chilled in an ice bath. To this suspension was added DMF (0.3mL) followed by oxalyl chloride (1.36mL, 15.59mmol). The solution was allowed to slowly warm up to room temperature overnight, then the solvents were removed under vacuum. This mixture was dissolved in DMF (30mL) and chilled in an ice bath. Et_3N (1.3mL, 9.32mmol) was added, followed by 2 (2.19g, 9.27mmol). The reaction mixture was allowed to warm up to room temperature for overnight. The mixture was then diluted with water and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and then concentrated to yield a brownish oil. The product was purified by precipitation from CH_2Cl_2 / hexane (1 /20) and

filtering (2.27g, 61%). ^{1}H NMR (DMSO-d_6) δ 10.85 (s, 1H), 8.21 (d, 1H), 7.89 (d, 1H), 7.58 (d, 2H), 7.20 (d, 2H), 6.89 (t, 1H), 3.11 (m, 2H), 2.67 (t, 2H), 1.37 (s, 9H).

c) Preparation of 5: 6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxy-3-nitrobenzamide

To a solution of 4 (4.60g, 10.12mmol) in DMSO (45mL) was added KOAc (2.98g, 30.36mmol) followed by 18-Crown-6 (8.03g, 30.38mmol). The reaction mixture was then heated to 100°C via an oil bath for overnight. The mixture was allowed to cool to room temperature, and 10% NaOH was added. The mixture was allowed to stir for 5 h and then acidified to pH=1 with 6N HCl. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated. Chromatography of the resulting brown oil on silica gel (7Hexane/ 3EtOAc to 7Hexane/ 3EtOAc/ 0.1HOAc) gave the desired product (2.02g, 46%). EI-MS m/z 434(M-H)$^-$.

d) Preparation of 6: 3-amino-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide

To a solution of 5 (2.55g, 5.85mmol) in EtOH (475mL) was added $SnCl_2 \cdot 2H_2O$ (5.21g, 23.09mmol) and the solution was allowed to stir at room temperature for 4 d. The reaction mixture was concentrated and then diluted with EtOAc and satd $NaHCO_{3(aq)}$ causing a white solid to crash out of solution. The entire mixture was filtered through celite and the celite was washed with EtOAc. The organic layer was separated and dried with $MgSO_4$. Concentration of the organic layer resulted in the desired product (1.76g, 74%). EI-MS m/z 404(M-H)$^-$.

e) Preparation of 7: 3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide

7 was prepared from 6 (1.74g, 4.29mmol) in DMF (9.0mL) according to the procedure in General Method A. The product was purified by precipitation from CH_2Cl_2/ hexane (1 equiv./ 20 equiv.) and filtering (1.82g, 71%). EI-MS m/z 601(M-H)$^-$.

f) Preparation of 8: *N*-[4-(2-aminoethyl)phenyl]-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide

7 (1.82g, 3.01mmol) was treated with trifluoroacetic acid (6.0mL). The solution bubbled and all of the solid dissolves. The solution was stirred for 25 min at room temperature and then diluted with MeOH. The solution was concentrated and then diluted with MeOH and concentrated again resulting in a slightly grey powder of the desired product (1.75g, 94%). EI-MS m/z 505(M-H)$^+$.

Preparation of *N*-[4-(2-aminoethyl)phenyl]-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide

a) Preparation of 3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide

This compound was prepared from 6 (0.140g, 0.985mmol) in DMF (1.5mL) according to the procedure in General Method A. The product was purified by precipitation from CH_2Cl_2/ hexane (1 equiv./ 20 equiv.) and filtering (0.133g, 65%). EI-MS m/z 591$(M-H)^-$.

b) Preparation of *N*-[4-(2-aminoethyl)phenyl]-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide

The above compound (0.102g, 0.172mmol) was treated with trifluoroacetic acid (1.5mL). The solution bubbled and all of the solid dissolves. The solution was stirred for 15 min at room temperature and then diluted with MeOH. The solution was concentrated and then diluted with MeOH and concentrated again resulting in a white powder of the desired product (0.0926g, 89%). EI-MS m/z 495$(M-H)^+$.

Preparation of *N*-(6-aminohexyl)-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide

a) Preparation of 9: 2,6-dichloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-3-nitrobenzamide

A suspension of 2,6-dichloro-3-nitrobenzoic acid (6.00g, 25.42mmol) in CH_2Cl_2 (90mL) was chilled in an ice bath. To this suspension was added DMF (0.6mL) followed by oxayly chloride (3.80mL, 43.56mmol). The solution was allowed to slowly warm up to room temperature overnight, then the solvents were removed under vacuum. This mixture was dissolved in DMF (80mL) and chilled in an ice bath. Et_3N (7.8mL, 55.96mmol) was added, followed by tert-butyl N-(6-aminohexyl)-carbamate hydrochloride (7.28g, 28.80mmol). The reaction mixture was allowed to warm up to room temperature overnight. The mixture was then diluted with water and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated to yield an oily yellow solid (9.54g, 86%) which was carried on to the next reaction. ^1H NMR (DMSO-d_6) δ 8.81 (t, 1H), 8.13 (d, 1H), 7.81 (d, 1H), 6.79 (t, 1H), 3.25 (q, 2H), 2.88 (m, 2H), 1.50 (m, 2H), 1.40 (s, 9H), 1.24 (m, 6H).

b) Preparation of 10: 6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxy-3-nitrobenzamide

To a solution of 9 (9.49g, 21.85mmol) in DMSO (90mL) was added KOAc (6.41g, 65.31mmol) followed by 18-Crown-6 (17.32g, 65.53mmol). The reaction mixture was then heated to 100°C via an oil bath overnight. The mixture was allowed to cool to room temperature, and 10% NaOH was added. The mixture was allowed to stir for 4 h and then acidified to pH=1 with 6N HCl. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated. Chromatography of the resulting brown oil on silica gel (7Hexane/ 3EtOAc to 7Hexane/ 3EtOAc/ 0.1HOAc to 6Hexane/ 4EtOAc/ 0.1HOAc) gave the desired product (4.07g, 45%). LC/MS m/z 416(M-H)$^+$.

c) Preparation of 11: 3-amino-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide

To a solution of 10 (1.50g, 3.61mmol) in EtOAc (330mL) was added 10% Pd/C (0.83g). The mixture was flushed with argon, then hydrogen was bubbled through the solution for 10 min. and a hydrogen atmosphere was maintained at balloon pressure for 2 h 30 min. The mixture was filtered through celite and the celite was washed with EtOAc. The solvent was evaporated to yield the desired product (1.27g, 91%). LC/MS m/z 386(M-H)$^+$.

d) Preparation of 12: 3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide

12 was prepared from 11 (1.27g, 3.29mmol) in DMF (8.0mL) according to the procedure in General Method A. The product was purified by precipitation from CH_2Cl_2/ hexane (1 equiv./ 20 equiv.) and filtering (1.16g, 60%). EI-MS m/z 582(M-H)$^-$.

e) Preparation of 13: *N*-(6-aminohexyl)-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide

To 12 (1.09g, 1.87mmol) slowly add trifluoroacetic acid (9.5mL). The solution bubbles and all of the solid dissolves. The solution was stirred for 25 min at room temperature and then diluted with MeOH. The solution was concentrated and then diluted with MeOH and concentrated two more times resulting in a beige powder of the desired product (1.12g, 100%). EI-MS m/z 483(M-H)$^+$.

Preparation of *N*-(6-aminohexyl)-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide

a) Preparation of 3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide

This compound was prepared from 11 (0.253g, 0.656mmol) in DMF (2.2mL) according to the procedure in General Method A. The product was purified by precipitation from CH_2Cl_2/ hexane (1 equiv./ 20 equiv.) and filtering (0.287g, 82%). ^1H NMR (DMSO-d_6) δ 9.97 (s, 1H), 9.20 (s, 1H), 9.14 (s, 1H), 8.42 (t, 1H), 8.10 (d, 1H), 7.91 (d, 1H), 7.30-7.34 (m, 2H), 6.93 (d, 1H), 6.79 (t, 1H), 3.24 (m, 2H), 2.90 (m, 2H), 1.51-1.27 (m, 17H).

b) Preparation of *N*-(6-aminohexyl)-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide

To the above compound (0.203g, 0.354mmol) slowly add trifluoroacetic acid (2.5mL). The solution bubbles and all of the solid dissolves. The solution was stirred for 25 min at room temperature and then diluted with MeOH. The solution was concentrated and then diluted with MeOH and concentrated two more times resulting in a beige powder of the desired product (0.201g, 97%). EI-MS m/z 473$(M-H)^+$.

METHOD OF TREATMENT

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicine for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated IL-8 cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages, or other chemokines which bind to the IL-8 α or β receptor, also referred to as the type I or type II receptor.

Accordingly, the present invention provides a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 α or β 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 are IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine function, in particular IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78, 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, NAP-2 or ENA-78 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, NAP-2 or ENA-78 above normal physiological levels;

or (iii) the presence of IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 above basal levels in cells or tissues in which IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 respectively, is produced.

The compounds of Formula (*I*), in generally have been shown to have a longer $t_{1/2}$ and improved oral bioavailabilty over the compounds disclosed in WO 96/25157 and WO 97/29743 whose disclosures are incorporated herein by reference.

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, osteo arthritis, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, multiple sclerosis, 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, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cells release and diseases caused by respiratory viruses, herpesviruses, and hepatitis viruses, meningitis, herpes encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, uveitis, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiolitis obliterans organizing pneumonia, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hypoxia, surgerical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertropy, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze and lupus.

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, NAP-2 or ENA-78 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, NAP-2 or ENA-78 have the unique property of promoting neutrophil chemotaxis, enzyme release including but not limited to elastase release as well as superoxide production and activation. The α-chemokines but particularly, GROα, GROβ, GROγ, NAP-2 or ENA-78, 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 inhibition of IL-8 induced chemotaxis or activation would lead to a direct reduction in the neutrophil infiltration.

Recent evidence also implicates the role of chemokines in the treatment of HIV infections, Littleman *et al.*, Nature 381, pp. 661 (1996) and Koup *et al.*, Nature 381, pp. 667 (1996).

Present evidence also indicates the use of IL-8 inhibitors in the treatment of atherosclerosis. The first reference, Boisvert et al., J. Clin. Invest. 1998, 101:353-363 shows, through bone marrow transplantation, that the absence of IL-8 receptors on stem cells (and, therefore, on monocytes/macrophages) leads to a reduction in the development of atherosclerotic plaques in LDL receptor deficient mice. Additional supporting references are: Apostolopoulos, et al., Arterioscler. Thromb. Vasc. Biol. 1996, 16:1007-1012; Liu, et al., Arterioscler. Thromb. Vasc. Biol. 1997, 17:317-323; Rus, et al., Atherosclerosis. 1996, 127:263-271.; Wang et al., J. Biol. Chem. 1996, 271:8837-8842; Yue, et al., Eur. J. Pharmacol. 1993, 240:81-84; Koch, et al., Am. J. Pathol., 1993, 142:1423-1431.; Lee, et al., Immunol. Lett., 1996, 53, 109-113.; and Terkeltaub et al., Arterioscler. Thromb., 1994, 14:47-53.

The present invention also provides for a means of treating, in an acute setting, as well as preventing, in those individuals deemed susceptible to, CNS injuries by the chemokine receptor antagonist compounds of Formula (I).

CNS injuries as defined herein include both open or penetrating head trauma, such as by surgery, or a closed head trauma injury, such as by an injury to the head region. Also included within this definition is ischemic stroke, particularly to the brain area.

Ischemic stroke may be defined as a focal neurologic disorder that results from insufficient blood supply to a particular brain area, usually as a consequence of an embolus, thrombi, or local atheromatous closure of the blood vessel. The role of inflammatory cytokines in this area has been emerging and the present invention provides a mean for the potential treatment of these injuries. Relatively little treatment, for an acute injury such as these has been available.

TNF-α is a cytokine with proinflammatory actions, including endothelial leukocyte adhesion molecule expression. Leukocytes infiltrate into ischemic brain lesions and hence compounds which inhibit or decrease levels of TNF would be useful for treatment of ischemic brain injury. See Liu *et al.*, Stroke, Vol. 25., No. 7, pp. 1481-88 (1994) whose disclosure is incorporated herein by reference.

Models of closed head injuries and treatment with mixed 5-LO/CO agents is discussed in Shohami *et al.*, J. of Vasc & Clinical Physiology and Pharmacology, Vol. 3, No. 2, pp. 99-

107 (1992) whose disclosure is incorporated herein by reference. Treatment, which reduced edema formation, was found to improve functional outcome in those animals treated.

The compounds of Formula (I) are administered in an amount sufficient to inhibit IL-8, binding to the IL-8 alpha or beta receptors, from binding to these receptors, such as evidenced by a reduction in neutrophil chemotaxis and activation. The discovery that the compounds of Formula (I) are inhibitors of IL-8 binding is based upon the effects of the compounds of Formulas (I) in the *in vitro* receptor binding assays which are described herein. The compounds of Formula (I) have been shown to be inhibitors of type II IL-8 receptors.

As used herein, the term "IL-8 mediated disease or disease state" refers to any and all disease states in which IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 plays a role, either by production of IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 themselves, or by IL-8, GROα, GROβ, GROγ, NAP-2 or ENA-78 causing another monokine to be released, such as but not limited to IL-1, IL-6 or TNF. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to IL-8, would therefore be considered a disease state mediated by IL-8.

As used herein, the term "chemokine mediated disease or disease state" refers to any and all disease states in which a chemokine which binds to an IL-8 α or β receptor plays a role, such as but not limited to IL-8, GRO-α, GRO-β, GROγ, NAP-2 or ENA-78. This would includs a disease state in which, IL-8 plays a role, either by production of IL-8 itself, or by IL-8 causing another monokine to be released, such as but not limited to IL-1, IL-6 or TNF. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to IL-8, would therefore be considered a disease stated mediated by IL-8.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule, which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epideral keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor beta (TNF-β).

As used herein, the term "chemokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response, similar to the term "cytokine" above. A chemokine is primarily secreted through cell transmembranes and causes chemotaxis and activation of specific white blood cells and leukocytes, neutrophils, monocytes, macrophages, T-cells, B-cells, endothelial cells and smooth muscle cells. Examples of chemokines include, but are not limited to IL-8, GRO-α, GRO-β, GRO-γ, NAP-2, ENA-78, IP-10, MIP-1α, MIP-β, PF4, and MCP 1, 2, and 3.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form

or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the Formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the Formulation.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents

such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of Formula (I) the daily oral dosage regimen will preferably be from about 0.01 to about 80 mg/kg of total body weight. The daily parenteral dosage regimen about 0.001 to about 80 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically

acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The IL-8, and GRO-α chemokine inhibitory effects of compounds of the present invention are determined by the following *in vitro* assay:

Receptor Binding Assays:

[^{125}I] IL-8 (human recombinant) is obtained from Amersham Corp., Arlington Heights, IL, with specific activity 2000 Ci/mmol. GRO-α is obtained from NEN- New England Nuclear. All other chemicals are of analytical grade. High levels of recombinant human IL-8 type α and β receptors were individually expressed in Chinese hamster ovary cells as described previously (Holmes, *et al.*, Science, 1991, *253*, 1278). The Chinese hamster ovary membranes were homogenized according to a previously described protocol (Hacur, *et al.*, J. Biol. Chem., 249 pp 2195-2205 (1974)). Except that the homogenization buffer is changed to 10mM Tris-HCL, 1mM $MgSO_4$, 0.5mM EDTA (ethylene-diaminetetra-acetic acid), 1mM PMSF (α-toluenesulphonyl fluoride), 0.5 mg/L Leupeptin, pH 7.5. Membrane protein concentration is determined using Pierce Co. micro-assay kit using bovine serum albumin as a standard. All assays are performed in a 96-well micro plate format. Each reaction mixture contains ^{125}I IL-8 (0.25 nM) or ^{125}I GRO-α and 0.5 μg/mL of IL-8Rα or 1.0 μg/mL of IL-8Rβ membranes in 20 mM Bis-Trispropane and 0.4 mM Tris HCl buffers, pH 8.0, containing 1.2 mM $MgSO_4$, 0.1 mM EDTA, 25 mM Na and 0.03% CHAPS. In addition, drug or compound of interest is added which has been pre-dissolved in DMSO so as to reach a final concentration of between 0.01nM and 100 uM. The assay is initiated by addition of ^{125}I-IL-8. After 1 hour at room temperature the plate is harvested using a Tomtec 96-well harvester onto a glass fiber filtermat blocked with 1% polyethyleneimine/ 0.5% BSA and washed 3 times with 25 mM NaCl, 10 mM TrisHCl, 1 mM $MgSO_4$, 0.5 mM EDTA, 0.03 % CHAPS, pH 7.4. The filter is then dried and counted on the Betaplate liquid scintillation counter. The recombinant IL-8 Rα, or Type I, receptor is also referred to herein as the non-permissive receptor and the recombinant IL-8 Rβ, or Type II, receptor is referred to as the permissive receptor.

Representative compounds of Formula (I), Examples 1 to 106 have exhibited positive inhibitory activity in this assay at IC_{50} levels < 30 uM.

Chemotaxis Assay :

The *in vitro* inhibitory properties of these compounds are determined in the neutrophil chemotaxis assay as described in Current Protocols in Immunology, vol. I, Suppl 1, Unit 6.12.3., whose disclosure is incorporated herein by reference in its entirety. Neutrophils where isolated from human blood as described in Current Protocols in Immunology Vol. I, Suppl 1 Unit 7.23.1, whose disclosure is incorporated herein by reference in its entirety. The chemoattractants IL-8, GRO-α, GRO-β, GRO-γ and NAP-2 are placed in the bottom chamber of a 48 multiwell chamber (Neuro Probe, Cabin John, MD) at a concentration between 0.1 and 100 nM. The two chambers are separated by a 5 uM polycarbonate filter. When compounds of this invention are tested, they are mixed with the cells (0.001 - 1000 nM) just prior to the addition of the cells to the upper chamber. Incubation is allowed to proceed for between about 45 and 90 min at about 37°C in a humidified incubator with 5% CO_2. At the end of the incubation period, the polycarbonate membrane is removed and the top side washed, the membrane then stained using the Diff Quick staining protocol (Baxter Products, McGaw Park, IL, USA). Cells which have chemotaxed to the chemokine are visually counted using a microscope. Generally, four fields are counted for each sample, these numbers are averaged to give the average number of cells which had migrated. Each sample is tested in triplicate and each compound repeated at least four times. To certain cells (positive control cells) no compound is added, these cells represent the maximum chemotactic response of the cells. In the case where a negative control (unstimulated) is desired, no chemokine is added to the bottom chamber. The difference between the positive control and the negative control represents the chemotactic activity of the cells.

Elastase Release Assay:

The compounds of this invention are tested for their ability to prevent Elastase release from human neutrophils. Neutrophils are isolated from human blood as described in Current Protocols in Immunology Vol. I, Suppl 1 Unit 7.23.1. PMNs 0.88 x 10^6 cells suspended in Ringer's Solution (NaCl 118, KCl 4.56, $NaHCO_3$ 25, KH_2PO_4 1.03, Glucose 11.1, HEPES 5 mM, pH 7.4) are placed in each well of a 96 well plate in a volume of 50 ul. To this plate is added the test compound (0.001 - 1000 nM) in a volume of 50 ul, Cytochalasin B in a volume of 50 ul (20ug/ml) and Ringers buffer in a volume of 50 ul. These cells are allowed to warm (37 °C, 5% CO2, 95% RH) for 5 min before IL-8, GROα, GROβ, GROγ or NAP-2 at a final concentration of 0.01 - 1000 nM was added. The reaction is allowed to proceed for 45 min before the 96 well plate is centrifuged (800 xg 5 min.) and 100 ul of the supernatant removed. This supernatant is added to a second 96 well plate followed by an artificial elastase substrate

(MeOSuc-Ala-Ala-Pro-Val-AMC, Nova Biochem, La Jolla, CA) to a final concentration of 6 ug/ml dissolved in phosphate buffered saline. Immediately, the plate is placed in a fluorescent 96 well plate reader (Cytofluor 2350, Millipore, Bedford, MA) and data collected at 3 min intervals according to the method of Nakajima et al J. Biol. Chem. 254 4027 (1979). The amount of Elastase released from the PMNs is calculated by measuring the rate of MeOSuc-Ala-Ala-Pro-Val-AMC degradation.

TNF-α in Traumatic Brain Injury Assay

The present assay provides for examination of the expression of tumor necrosis factor mRNA in specific brain regions, which follow experimentally, induced lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) were anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury, n=18). Animals are sacrificed by decapitation at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) are prepared. Total RNA are isolated and Northern blot hybridization is performed and quantitated relative to an TNF-α positive control RNA (macrophage = 100%). A marked increase of TNF- α mRNA expression is observed in LH (104±17% of positive control, $p < 0.05$ compared with sham), LC (105±21%, $p< 0.05$) and LA (69±8%, $p < 0.01$) in the traumatized hemisphere 1 hr. following injury. An increased TNF- α mRNA expression is also observed in LH (46±8%, $p < 0.05$), LC (30±3%, $p < 0.01$) and LA (32±3%, $p < 0.01$) at 6 hr which resolves by 24 hr following injury. In the contralateral hemisphere, expression of TNF- α mRNA is increased in RH (46±2%, $p < 0.01$), RC (4±3%) and RA (22±8%) at 1 hr and in RH (28±11%), RC (7±5%) and RA (26±6%, $p < 0.05$) at 6 hr but not at 24 hr following injury. In sham (surgery without injury) or naive animals, no consistent changes in expression of TNF- α mRNA are observed in any of the 6 brain areas in either hemisphere at any times. These results indicate that following parasagittal fluid-percussion brain injury, the temporal expression of TNF-α mRNA is altered in specific brain regions, including those of the non-traumatized hemisphere. Since TNF-α is able to induce nerve growth factor (NGF) and stimulate the release of other cytokines from activated astrocytes, this post-traumatic alteration in gene expression of TNF-α plays an important role in both the acute and regenerative response to CNS trauma.

CNS Injury model for IL-1β mRNA

This assay characterizes the regional expression of interleukin-1β (IL-1β) mRNA in specific brain regions following experimental lateral fluid-percussion traumatic brain injury

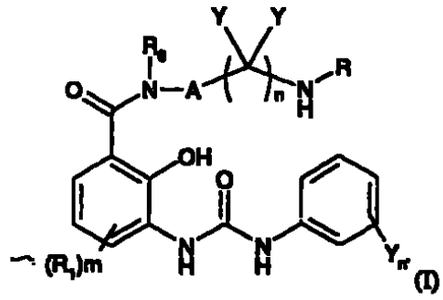
(TBI) in rats. Adult Sprague-Dawley rats (n=42) are anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury). Animals are sacrificed at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) are prepared. Total RNA is isolated and Northern blot hybridization was performed and the quantity of brain tissue IL-1β mRNA is presented as percent relative radioactivity of IL-1β positive macrophage RNA which was loaded on the same gel. At 1 hr following brain injury, a marked and significant increase in expression of IL-1β mRNA is observed in LC (20.0±0.7% of positive control, n=6, $p < 0.05$ compared with sham animal), LH (24.5±0.9%, $p < 0.05$) and LA (21.5±3.1%, $p < 0.05$) in the injured hemisphere, which remained elevated up to 6 hr. post injury in the LC (4.0±0.4%, n=6, $p < 0.05$) and LH (5.0±1.3%, $p < 0.05$). In sham or naive animals, no expression of IL-1β mRNA is observed in any of the respective brain areas. These results indicate that following TBI, the temporal expression of IL-1β mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1β play a role in the post-traumatic.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed Is:

1. A compound of the formula (I):



wherein:

R represents R_6, $C(O)OR_8'$, COR_8', or $S(O)_2R_8'$;

A represents heteroaryl, heterocyclic, aryl or a covalent bond;

n represents an integer from 1 to 8;

R_8' is an alkyl, aryl, arylC$_{1-4}$alkyl, heteroaryl, heteroaryl C$_{1-4}$alkyl, heterocyclic or a heterocyclic C$_{1-4}$alkyl moiety, all of which moieties may be optionally substituted;

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

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

n' is an integer having a value of 1 to 3;

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;

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

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, $(CR_8R_8)_q NR_4R_5$, $(CR_8R_8)_qC(O)NR_4R_5$, C$_{2-10}$ alkenyl $C(O)NR_4R_5$, $(CR_8R_8)_q C(O)NR_4R_{10}$, $S(O)_3R_8$, $(CR_8R_8)_q C(O)R_{11}$, C$_{2-10}$ alkenyl $C(O)R_{11}$, C$_{2-10}$ alkenyl $C(O)OR_{11}$, $(CR_8R_8)_q C(O)OR_{11}$, $(CR_8R_8)_q OC(O)R_{11}$, $(CR_8R_8)_qNR_4C(O)R_{11}$, $(CR_8R_8)_q C(NR_4)NR_4R_5$, $(CR_8R_8)_q NR_4C(NR_5)R_{11}$, $(CR_8R_8)_q NHS(O)_tR_{13}$, $(CR_8R_8)_q S(O)_tNR_4R_5$, or two R_1 moieties together may form O-(CH$_2$)$_s$O or a 5

to 6 membered saturated or unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heterocyclic moieties may be optionally substituted;

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, heterocyclicC_{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 and S;

R_6 is selected from the group consisting of 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, and heterocyclicC_{1-4} alkyl;

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, $(CR_8R_8)_qS(O)_tR_8$, $(CR_8R_8)_qOR_8$, 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$C(O)OR_{11}$, $(CR_8R_8)_qOC(O)R_{11}$, $(CR_8R_8)_qNR_4C(O)R_{11}$, $(CR_8R_8)_q$ $NHS(O)_tR_{13}$, $(CR_8R_8)_q$ $S(O)_tNR_4R_5$, $(CR_8R_8)_qC(NR_4)NR_4R_5$, $(CR_8R_8)_q$ $NR_4C(NR_5)R_{11}$, or two Y moieties together may form $O\text{-}(CH_2)_2\text{-}O$ or a 5 to 6 membered saturated or unsaturated ring, and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

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

R_9 is hydrogen or a 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_{13} is suitably C_{1-4} alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclic, or heterocyclicC_{1-4}alkyl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein R_1 is substituted in the 4- position by an electron withdrawing moiety.

3. The compound according to Claim 2 wherein R_1 is halogen, cyano or nitro.

4. The compound according to Claim 3 wherein R_1 is halogen.

5. The compound according to Claim 4 wherein R_1 is independently, fluorine, chlorine, or bromine.

6. The compound according to Claim 1 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.

7. The compound according to Claim 6 wherein Y is halogen.

8. The compound according to Claim 4 wherein Y is independently fluorine, chlorine, or bromine.

9. The compound according to Claim 1 wherein Y is halogen, n' is 1 or 2, R_1 is halogen, and m is 1 or 2.

10. The compound according to Claim 1 which is selected from the group consisting of:
3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide;
3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide;
N-[4-(2-aminoethyl)phenyl]-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide;
N-[4-(2-aminoethyl)phenyl]-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide;
3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide;
3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide;

N-(6-aminohexyl)-3-[[[(2,3-dichlorophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide; and

N-(6-aminohexyl)-3-[[[(2-bromophenyl)amino]carbonyl]amino]-6-chloro-2-hydroxybenzamide;

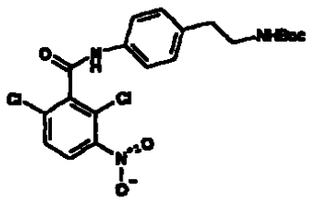
or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound according to any of Claims 1 to 10 and a pharmaceutically acceptable carrier or diluent.

12. A method of treating a chemokine mediated disease, wherein the chemokine binds to an IL-8 a or b receptor in a mammal, which method comprises administering to said mammal an effective amount of a compound of the formula according to any one of Claims 1 to 14.

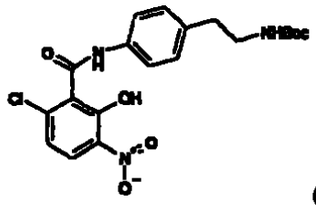
13. The method according to Claim 12 wherein the mammal is afflicted with a chemokine mediated disease selected from atopic dermatitis, osteo arthritis, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, stroke, septic shock, multiple sclerosis, endotoxic shock, psoriasis, gram negative sepsis, toxic shock syndrome, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, graft vs. host reaction, alzheimers disease, allograft rejections, malaria, restinosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cells release, diseases caused by respiratory viruses, herpesviruses, and hepatitis viruses, meningitis, herpes encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, cystic fibrosis, pre-term labour, cough, pruritus, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, lyme arthritis, fibrodysplasia ossificans progressiva, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, uveitis, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiolitis obliterans organizing pneumonia, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hypoxia, surgerical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertropy, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze and lupus.

14. A compound selected from the group consisting of formulas (II), (III), (IV), (V), (VI) and (VII) hereinbelow:



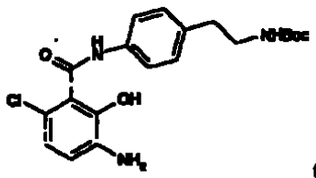
(II)

2,6-dichloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-3-nitrobenzamide;



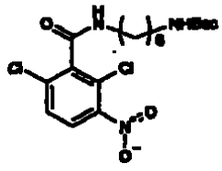
(III)

6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxy-3-nitrobenzamide;



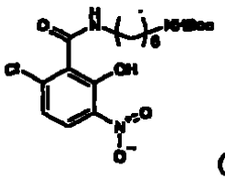
(IV)

3-amino-6-chloro-*N*-[4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]ethyl]phenyl]-2-hydroxybenzamide;



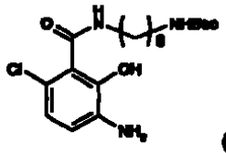
(V)

2,6-dichloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-3-nitrobenzamide;



(VI)

6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxy-3-nitrobenzamide;



(VII)

3-amino-6-chloro-*N*-[6-[[(1,1-dimethylethoxy)carbonyl]amino]hexyl]-2-hydroxybenzamide.

ABSTRACT OF THE DISCLOSURE

This invention relates to novel compounds and compositions thereof, useful in the treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8).

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LOS ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS A QUIENES LLEGUEN ESTOS PRESENTES
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OFICINA DE PATENTES Y MARCAS DE FABRICA

NOVIEMBRE 7, 2000

ESTA ES PARA CERTIFICAR QUE LOS ANEXOS SON COPIA DE LOS ARCHIVOS DE LA OF. DE PATENTES Y MARCAS DE FABRICA DE AQUELLOS PAPELES QUE IDENTIFICAN ADELANTE LA SOLICITUD DE PATENTE QUE REUNIO LOS REQUISITOS PARA SER OTORGADA UNA FECHA DE REGISTRO BAJO EL # 35 USC111

SOLICITUD # 60/164,350
FECHA DE LA SOLICITUD: NOV. 09, 1999

SELLO CIRCULAR EN PAPEL DORADO, OF. DE PATENTES Y MARCAS DE FABRICA (EN EL CENTRO EL AGUILA AMERICANA)

CON LA AUTORIDAD DEL COMISIONADO DE MARCAS Y PATENTES

FIRMA
L. EDELEN
OFICIAL CERTIFICADOR

CERTIFICADO "EXPRESS MAIL"

Correo "Express Mail" Número de Guía de CorreoEL175493222US
Fecha de Depósito: Noviembre 9, 1999

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Nombre de la persona que envía el papel o valor
(letra de imprenta o a máquina) (Ilegible)
Firma (Ilegible)

Carta Cubierta de Solicitud Provisional

Esta es una solicitud para registro de una SOLICITUD PROVISIONAL para PATENTE de acuerdo al 37 CFR 1.53 (c).

Certificado No.	P51055P		
INVENTOR (es) / SOLICITANTE (s)			
Apellidos	Primer Nombre	Inicial media	Residencia (Ciudad y Estado o País Extranjero
Widdowson McCleland	Catherine Brent	L	King of Prussia, Pennsylvania Greenlane, Pennsylvania
TITULO DE LA INVENCION (Máximo 280 caracteres) ANTAGONISTAS DEL RECEPTOR DE IL-8			

DIRECCIÓN PARA CORRESPONDENCIA SMITHKLINE BEECHAM CORPORATION Corporate Intellectual Property – UW2220 709 Swedeland Road King of Prussia				Telephone No. 610-270-5019 Facsimil No. 610-270-5090	
Estado	PA	Código Postal	19406-2799	País	Estados Unidos de América
PARTES ANEXAS A LA SOLICITUD (Chequear que todas apliquen)					
[X] Especificaciones	Número de Páginas	36	[ ] Especificaciones de pequeñas entidades		
[ ] Dibujos	Número de Hojas		[ ] Otros (Especifique)		

FORMA DE PAGO DE LOS VALORES DE REGISTRO PARA ESTA SOLICITUD PROVISIONAL DE PATENTE		
[X] El comisionado está autorizado por medio del presente para cargar las cuotas de registro y crédito a la Cuenta de Depósito No19-2570	VALOR DE CUOTA DE REGISTRO PROVISIONAL	$150.00

Sometido en forma respetuosa,

FIRMA: (Firmado) Soma G. Simon

FECHA: Noviembre 9 de 1999

Registro No.: 37,444

☐ Invenciones adicionales nombradas separadamente en hojas numeradas se anexan aquí.

REGISTRO DE SOLICITUD PROVISIONAL SOLAMENTE

Enviar a: Assistant commissioner for Patents, Box Provisional Application, Washington, D. C. 20231.
La invención fue hecha por una agencia del Gobierno de los Estados Unidos o bajo un contrato con una agencia del gobierno de los Estados Unidos

☐ No

☐ Sí, el nombre de la agencia del Gobierno de los Estados Unidos y el número del Contrato del Gobierno son:

n:/Soma/Cases/P51055P/Tprov.doc

En la parte superior izquierda se encuentra un sello con Código de Barras que dice:

JC713 U.S. PTO 11/09/99

En la parte superior derecha se encuentra un sello con Código de Barras que dice:

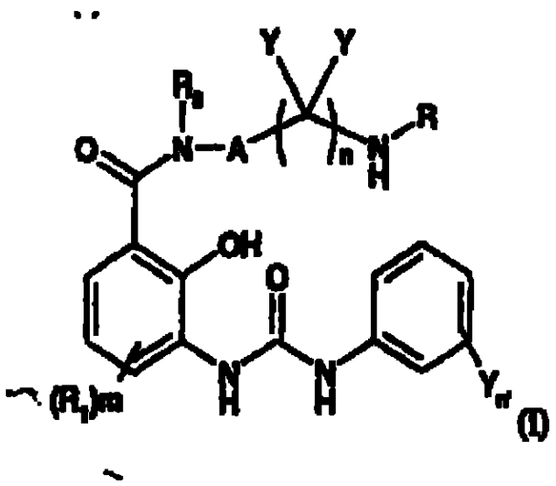
JC3553 U.S. PTO 60/164359 11/09/99

Hay un número impreso en la parte izquierda del formulario y que dice así:

60164359.110999

Lo que se reivindica es:

1. Un compuesto con la fórmula (I):



En el cual:

R representa R_6 C (O) Or_a; COR_a o S $(O)_2R_a$

A representa heteroarilo, heterocíclica, aril o un vínculo covalente;

n representa un número entero del 1 al 8;

R_a es una molécula alquilo, arilo, ariloC_{1-4}alquilo, heteroarilo, heteroarilo C_{1-4}alquilo, heterocíclico o

Heterocíclico C_{1-4}alquilo, todas las cuales moléculas pueden ser sustituidas opcionalmente.

m es un número entero con un valor de 1 a 3;

m' es 0 o un entero con un valor de 1 ó 2;

n' es un entero con valor de 1 a 3;

q es 0 o un entero con valor de 1 a 10;

t es 0 o un entero con un valor de 1 a 2;

s es un entero con valor de 1 a 3;

R_1 es seleccionado independientemente de hidrógeno, halógeno, nitro, ciano, C_{1-10}alquilo, halo sustituido C_{1-10}alquilo, C_{2-10} alquenilo, C_{1-10}alcoxi, halo sustituidoC_{1-10}alcoxi, azida, $S(O)_tR_4$, (CR_8R_8) q $S(O)_t$ R_4, hidroxi, hidroxi sustituido C_{1-4}alquilo, aril, aril C_{1-4} alquilo, arilC_{2-10} alquenilo, ariloxi, arilC_{1-4}alquiloxi, heteroaril, heteroarilalquilo, heteroariloC_{2-10} alquenilo, heteroarilC_{1-4}alquiloxi, heterocíclico, heterocíclico C_{1-4}alquilo, hetereocíclico C_{1-4}alquiloxi, heterocíclico C_{2-10}alquenilo, $(CR_8R_8)q$ NR_4R_5, $(CR_8R_8)q$ $C(O)NR_4R_5$, C_{2-10}alquenilo $C(O)$ NR_4R_5, $(CR_8R_8)q$, $C(O)NR_4R_{10}$, $S(O)_3$ R_8, $(CR_8R_8)q$ $C(O)R_{11}$, C_{2-10}alquenilo $C(O)R_{11}$, C_{2-10}alquenil $C(O)OR_{11}$, $(CR_8R_8)q$ $C(O)OR_{11}$, $(CR_8R_8)q$ O $C(O)R_{11}$, $(CR_8R_8)q$ NR_4 $C(O)R_{11}$, $(CR_8R_8)q$ $C(NR_4)$ NR_4R_5, $(CR_8R_8)q$ NR_4 $C(NR_5)$ R_{11}, $(CR_8R_8)q$ $(NHS(0)_t$ R_{13}, $(CR_8R_8)q$ S $(O)_t$ NR_4R_5, o dos moléculas R_1 juntas pueden formar $O-(CH_2)_sO$ o un anillo saturado o insaturado de 5 ó 6 miembros, y donde las moléculas alquilo, arilo, arilalquillo, heteroarilo, heterocíclicas pueden ser sustituidas opcionalmente.

R_4 y R_5 son independientemente hidrógeno, C_{1-4}alquilo opcionalmente sustituido, arilo opcionalmente sustituido, ariloC_{1-4}alquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heteroariloC_{1-4}alquilo opcionalmente sustituido, heterocíclico, heterocíclicoC_{1-4}alquilo o R_4 y R_5 juntos con el nitrógeno al cual están unidos forman un anillo de 5 a 7

miembros que opcionalmente puede comprender un heteroátomo adicional seleccionado de entre O, N y S.

R_6 es seleccionado del grupo compuesto por hidrógeno, C_{1-4}alquilo opcionalmente sustituido, arilo opcionalmente sustituido, ariloC_{1-4}alquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heteroariloC_{1-4}alquilo opcionalmente sustituido, heterocíclico, y heterocíclicoC_{1-4}alquilo;

Y es hidrógeno, halógeno, nitro, ciano, C_{1-10}alquilo halo sustituido, C_{1-10}alquilo, C_{1-10}alquilo, C_{2-10}alquenilo, C_{1-10}alcoxi, halo sustituido C_{1-10}alcoxi, azida, $(CR_8R_8)q\ S(O)_t\ R_{13}$, $(CR_8R_8)q\ OR_8$, hidroxi, hidroxisustituido C_{1-4}alquilo, arilo; ariloC_{1-4}alquilo, ariloxi, arilo C_{1-4}alquiloxi, arilo C_{2-10}alquenilo, heteroarilo, herteroarilalquilo, heteroarilC_{1-4}alquiloxi, heteroarilo C_{2-10}alquenilo, heterocíclico, heterocíclico C_{1-4}alquilo, hereocíclicoC_{2-10} alquenilo, $(CR_8R_8)q\ NR_4R_5$, C_{2-10}alquenil $C(O)NR_4R_5$, $(CR_8R_8)q\ C(O)NR_4R_5$, $(CR_8R_8)q\ C(O)NR_4R_{10}$, $S(O)_3R_8$, $(CR_8R_8)q\ C(O)R_{11}$, C_{2-10}alquenilo $C(O)R_{11}$, $(CR_8R_8)q\ C(O)R_{11}$, C_{2-10}alquenilo$C(O)OR_{11}$, $(CR_8R_8)q\ OC(O)R_{11}$, $(CR_8R_8)q\ NR_4C(O)R_{11}$, $(CR_8R_8)q\ NHS(O)_t\ R_{13}$, $(CR_8R_8)q\ S(O)_tNR_4R_5$, $(CR_8R_8)q\ C(NR_4)\ NR_4R_5$, $(CR_8R_8)q\ NR_4C\ (NR_5)R_{11}$ o dos moléculas Y juntas pueden formar $O-(CH_2)_s$ o un anillo saturado o insaturado de 5 o 6 miembros, y donde los grupos alquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, heterocíclico, heterocíclicoalquilo pueden ser sustituidas opcionalmente;

R_8 es hidrógeno C_{1-4}alquilo;

R_9 es hidrógeno o un C_{1-4}alquilo
R_{10} es C_{1-10}alquil$C(O)_2R_8$;

R_{11} es hidrógeno, C_{1-4}alquilo opcionalmente sustituido, arilo opcionalmente sustituido, ariloC_{1-4} alquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, heteroariloC_{1-4}alquilo opcionalmente sustituido, heterocíclico opcionalmente sustituido o heterocóclico C_{1-4}alquilo opcionalmente sustituido;

R_{13} es según sea apropiado, C_{1-4}alquilo, arilo, arilo C_{1-4}alquilo, heteroarilo, heteroarilo C_{1-4}alquilo, heterocíclico o heterocíclico C_{1-4}alquilo;

o una sal del mismo farmacéuticamente aceptable.

2. El compuesto de acuerdo con la Reivindicación 1 en la cual R_1 es sustituido en la posición 4 por una molécula que sustrae electrones.

3. El compuesto de acuerdo con la Reivindicación 2 en la cual R_1 es halógeno, ciano o nitro.

4. El compuesto de acuerdo con la Reivindicación 3 en la cual R_1 es halógeno.

5. El compuesto de acuerdo con la Reivindicación 4 en la cual R_1 es independientemente cloro, flúor o bromo.

6. El compuesto de acuerdo con la Reivindicación 1 en la cual Y está monosustituido en la posición 2' o 3' o está distribuido en la posición 2' o 3' de un anillo monocíclico.

7. El compuesto de acuerdo con la Reivindicación 6 en la cual Y es halógeno.

8. El compuesto de acuerdo con la Reivindicación 4 en la cual Y es independientemente cloro, flúor o bromo.

9. El compuesto de acuerdo con la Reivindicación 1 en la cual Y es halógeno, n' es 1 o 2, R_1 es halógeno y m es 1 o 2.

10. El compuesto de acuerdo con la Reivindicación 1 el cual es seleccionado del grupo que consta de: 3-[[[(2-bromofenil) amino] carbonil] amino]-6-cloro-*N* -[4-[2-[[(1,1-dimetiletoxi) carbonil] amino] etil] fenil] -2-hidroxibenzamida;

3-[[[(2,3-diclorofenil)amino] carbonil] amino]-6-cloro-*N*-[4-[2-[[(1,1-dimetiletoxi) carbonil] amino] etil] fenil]-2-hidroxibenzamida;

N-[4-(2-aminoetil) fenil] -3-[[[(2-bromofenil) amino] carbonil] amino] -6-cloro- 2- hidroxibenzamida;

N-[4 -(2- aminoetil) fenil]-3-[[[(2-diclorofenil) amino] carbonil] amino]-6-cloro-2- hidroxibenzamida;

3-[[[(2,3-diclorofenil) amino] carbonil] amino] -6-cloro-*N*-[4-[2-[[(1,1-dimetiletoxi) carbonil] amino] etil] fenil]- 2-hidroxibenzamida;

3-[[[(2,3-bromofenil) amino] carbonil] amino]-6-cloro-*N*-[6-[[(1,1-dimetiletoxi) carbonil] amino] hexil]-2-hidroxibenzamida;

N-(6-aminohexil)-3-[[[(2,3-diclorofenil)amino]carbonil]amino]-6-cloro-2-hidroxibenzamida; y

N-(6-aminohexil)-3-[[[(2,3-bromofenil)amino]carbonil]amino]-6-cloro-2-hidroxibenzamida;

o una sal de la misma, farmacéuticamente aceptable.

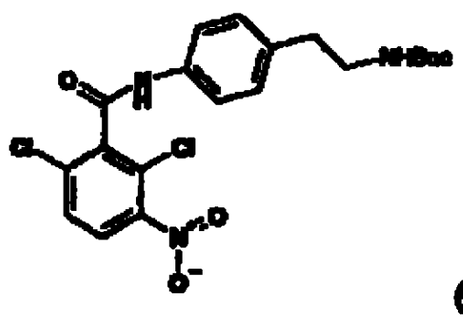
11. Una composición farmacéutica que comprende un compuesto de conformidad con cualquiera de las Reivindicaciones 1 a 10 o un vehículo o diluyente, farmacéuticamente aceptable.

12. Un método para tratar una enfermedad mediada por quimocinas, en la cual la quimocina se une a un receptor de IL-8 o a un receptor b de un mamífero, cuyo método comprende la administración al mencionado mamífero de una cantidad efectiva de un compuesto de la fórmula de acuerdo con cualquiera de las Reivindicaciones 1 a 14.

13. El método conforme a la Reivindicación 12, en la cual el mamífero está afectado por una enfermedad mediada por una quimocina seleccionada de entre dermatitis atópica, osteoartritis, artritis reumatoidea, asma, enfermedad pulmonar obstructiva crónica, síndrome de dificultad respiratoria del adulto, enfermedad intestinal inflamatoria, enfermedad de Crohn, colitis ulcerativa, accidente cerebrovascular, shock séptico, esclerosis múltiple, shock endotóxico, psoriasis, sepsis por gramnegativos, síndrome de shock tóxico, lesión cardiaca o renal por reperfusión, glomerulonefritis, trombosis, reacción injerto contra huésped, enfermedad de Alzheimer, rechazo de aloinjertos, malaria, retinosis pigmentaria, angiogénesis, aterosclerosis, osteoporosis, gingivitis y liberación indeseada de células madre hematopoyéticas, enfermedades causadas por virus respiratorios, virus herpes y virus de la hepatitis, meningitis, encefalitis herpética, vasculitis del sistema nervioso central, lesión cerebral traumática, tumores del sistema nervioso central, hemorragia subaracnoidea, traumatismo posquirúrgico, fibrosis quística, parto pretérmino, tos, prurito, neumonitis intersticial, hipersensibilidad, artritis inducida por cristales, artritis de la enfermedad de Lyme, fibrodisplasia osificante progresiva, pancreatitis aguda y crónica, hepatitis alcohólica

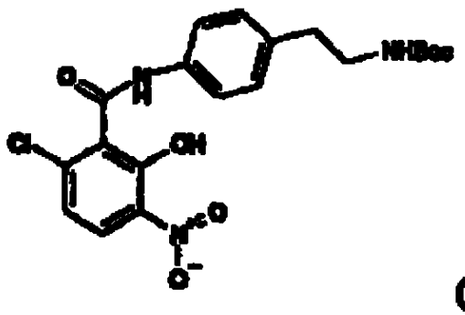
aguda, enterocolitis necrotizante, sinusitis crónica, uveítis, polimiositis, vasculitis, acné, úlceras gástricas y duodenales, enfermedad celíaca, esofagitis, glositis, obstrucción del flujo aéreo, hiperreactividad de la vía aérea, neumonía en organización por bronquiolitis obliterante, bronquiectasias, bronquiolitis, bronquiolitis obliterante, bronquitis crónica, cor pulmonale, disnea, enfisema, hipercapnia, hiperinflación, hipoxemia, hipoxia, reducción quirúrgica del volumen pulmonar, fibrosis pulmonar, hipertensión pulmonar, hipertrofia del ventrículo derecho, sarcoidosis, enfermedad de las pequeñas vías aéreas, falta de concordancia entre ventilación y perfusión, sibilancias y lupus eritematoso sistémico.

14. Un compuesto seleccionado del grupo que consta de las fórmulas (II), (III), (IV), (V), (VI) y (VII) que aparecen a continuación en este documento:



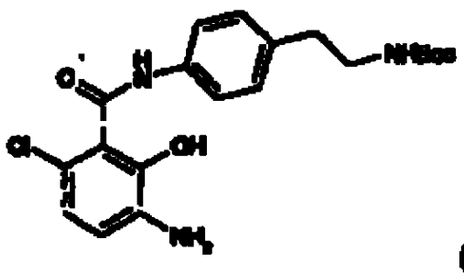
(II)

2,6-dicloro-*N*-[4-[2[[(1,1-dimetiletoxi)carbonil]amino]etil]fenil]-3-nitrobenzamida;



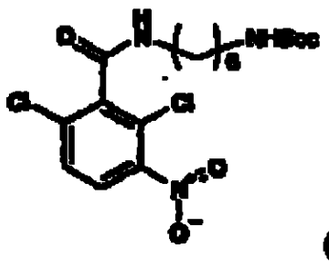
(III)

6-cloro-*N*-[4-[2-[[(1,1-dimetiletoxi)carbonil]amino]etil]fenil]-2-hidroxi-3-nitrobenzamida;



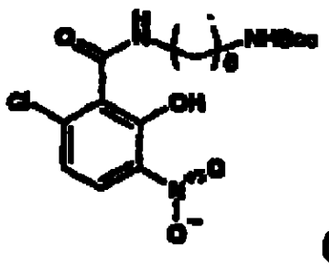
(IV)

3-amino-6-cloro-*N*-[4-[2-[[(1,1-dimetiletoxi)carbonil]amino]etil]fenil]-2-hidroxibenzamida;



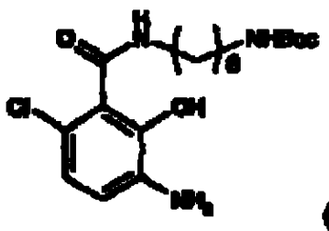
(V)

2,6-dicloro-*N*-[6-[[(1,1-dimetiletoxi)carbonil]amino]hexil]-3-nitrobenzamida:



(VI)

6-cloro-*N*-[6-[[(1,1-dimetiletoxi)carbonil]animo]hexil]-2-hidroxi-3-nitrobenzamida;



(VII)

3-amino-6-cloro-*N*-[6-[[(1,1-dimetiletoxi)carbonil]amino]hexil]-2-hidroxibenzamida.

Se retiraron los folios del 110 al 113
de extracto para publicación y tarjetas ~~de o~~ para
archivo temático y de propietario

13-09-02

[redacted]

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S.A.

Item	Expediente No		No de Folio
		No de unidades	√
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO	1	✓
10	OTROS:		

Observaciones: Contiene orle Final

109

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 1/7

Radicación no 00- 84288

Concepto Técnico no 1259 Clasificación Internacional de Patentes: A 61 K 31/17 // 31/16 // 3105

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

SI [✓]	NO [ ]	Contiene un resumen de la invención (Art.26-e).
SI [✓]	NO [ ]	Contiene el título o nombre de la invención (Art.27-d).
SI [✓]	NO [ ]	Contiene la descripción de la invención (Art.26-b).
SI [✓]	NO [ ]	NO ES APLICABLE [ ] Contiene los dibujos necesarios para comprender la invención (Art.26-d)
SI [✓]	NO [ ]	Contiene una o más reivindicaciones. (Art.26-c).
SI [ ]	NO [ ]	NO ES APLICABLE [✓] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
SI [ ]	NO [ ]	NO ES APLICABLE [✓]Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-l).
SI [ ]	NO [✓]	La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
SI [✓]	NO [ ]	La prioridad coincide con la materia reivindicada.
SI [✓]	**NO [ ]**	**CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI [✓] NO [ ] ver hoja(s) anexa(s)

EXAMINADOR TÉCNICO
202049

Bogotá D. C., Septiembre 16 de 2002

Concepto Técnico no 1259

Observaciones

Se anexó nuevo título en el folio 57

EXAMINADOR TÉCNICO
202049

Bogotá D. C., 16 de septiembre de 2002

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

Industria y Comercio
SUPERINTENDENCIA

14

Folio 119

2020
Bogotá, D.C.

Doctor(a)
GERMAN CASTILLO GRAU
Apoderado(a)

REFERENCIA: Radicación No. 00- 84288
Trámite 002
Evento 001
Actuación 416
Oficio No. 1913
Folios 001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la comunidad andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá, D.C., a los 02 DIC. 2002

ALIX CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Bogotá, D.C., NOV-2003 El extracto de esta solicitud fue publicado en el número 527 de la Gaceta de Propiedad Industrial, de fecha 30-04-2003 . El término hábil señalado por la ley expiró 29-07-2003 el y SI__NO_X se presentaron oposiciones por parte de terceros.

202049

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

112

RADICACIÓN: 0-84288 **EDICTO No. 19907**

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 34303 de 28-NOV-2003. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Declarar abandonada la solicitud de privilegio de patente de invención contenida en el expediente de la referencia.

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Germán Castillo Grau, o a quien haga sus veces, quien actúa como 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. 2003

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIME [illegible] 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.

Secretaria General Ad-Hoc 31-DIC-2003 Dfo **Este edicto se desfija hoy 16-ENE-2004 a las cinco (5:00 p.m.)** Dfo
Secretaria General Ad-Hoc
EDICTO No. 19907