Señor Jefe

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá, D.C.

RE: Expediente No. 01 23.846

Solicitud de patente

SMITHKLINE BEECHAM CORPORATION

Código 02 - 01 - 444

En relación con la solicitud contenida en el expediente de la referencia y para dar respuesta a su último oficio proferido dentro del mismo, con el presente escrito acompaño:

1. Copia certificada su conformidad por la administración que la recibió, de la solicitud estadounidense No. 60/192,132 del 24 de Marzo de 2000, de la cual se reivindica prioridad.

2. Documento en que consta la cesión del derecho a la patente, otorgado por los inventores a la sociedad solicitante, debidamente firmado, autenticado ante Notario Público y legalizado por Apostilla.

115 TH9

Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 01023846 00000002 Folios: 40
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Tramite : 002 PATENTES D 1 REGISTRO/ 4AA REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 1 - 30,880
FECHA : MAYO 17 DE 2001

C O P I A

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

DE[illegible]TANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4067608	17/05/2001	1,697,716.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
263	50005-01-01 SOLICITUDES	9 POR PALABRA ADICIONAL (A PARTIR D	142,020.00
		TOTAL : $	142,020.00

SON: CIENTO CUARENTA Y DOS MIL VEINTE PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
e-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C.,Colombia

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3. La dirección del solicitante, o sea, la sociedad Smithkline Beecham Corporation, se encuentra localizada en One Franklin Plaza, Filadelfia, Estado de Pennsylvania, Estados Unidos de América.

4. Comprobante de pago por concepto de doscientas sesenta y tres (263) palabras adicionales en exceso a partir de la 150 en el extracto para publicación de la solicitud, Recibo No. 30.880/04

Le solicito se sirva agregar este escrito y sus anexos al expediente.

De Usted atentamente,

GERMAN CASTILLO GRAU

T.P.#2978 del C.S.J.

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APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: United States of America
2. This public document has been signed by **Deborah Ann Spearman**
3. acting in the capacity of **Notary Public, Montgomery County**
4. bears the seal/stamp **Deborah Ann Spearman, Notary Public, Commonwealth of Pennsylvania**

Certified

5. at Harrisburg, Pennsylvania
6. The 26th day of March, 2001
7. by Kim Pizzingrilli, Secretary of the Commonwealth of Pennsylvania
8. No. C106896
9. Seal/Stamp
10. Signature:

Kim Pizzingrilli

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P51116

Colombia

118 T2

Insert here full name and address of inventor	El abajo firmado	The undersigned Michael R. Palovich of 805 Mill Grove Drive, Norristown, Pennsylvania 19403, a citizen of the United States of America; Katherine L. Widdowson of 1047 Old Valley Forge Road, King of Prussia, Pennsylvania 19406, a citizen of Canada; and Hong Nie of 1300 Fayette Street, Apt. 149, Conshohocken, Pennsylvania 19428, a citizen of China
Leave blank		
	nombra por el presente al Dr. Pedro Castillo Pineda, y/o Dr. Germán Castillo Grau, y/o Dr. Alvaro Castillo Grau, y/o Dr. Fernando Pérez Caballero	hereby appoints Dr. German Castillo Grau, and/or Dr. Alvaro Castillo Grau, and/or Luis Felipe Castillo Gibsone
Title of Invention	domiciliados en Bogotá República de Colombia, con dirección en la carrera 6a. No. 11-87, Oficina No. 206 de la misma ciudad, como su representante con poder amplio y suficiente, incluyendo el de recibir notificaciones y nombrar apoderados judiciales y extra-judiciales, para solicitar y obtener de las oficinas y autoridades nacionales Patentes de Invención para	domiciled in Carrera 13 N° 37-43 Piso 12 in Bogotá Colombia as attorney with ample and sufficient power, including that of receiving notifications and appointing judicial and extra-judicial attorneys, to apply for and obtain from the national offices and authorities Patent of invention for "IL-8 RECEPTOR ANTAGONISTS"
Name and adress of assignee	cuyo título deberá extenderse a	to be issued in the name of SMITHKLINE BEECHAM CORPORATION of One Franklin Plaza, Philadelphia, Pennsylvania 19103, United States of America
Amount of consideration, if any	a quien ha cedido todos sus derechos a la invencion anteriormente citada en cuanto se refiere al territorio de Colombia, sin restriccion de ninguna clase, mediante el pago de que declara haber recibido. El cesionario firma también el presente en prueba de aceptación de la cesión y nombra igualmente al expresado apoderado como su representante en Bogotá con iguales facultades, y para dar ante dichas oficinas y autoridades todos los pasos necesarios al objeto indicado: elevar solicitudes, declaraciones, reclamos; formular y firmar descripciones, enmiendas y apelaciones; pagar todos los impuestos y cuotas y efectuar toda clase de pagos determinados por la ley y retirar los mismos si fuere necesario: recibir todos los documentos y valores dando el descargo respectivo: desistir y percibir, llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyere conducentes al resguardo de los intereses del mandante, quien ratifica y confirma por el presente todo cuanto hicire legalmente dicho apoderado en virtud del presente poder, con plena facultad de sustitución y renovación y de nombrar apoderados judiciales y extra-judiciales y recibir notificaciones.	to whom assignment has been made of all rights and titles on said invention for the territory of Colombia, without any restriction whatsoever, the consideration for said assignment being the sum of receipt whereof is hereby acknowledged. The assignee also signs this document in acknowledgement of acceptance of said assignment and hereby appoints the above mentioned attorney as his representative in Bogotá with the same faculties; and to take all necessary steps before said offices and authorities for the purpose stated above, to file applications, declarations and claims; to draw and sign specifications, amendments and appeals; to pay all fees and installments and to make all payments required by law and withdraw the same if necessary; to receive all documents and securities issuing receipts therefor, to desist and to receive; to fulfill all other requirements and finally, to use all means which said attorney shall deem proper for the safe guard of the interests of the constituent, who hereby ratifies and confirms all and whatsoever the said attorney shall lawfully do by virtue of these present with full powers of substitution and to receive notifications and to appoint extra-judicial or judicial attorneys.
Place and date of execution		Given and signed at King of Prussia, PA, USA
	Michael R. Palovich Katherine L. Widdowson Hong Nie	SMITHKLINE BEECHAM CORPORATION BY Stephen Venetianer Vice President, Pharmaceuticals Corporate Intellectual Property
Notarize both inventor's and applicant's signature.		Le declaración Notarial a la vuelta Notarial acknowledgment on other side
Legalize by Colombian Consular Officer		

F

DECLARACION NOTARIAL
(Individuals)

A los días del mes de 2001 compareci personalmente ante mi Notario Público

a quien(es) doy fe de conocer y me consta que es (son) la(s) persona(s) descrita(s) y firmante(s) del documento que precede, declarando ante mi que otorga(n) el mismo para los fines que en él se expresan.

El Notario Público,

NOTARIAL CERTIFICATE
(Individual)

On this 16th day of March, 2001 personally appeared before me, a Notary Public, **Michael R. Palovich, Katherine L. Widdowson, and Hong Nie** to me known, and known to me to be the person(s) described in and who executed the foregoing document, and he (they) duly acknowledged to me that he (they) executed same for the uses and purposes therein expressed.

Deborah Ann Spearman
Notary Public

Notarial Seal
Deborah Ann Spearman, Notary Public
Upper Merion Twp. Montgomery County
My Commission Expires Jan. 10, 2004
Member, Pennsylvania Association of Notaries

(Sociedades)

El infrascrito Notario certifica: que la(s) firma(s) que antecede(n) y dice(n).....
es (son) auténtica(s); que el (los) signatario(s) es (son)

de

que tiene(n) facultad para otorgar este poder; y que dicha compañía exists y está domiciliada en

conforme a las leyes de

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo ello da fe.

Dado y firmado en

a

El Notario Público,

(Corporations)

The undersigned Notary Public certifies: that the preceding signature(s) reading Stephen Venetianer is (are) authentic(s); that the signer(s) is (are) Vice President, Pharmaceuticals of **SMITHKLINE BEECHAM CORPORATION**

and that he (they) is (are) empowered to grant this power; and that said company exists and is domiciled at One Franklin Plaza, Philadelphia, Pennsylvania 19103, United States of America in accordance with the laws of the Commonwealth of Pennsylvania.

All the foregoing facts are known to the Notary who examined the respective documents, to which he, the Notary attests.

Granted and signed in King of Prussia, Pennsylvania, United States of America on this 16th day of March, 2001.

Deborah Ann Spearman
Notary Public

Notarial Seal
Deborah Ann Spearman, Notary Public
Upper Merion Twp. Montgomery County
My Commission Expires Jan. 10, 2004
Member, Pennsylvania Association of Notaries

PA 386343

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 12, 2001

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: ***60/192,132***
FILING DATE: ***March 24, 2000***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

W. MONTGOMERY
Certifying Officer

3-27-.00

A/PROV #120

"EXPRESS MAIL CERTIFICATE"

"Express Mail" Mailing Label Number: EL421195745US

Date Of Deposit: 24 March 2000

I Hereby Certify That This Paper Or Fee Is Being Deposited With The United States Postal Service "Express Mail Post Office To Addressee" Service Under 37 CFR 1.10 On The Date Indicated Above And Is Addressed To: Assistant Commissioner for Patents, Washington, D.C. 20231.

Name Of Person Mailing Paper Or Fee

(Type Or Print) Susan H. Gates

Signature: Susan H. Gates

JC553 U.S. PTO 03/24/00

JC553 U.S. PTO 60/192132 03/24/00

PROVISIONAL APPLICATION COVER SHEET

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

Docket No.	P51116P		

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
PALOVICH	Michael	R.	Norristown, Pennsylvania
WIDDOWSON	Katherine	L.	King of Prussia, Pennsylvania
NIE	Hong		Conshohocken, Pennsylvania

TITLE OF THE INVENTION (280 characters max)

IL-8 RECEPTOR ANTAGONISTS

CORRESPONDENCE ADDRESS

SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property - UW2220
709 Swedeland Road
King of Prussia

Telephone No. 610-270-5019
Facsimile No. 610-270-5090

State	PA	Zip Code	19406-2799	Country	United States of America

ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	53	☐ 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

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: _____.

Respectfully submitted,
Signature: Soma G. Simon
Soma G. Simon

Date: March 24, 00
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.

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IL-8 RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to novel sulfonamide substituted diphenyl thiourea 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); Cassatella 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,

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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.

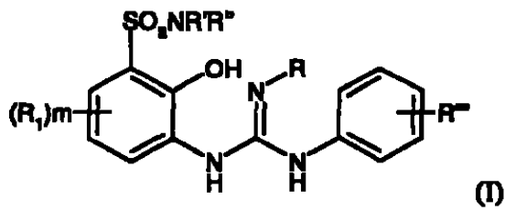
SUMMARY OF THE INVENTION

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 is selected from the group consisting of cyano, OR_{11}, $C(O)NR_{15}R_{16}$, R_{18}, $C(O)OR_{11}$, $C(O)R_{11}$, and $S(O)_2R_{17}$;

R'R" is independently selected from the group consisting of hydrogen, NR_6R_7, OH, OR_a, C_{1-5}alkyl, aryl, arylC_{1-4}alkyl, aryl C_{2-4}alkenyl; cycloalkyl, cycloalkyl C_{1-5} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, and a heterocyclic C_{2-4}alkenyl moiety, all of which moieties may be optionally substituted one to three times independently

by a substituent selected from the group consisting of halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR_9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_tNR_6R_7$, and $NHS(O)_tR_a$; or the two R_b substituents join to form a 3-10 membered ring, optionally substituted and containing, in addition to optionally substituted C_{1-4} alkyl, independently, 1 to 3 NR_a, O, S, SO, or SO_2 moieties, which moieties can be optionally unsaturated;

R''' is selected from the group consisting of Y 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, $(CR_8R_8)qS(O)_tR_a$, $(CR_8R_8)qOR_a$, 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$C(O)OR_{11}$, $(CR_8R_8)qOC(O)R_{11}$, $(CR_8R_8)qNR_4C(O)R_{11}$, $(CR_8R_8)q$ $NHS(O)_tR_{13}$, $(CR_8R_8)q$ $S(O)_tNR_4R_5$, $(CR_8R_8)qC(NR_4)NR_4R_5$, and $(CR_8R_8)q$ $NR_4C(NR_5)R_{11}$; or two Y moieties together form $O-(CH_2)_s-O$ or a 5 to 6 membered saturated or unsaturated ring, such that the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, and heterocyclicalkyl groups may be optionally substituted;

R_1 is independently selected from the group consisting of 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 $C(O)OR_{11}$, $(CR_8R_8)_q$ $C(O)OR_{11}$, $(CR_8R_8)_q$ $OC(O)R_{11}$, $(CR_8R_8)_qNR_4C(O)R_{11}$, $(CR_8R_8)_q$ $C(NR_4)NR_4R_5$, $(CR_8R_8)_q$ $NR_4C(NR_5)R_{11}$, $(CR_8R_8)_q$ $NHS(O)_tR_{13}$, and $(CR_8R_8)_q$ $S(O)_tNR_4R_5$; or two R_1 moieties together form $O-(CH_2)_sO$ or a 5 to 6 membered saturated or unsaturated ring, wherein the alkyl, aryl, arylalkyl, heteroaryl, and heterocyclic moieties may be optionally substituted.

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.

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; $NHC(O)R_4$; $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$; $NHS(O)_2R_{20}$, 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; $S(O)_mC_{1-10}$ 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.

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:

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N",N"dimethylaminosulfonyl)phenyl] cyanoguanidine;

N-[4-chloro-2-hydroxy-3- (N",N"-dimethylaminosulfonyl)phenyl]-N'-(2,3-dichlorophenyl) cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-phenyl-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[R-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[R-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(4-thiomorpholinylaminosulfonyl)phenyl] cyanoguanidine;

N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) propylguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(4-oxidothiomorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2,3-chlorophenyl)-N'-[4-chloro-2-hydroxy-3-(4-oxidothiomorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-methylpiperazino)amino sulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-methylpiperazino)amino sulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-ethylmorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-ethylmorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-{4-chloro-2-hydroxy-3-[N"-ethyl-2-(2-ethylpyrrolidino)]amino sulfonylpheny} cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-{4-chloro-2-hydroxy-3-[N"-ethyl-2-(2-ethylpyrrolidino)]amino sulfonylpheny} cyanoguanidine;

N-(2-bromophenyl)-N'-{4-chloro-2-hydroxy-3-[S-(+)-(2-carboxy)pyrrolidin-1-yl]amino sulfonylpheny} cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-{4-chloro-2-hydroxy-3-[S-(+)-(2-carboxy)pyrrolidin-1-yl]amino sulfonylpheny} cyanoguanidine;

N-(2-bromo-3-fluorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] cyanoguanidine;

N-(2-phenoxyphenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] cyanoguanidine; and

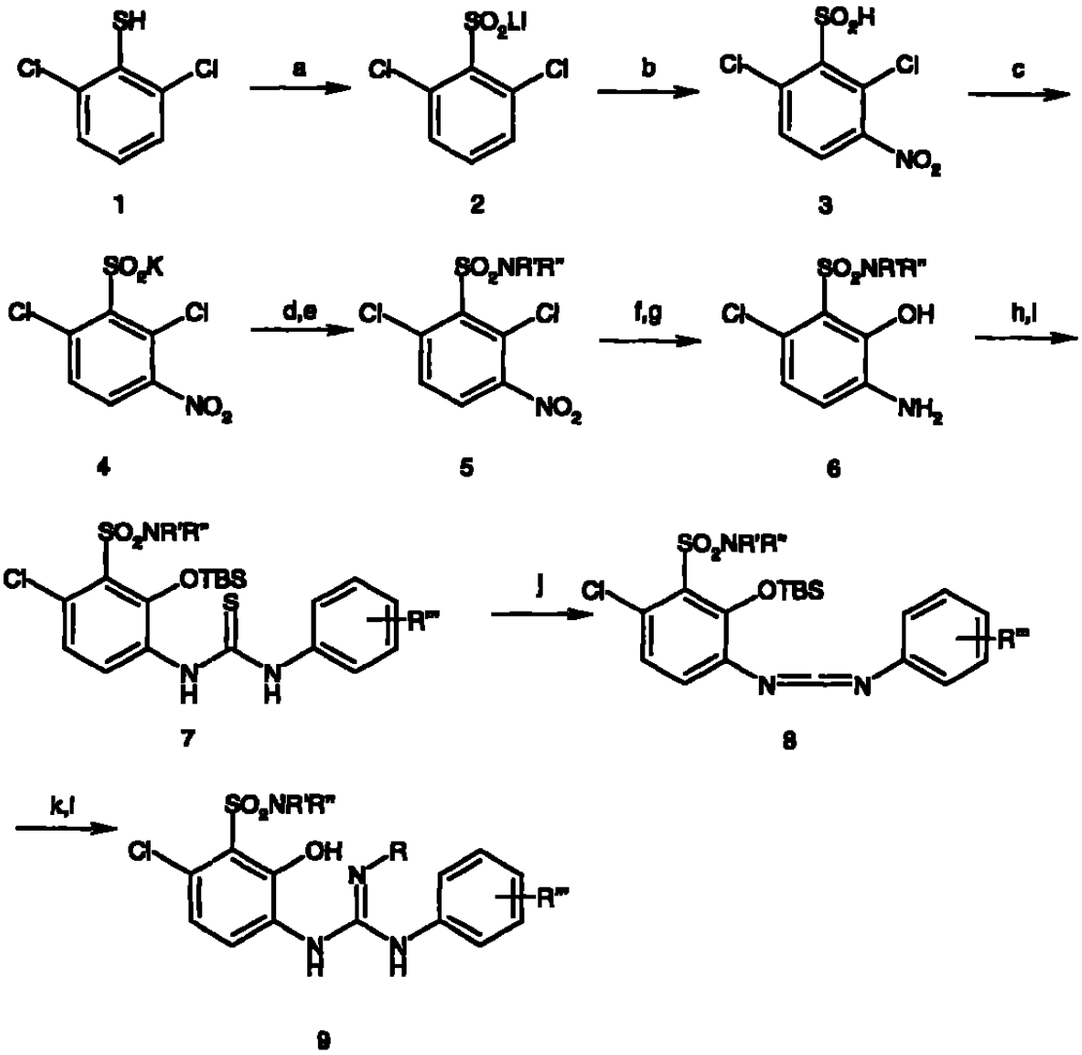
N-(2-benzoxyphenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] cyanoguanidine;

or a pharmaceutically acceptable salt thereof.

METHODS OF PREPARATION

The compounds of Formulas (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below.

Scheme 1



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Scheme 1

a) i) NCS, AcOH, H_2O, ii) LiOH, MeOH b) H_2SO_4, HNO_3 c) KOH, MeOH d) PCl_5,$POCl_3$ e) NR'R"H, Et_3N f) NaH, H_2O g) Pd/C, H_2 h)RCNO, DMF i) TBSCl, Imidazole j) MsCl, Et_3N k) NH_2CN, Hunig's base l) CsF/TBAF, MeOH/THF

The desired 4-chloro-N-(3-sulfonamido-2-hydroxyphenyl)-N"-phenyl cyanoguanidine can be synthesized from the commercially available 2,6-dichloro thiophenol using procedure elaborated in scheme 1. The thiol can be oxidized to the sulfonyl halide using a halogenating agent such as NCS, NBS, chlorine or bromine in the presence of a protic solvent such as alcohol, acetic acid or water. The sulfonyl halide can be hydrolyzed by using a metal hydroxide such as lithium or potassium hydroxide to form the corresponding sulfonic acid salt.

The sulfonic acid salt can then be nitrated under nitration conditions such as nitric acid in a solvent of strong acid such as sulfuric acid to form the nitro phenyl sulfonic acid 3-scheme 1. The sulfonic acid 3-scheme 1 can be converted to the sulfonamide 5-scheme 1 using a three step procedure involving the formation of the metal salt using a base such as potassium hydroxide, sodium hydride or sodium carbonate to form 4-scheme 1. The sulfonic acid salt is then converted to the sulfonyl chloride using PCl_5 with $POCl_3$ as a solvent. The sulfonyl chloride can then be converted to the corresponding sulfonamide using the desired amine HNR'R" in triethyl amine at temperatures ranging from –78 °C to 25 °C to form the corresponding sulfonamide 5-scheme 1.

The chlorine ortho to the nitro group can be selectively hydrolyzed using sodium hydride/ water in THF at room temperature to form the phenol. The nitro can be reduced by conditions well known in the art such as hydrogen and palladium on carbon to form the corresponding aniline 6-scheme 1. The aniline can then be coupled with a commercially available thioisocyanate to form the desired thiourea.

The phenol in thiourea can be protected with TBSCl to form the corresponding compounds 7-scheme 1. The protected thiourea can be converted to the corresponding carbodiimide 8-scheme 1 using methanesulfonyl chloride and triethyl amine at 0°C. The carbodiimide can then be converted to the corresponding

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protected cyanoguanidine using cyanamide and Hunig's base, followed by desilylation with CsF or TBAF to form the desired the cyanoguanidine 9-scheme1.

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 are highest available purity and all reactions run under anhydrous conditions in an argon 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.

Example 1& 2

Preparation of N-[4-chloro-2-hydroxy-3- (N",N"-dimethylaminosulfonyl) phenyl]-N'-(2,3-dichlorophenyl) cyanoguanidine and N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N",N"dimethylaminosulfonyl)phenyl] cyanoguanidine

2,6-Dichloro-3-nitrobenzenesulfonic acid

Lithium hydroxide hydrate (8.96 g, 0.214mol) was added to a solution of 2,6-dichlorobenzenesulfonyl chloride (35 g, 0.146mol) in MeOH (300mL) and the reaction was allowed to stir at room temperature for 16 hr. The reaction mixture was filtered to remove suspended solids and then concentrated. The resulting solid was dried *in vacuo* overnight to remove any residual MeOH. The solid was then dissolved in H_2SO_4 (300mL) and chilled in an ice bath. A solution of H_2SO_4 (35mL) and HNO_3 (70 %, 10.7 mL) was slowly added to the above reaction over 90 min. The reaction was allowed to warm up to room temperature overnight and then slowly poured into ice water (1200mL) and extracted with EtOAc. The combined

organic layers were dried ($MgSO_4$) and concentrated to yield 2,6-dichloro-3-nitrobenzenesulfonic acid (37.38 g, 96%) as the dihydrate. EI-MS (m/z) 270 (M).

2,6-Dichloro-3-nitrobenzenesulfonyl chloride

Potassium hydroxide (11.54 g, 0.206mol) was added to a solution of 2,6-dichloro-3-nitrobenzenesulfonic acid dihydrate (37.38 g, 0.137mol) in MeOH (500mL) and the reaction was allowed to stir at room temperature for 14 hr. The reaction mixture was concentrated and the resulting solid was dried *in vacuo* overnight. To this was added PCl_5 (29.60 g, 0.142mol) followed by $POCl_3$ (400mL) and the mixture was refluxed overnight. The reaction was then cooled to room temperature and concentrated. The resulting mixture was taken up in EtOAc and chilled in an ice bath. Ice chunks were slowly added to the reaction mixture to quench any leftover PCl_5. When bubbling ceased, water was added and the reaction mix was extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated to yield 2,6-Dichloro-3-nitrobenzenesulfonyl chloride (31.4 g, 79%). ^1H NMR (DMSO-d_6) δ 7.88 (d, 1H), 7.75 (d, 1H).

The following is the general procedure for sulfonamide formation:

N,N-Dimethyl-2,6-dichloro-3-nitrobenzenesulfonamide

Into a solution of 2,6-dichloro-3-nitrobenzenesulfonyl chloride (200 mg, 0.69 mmol) in 15 mL of dichloromethane at –78°C was added dropwise a solution of dimethylamine (2.0 M in MeOH, 0.345mL, 0.69 mmol) and triethylamine (0.14 mL, 1.04 mmol) in 10 mL of dichloromethane. The mixture was warmed to room temperature and stirred for 16 hours. The mixture was acidified to pH >1 with 1N aq. HCl, then extracted with ethyl acetate. The combined organic layer was then concentrated to give the crude material. Column chromatography on silica gel, eluting with ethyl acetate/hexane (30/70, v/v/), gave the desired (240mg, 70 %). EI-MS (m/z) 298 (M).

The following is the general procedure for the hydrolysis of dichlorosulfonamide to phenol:

N, N-Dimethyl-6-chloro-2-hydroxy-3-nitrobenzenesulfonamide

A mixture of N, N-dimethyl-2,6-dichloro-3-nitrobenzenesulfonamide (2.64 g, 8.83 mmol), 60% sodium hydride (1.06 g, 26.5 mmol) and water (191 mg, 10.6 mmol) was heated to 35 °C while kept under argon atmosphere for 16 hours. The solvent was evaporated. when The reaction was almost complete as indicated by ^{1}H NMR. The residue was diluted with ethyl acetate and washed with 1N aq. HCl. The solvent was concentrated to give the crude material. Column chromatography on silica gel, eluting with ethyl acetate/hexane/acetic acid (40/58/2, v/v/v), gave the desired product (2.3 g, 93%). EI-MS (m/z) 279.5 (M$^+$).

The following is the general procedure for the hydrogenation of nitro compound to aniline:

N, N-Dimethyl-3-amino-6-chloro-2-hydroxybenzenesulfonamide

To a solution of N, N-dimethyl-6-chloro-2-hydroxy-3-nitrobenzenesulfonamide (2.3 g, 8.2 mmol) in ethyl acetate, was added 10% Pd/C (2.0 g). The mixture was flushed with argon, and then stirred under a hydrogen atmosphere at balloon pressure for 3 hours at room temperature. The mixture was filtered through celite and the celite was washed with methanol. The solvent was evaporated to give the desired product (2.0 g, 97%). EI-MS (m/z) 249.5 (M$^+$).

The following is the general procedure for thiourea formation:

N-[4-Chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2,3-dichlorophenyl) thiourea

A solution of N,N-dimethyl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (356 mg, 1.42 mmol) and 2,3-dichlorophenylisothiocyanate (318 mg, 1.57 mmol) in 1.0 mL of N,N-dimethylformamide was stirred at room temperature for 3 hours. Purification by column chromatography on silica gel, eluting with ethyl acetate/hexane (30/70, v/v) to give the desired product (440 mg, 68 %). EI-MS (m/z) 455.5 (M$^+$).

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N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) thiourea

A solution of N,N-dimethyl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (50 mg, 0.2 mmol) and 2-bromophenylisothiocyanate (43 mg, 0.2 mmol) in 0.5 mL of N,N-dimethylformamide was stirred at room temperature for 3 hours. Purification by column chromatography on silica gel, eluting with ethyl acetate/hexane (30/70, v/v) to give the desired product (66 mg, 74 %). EI-MS (m/z) 465.5 (M^+).

The following is the general procedure for protected phenyl thiourea formation:

N-[4-Chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2-bromophenyl) thiourea

To a solution of N-[4-chloro-2-hydroxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2-bromophenyl) thiourea (500 mg, 1.07 mmol) in THF (20 mL), *tert*-butyldimethylsilyl chloride (810 mg, 5.35 mmol) and imidazole (144 mg, 2.14 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours. Then it was partitioned between ethyl acetate and water. The combined organic phase was dried and concentrated. Chromatography of the residue on silica gel (30%Ethyl acetate/Hexane) gave desired product (240 mg, 40%) and recovered starting material (280 mg). EI-MS m/z 580 (M^+).

N-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2,3-dichlorophenyl) thiourea

To a solution of N-[4-chloro-2-hydroxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2,3-dichlorophenyl) thiourea (440 mg, 1.07 mmol) in THF (20 mL), *tert*-butyldimethylsilyl chloride (730 mg, 4.85 mmol) and imidazole (132 mg, 1.94 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours. Then it was partitioned between ethyl acetate and water. The combined organic phase was dried and concentrated. Chromatography of the residue on silica gel (30%Ethyl acetate/Hexane) gave desired product (270 mg, 50%). EI-MS m/z 570 (M^+).

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The following is the general procedure for carbodiimide formation:

N-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2-bromophenyl)carbodiimide

To a solution of N-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2-bromophenyl) thiourea (240 mg, 0.42 mmol) in dichloromethane (10 mL) at 0°C, methanesulfonyl chloride (0.065 mL, 0.84 mmol) and triethylamine (0.12 mL, 0.84 mmol) were added. 4-Dimethylaminopyridine was added as a catalyst. The reaction mixture was stirred at 0°C for 1 hour, then it was partitioned between dichloromethane and water. The combined organic phase was dried and concentrated to give the desired product (266.2 mg, crude). ^{1}H NMR ($CDCl_3$) δ 0.4 (s, 6H), 1.09 (s, 9H), 2.86 (s, 6H), 7.06 (d, 2H), 7.1-7.37 (m, 4H).

N-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2,3-dichlorophenyl)carbodiimide

To a solution of N-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2,3-dichlorophenyl) thiourea (270 mg, 0.45 mmol) in dichloromethane (10 mL) at 0°C, methanesulfonyl chloride (0.07 mL, 0.9 mmol) and triethylamine (0.13 mL, 0.9 mmol) were added. 4-Dimethylaminopyridine was added as a catalyst. The reaction mixture was stirred at 0°C for 1 hour, then it was partitioned between dichloromethane and water. The combined organic phase was dried and concentrated to give the desired product (270 mg, crude). ^{1}H NMR ($CDCl_3$) δ 0.47 (s, 6H), 1.05 (s, 9H), 2.9 (s, 6H), 7.08 (d, 1H), 7.12 (d, 1H), 7.2 (t, 1H), 7.31 (m, 2H).

The following is the general procedure for cyanoguanidine formation:

N-[4-chloro-2-hydroxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2-bromophenyl) cyanoguanidine

To a solution of N-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2-bromophenyl)carbodiimide (266 mg, 0.49 mmol) in acetonitrile (5 mL) at room temperature, cyanamide (83 mg, 1.96 mmol) and N,N-diisopropylethylamine (76 mg, 0.59 mmol) was added. The reaction

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mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was diluted with a mixture of THF (3mL) and methanol (1 mL). Cesium fluoride (90 mg, 0.59 mmol) was added at 0°C. The reaction mixture was stirred at 0°C for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by Gilson HPLC to give the desired product (70 mg, 30 %). EI-MS m/z 473.75(M^+).

N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2,3-dichlorophenyl) cyanoguanidine

To a solution of N-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N",N"-dimethylaminosulfonyl)phenyl]-N'-(2,3-dichlorophenyl)carbodiimide (270 mg, 0.47 mmol) in acetonitrile (5 mL) at room temperature, cyanamide (79 mg, 1.88 mmol) and N,N-diisopropylethylamine (76 mg, 0.56 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was diluted with a mixture of tetrahydrofuran (3mL) and methanol (1 mL). Cesium fluoride (86 mg, 0.56 mmol) was added at 0°C. The reaction mixture was stirred at 0°C for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by Gilson HPLC to give the desired product (98 mg, 48 %). EI-MS m/z 473.75(M^+).

Example 3, 4 & 5

Preparation of N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine and N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine

S-(+)-N-(2-Methoxymethyl)pyrrolidin-1-yl -2,6-dichloro-3-nitrobenzenesulfonamide

Following the general procedure for sulfonamide formation outlined in example 1,

6-dichloro-3-nitrobenzenesulfonyl chloride (1.0 g, 3.44 mmol), (S)-(+)-2(methyoxymethyl)pyrrolidine (0.476 mL, 4.13 mmol) and triethylamine (0.72 mL, 5.16 mmol) were reacted to form the desired product (1.15 g, 91 %). EI-MS m/z 368 (M^+).

S-(+)-N-(2-Methoxymethyl)pyrrolidin-1-yl-6-chloro-2-hydroxy-3-nitrobenzenesulfonamide

Following the general hydrolysis procedure outlined in example 1, S-(+)-N-(2-methoxymethyl)pyrrolidin-1-yl-2,6-dichloro-3-nitrobenzenesulfonamide (1.15 g, 3.12 mmol), 60% sodium hydride (374 mg, 9.36 mmol) and water (73 mg, 4.02 mmol) were reacted to form the desired product (1.0 g, 91 %). EI-MS m/z 349.1 (M^+).

S-(+)-N-(2-Methoxymethyl)pyrrolidin-1-yl-3-amino-6-chloro-2-hydroxybenzenesulfonamide

Following the general hydrogenation procedure outlined in example 1, S-(+)-N-(2-methoxymethyl)pyrrolidin-1-yl-6-chloro-2-hydroxy-3-nitrobenzenesulfonamide (1.0 g, 2.86 mmol) was reduced with hydrogen and Pd/C (600 mg) to form the desired product (0.9 g, 98 %). EI-MS m/z 319.1 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, S-(+)-N-(2-methoxymethyl)pyrrolidin-1-yl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (260 mg, 0.85 mmol) and 2-bromophenylisothiocyanate (182 mg, 0.85 mmol) were coupled to form the desired thiourea (231 mg, 53%). EI-MS m/z 535.1 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl) pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, S-(+)-N-(2-methoxymethyl)pyrrolidin-1-yl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (407 mg, 1.27 mmol) and 2,3-

dichlorophenylisothiocyanate (285 mg, 1.4 mmol) were coupled to form the desired thiourea (370 mg, 54%). EI-MS m/z 525.1 (M^+).

N-Phenyl-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, S-(+)-N-(2-methoxymethyl)pyrrolidin-1-yl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (310 mg, 0.97 mmol) and phenylisothiocyanate (144 mg, 1.07 mmol) were coupled to form the desired thiourea (210 mg, 54%). EI-MS m/z 456 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (230 mg, 0.44 mmol), *tert*-butyldimethylsilyl chloride (332 mg, 2.2 mmol) and imidazole (60 mg, 0.88 mmol) were reacted to form the desired product (136 mg, 48%). EI-MS m/z 650 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (370 mg, 0.71 mmol), *tert*-butyldimethylsilyl chloride (370 mg, 0.71 mmol) and imidazole (97 mg, 1.42 mmol) were reacted to form the desired product (187 mg, 41%). EI-MS m/z 640.2 (M^+).

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N-Phenyl-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-phenyl-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (210 mg, 0.46 mmol), *tert*-butyldimethylsilyl chloride (349 mg, 2.3 mmol) and imidazole (63 mg, 0.92 mmol) were reacted to form the desired product (125 mg, 41%). EI-MS m/z 571 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (136 mg, 0.21 mmol), methanesulfonyl chloride (0.03 mL, 0.42 mmol) and triethylamine (0.06 mL, 0.42 mmol) were reacted to form the desired product (120 mg, 93%). ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 6H), 1.01 (s, 9H), 1.72 (m, 4H), 3.25 (s, 3H), 3.3 (m, 2H), 3.45 (m, 2H), 4.15 (m, 1H), 7.10 (d, 2H), 7.2 (d, 1H), 7.3 (m, 1H), 7.39 (d, 1H), 7.6 (d, 1H).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (187 mg, 0.3 mmol), methanesulfonyl chloride (0.05 mL, 0.6 mmol) and triethylamine (0.08 mL, 0.6 mmol) were reacted to form the desired product (160 mg, 90%). ^{1}H NMR ($CDCl_3$) δ 0.32 (s, 6H), 1.01 (s, 9H), 1.35 (m, 4H), 3.24 (s, 3H), 3.42 (m, 4H), 4.14 (m, 1H), 7.10 (d, 1H), 7.12 (d, 1H), 7.2 (t, 1H), 7.29 (d, 1H), 7.32 (d, 1H).

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N-Phenyl-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-phenyl-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (125 mg, 0.22 mmol), methanesulfonyl chloride (0.04 mL, 0.44 mmol) and triethylamine (0.06 mL, 0.44 mmol) were reacted to form the desired product (125 mg, crude). ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 6H), 1.04 (s, 9H), 1.35 (m, 4H), 3.24 (s, 3H), 3.42 (m, 4H), 4.14 (m, 1H), 7.06 (d, 1H), 7.16 (d, 1H), 7.19 (m, 2H), 7.25 (d, 1H), 7.35 (t, 2H).

N-(2-Bromophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine

Following the general procedure for cyanoguanidine formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide (152 mg, 0.25 mmol), cyanamide (42 mg, 1.0 mmol) and N,N-diisopropylethylamine (39 mg, 0.3 mmol) were reacted, followed by desilylation with Cesium fluoride (45.6 mg, 0.3 mmol) to form the desired product (33 mg, 25%). EI-MS m/z 543.6 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine

Following the general procedure for carbodiimide formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] carbodiimide (160 mg, 0.26 mmol), cyanamide (44 mg, 1.04 mmol) and N,N-diisopropylethylamine (41 mg, 0.31 mmol) were reacted, followed by desilylation with Cesium fluoride (48 mg, 0.31 mmol) to form the desired product (35 mg, 25%). EI-MS m/z 532 (M^+).

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N-Phenyl-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine

Following the general procedure for carbodiimide formation outlined in example 1, N-phenyl-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] carbodiimide (125 mg, 0.23 mmol), cyanamide (38.6 mg, 0.92 mmol) and N,N-diisopropylethylamine (36.2 mg, 0.28 mmol) were reacted, followed by desilylation with Cesium fluoride (42 mg, 0.28 mmol) to form the desired product (38 mg, 35%). *LC-MS* m/z 462.2.

Example 6& 7

Preparation of N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[R-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine and N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[R-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine

R-N-(2-Methoxymethyl)pyrrolidin-1-yl-2,6-dichloro-3-nitrobenzenesulfonamide

Following the general procedure for sulfonamide formation outlined in example 1, 6-dichloro-3-nitrobenzenesulfonyl chloride (2.0 g, 6.89 mmol), (R)–2-(methyoxymethyl)pyrrolidine (0.783 mL, 8.27 mmol) and triethylamine (1.44 mL, 10.34 mmol) were reacted to form the desired product (1.69 g, 66 %). EI-MS m/z 368 (M).

R-N-(2-methoxymethyl)pyrrolidin-1-yl-6-chloro-2-hydroxy-3-nitrobenzenesulfonamide

Following the general hydrolysis procedure outlined in example (R)-N-(2-methoxymethyl)pyrrolidin-1-yl -2,6-dichloro-3-nitrobenzenesulfonamide (2.16 g, 5.85 mmol), 60% sodium hydride (702 mg, 17.55 mmol) and water (137 mg, 7.6 mmol) were reacted to form the desired product (2.0 g, 97 %). EI-MS m/z 349.1 (M).

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(R)-N-(2-Methoxymethyl)pyrrolidin-1-yl-3-amino-6-chloro-2-hydroxybenzenesulfonamide

Following the general hydrogenation procedure outlined in example 1, (R)-N-(2-methoxymethyl)pyrrolidin-1-yl-6-chloro-2-hydroxy-3-nitrobenzenesulfonamide (2.0 g, 4.44 mmol) was reduced with hydrogen and Pd/C (1.5 g) to form the desired product (1.75 g, 96 %). EI-MS m/z 319.1 (M^+).

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, (R)-N-(2-methoxymethyl)pyrrolidin-1-yl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (390 mg, 1.21 mmol) and 2-bromophenylthioisocyanate (286 mg, 1.33 mmol) were coupled to form the desired thiourea (462 mg, 71%). EI-MS m/z 535.1 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[(R)-2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, (R)-N-(2-methoxymethyl)pyrrolidin-1-yl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (360 mg, 1.12 mmol) and 2,3-dichlorophenylisothiocyanate (251 mg, 1.23 mmol) were coupled to form the desired thiourea (410 mg, 70%). EI-MS m/z 525.1 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (462 mg, 0.86 mmol), *tert*-butyldimethylsilyl chloride (651 mg, 4.3 mmol) and imidazole (118 mg, 1.73 mmol) were reacted to form the desired product (216 mg, 39%). EI-MS m/z 650 (M^+).

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N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (410 mg, 0.78 mmol), *tert*-butyldimethylsilyl chloride (589 mg, 3.9 mmol) and imidazole (106 mg, 1.56 mmol) were reacted to form the desired product (202 mg, 40%). EI-MS m/z 640.2 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (216 mg, 0.33 mmol), methanesulfonyl chloride (0.05 mL, 0.66 mmol) and triethylamine (0.09 mL, 0.66 mmol) were reacted to form the desired product (200 mg, 97%). %). ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 6H), 1.02 (s, 9H), 1.9 (m, 4H), 3.23 (m, 4H), 3.42 (m, 3H), 4.13 (m, 1H), 7.08 (d, 2H), 7.20 (d, 1H), 7.3 (t, 1H), 7.38 (d, 1H), 7.6 (d, 1H).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] thiourea (202 mg, 0.32 mmol), methanesulfonyl chloride (0.05 mL, 0.64 mmol) and triethylamine (0.09 mL, 0.64mmol) were reacted to form the desired product (190 mg, 99%). ^{1}H NMR ($CDCl_3$) δ 0.34 (s, 6H), 1.04 (s, 9H), 1.4 (m, 2H), 1.8 (m, 2H), 3.15 (s, 3H), 3.25 (m, 2H), 3.43 (m, 2H), 4.13 (m, 1H), 7.09 (d, 2H), 7.12 (d, 1H), 7.19 (t, 1H), 7.3 (d, 1H), 7.34 (d, 1H).

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N-(2-Bromophenyl)-N'-[4-chloro-2-hydroxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine

Following the general procedure for cyanoguanidine formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide (240 mg, 0.39 mmol), cyanamide (66 mg, 1.56 mmol) and N,N-diisopropylethylamine (63 mg, 0.47 mmol) were reacted, followed by desilylation with Cesium fluoride (72 mg, 0.47 mmol) to form the desired product (75 mg, 35%). EI-MS m/z 543.6 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine

Following the general procedure for cyanoguanidine formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-[(R)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] carbodiimide (224 mg, 0.37 mmol), cyanamide (63 mg, 1.48 mmol) and N,N-diisopropylethylamine (60 mg, 0.43 mmol) were reacted, followed by desilylation with Cesium fluoride (67 mg, 0.43 mmol) to form the desired product (70 mg, 36%). EI-MS m/z 533.5 (M^+).

Example 8 & 9

Preparation of N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine and N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine

N-(ethoxycarbonyl)isoxazolidine

To a solution of KOH (6.4g, 0.11mol) and hydroxyurethane (12g, 0.11mol) in ethanol (50mL) was added 1,3–dibromopropane (5.8mL, 0.057mol). The resulting suspension was heated at reflux for 1 hour. After the mixture was cooled to room temperature, an additional portion of KOH (3.2g, 0.055mol) and of dibromopropane (2.9mL, 0.028mol) was added. The mixture was then refluxed for 1 hour, cooled to room temperature, and solvent was evaporated. The residue was suspended in boiling ether three times and filtered. The combined filtrates were dried over sodium sulfate, filtered, and evaporated. A portion of 3g of the crude product was purified

by flush column chromatography (EtOAC/Hexane, gradient elution), yielding 1.18g of N-(ethoxycarbonyl)isoxazolidine. ^{1}H NMR (CDCl3) δ 1.15(t, 3H), 2.15 (q, 2H), 3.55(t, 2H), 3.8 (t, 2H),4.1(q, 2H).

Isoxazolidine hydrochloride

N-(ethoxycarbonyl)isoxazolidine (1.18g, 9.1mmol) was dissolved in aqueous HCl (6N, 7mL)and heated at reflux for 2 hours. After being cooled to room temperature, this solution was washed with ether (3x) and then evaporated affording crude isoxazolidine hydrochloride which was recrystalized from ethanol/ether yielding 0.79 g (80%) of isoxazolidine hydrochloride.^{1}H NMR ($CDCl_3$; CH_3OD), δ 2.5 (q, 2H), 3.55 (t, 2H), 4.2(t, 2H).

(N-Isoxazolidinyl)-2,6-dichloro-3-nitrobenzenesulfonamide

Following the general procedure for sulfonamide formation outlined in example 1, 2,6-dichloro-3-nitrobenzenesulfonyl chloride (1.5 g, 5.2 mmol), isoxazolidine hydrochloride (0.56 g, 5.2 mmol) and triethylamine (2.2 mL, 15.5 mmol) were reacted to form the desired product (1.2 g, 71 %). EI-MS m/z 327 (M^+).

(N-Isoxazolidinyl)-2-hydroxy-6-dichloro-3-nitrobenzenesulfonamide

Following the general hydrolysis procedure outlined in example 1, (N-isoxazolidinyl)-2,6-dichloro-3-nitrobenzenesulfonamide (1.08 g, 3.3 mmol), 80% sodium hydride (0.3 g, 10.0 mmol) and water (72 mg, 4.0 mmol) were reacted to form the desired product (0.79 g, 77 %). EI-MS m/z 309 (M^+).

(N-Isoxazolidinyl)-2-hydroxy-3-amino-6-dichloro-benzenesulfonamide

Following the general hydrogenation procedure outlined in example 1, (N-isoxazolidinyl)-2-hydroxy-6-dichloro-3-nitrobenzenesulfonamide (0.84 g, 2.7 mmol) was reduced with hydrogen and Pd/C (840 mg) to form the desired product (0.75 g crude). EI-MS m/z 279 (M^+).

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N-(2-Bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, (N-isoxazolidinyl)-2-hydroxy-3-amino-6-dichloro-benzenesulfonamide (624 mg, 2.24 mmol) and 2-bromophenylisothiocyanate (528 mg, 2.46 mmol) were coupled to form the desired thiourea (620 mg, 56%). EI-MS m/z 493 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, (N-isoxazolidinyl)-2-hydroxy-3-amino-6-dichloro-benzenesulfonamide (590 mg, 2.11 mmol) and 2,3-dichlorophenylisothiocyanate (474 mg, 2.53 mmol) were coupled to form the desired thiourea (753 mg, 74%). EI-MS m/z 481.75 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] thiourea (726 mg, 1.51 mmol), *tert*-butyldimethylsilyl chloride (1.14 mg, 7.55 mmol) and imidazole (205 mg, 3.02 mmol) were reacted to form the desired product (355 mg, 66%). EI-MS m/z 597.83 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] thiourea (480 mg, 0.79 mmol), methanesulfonyl chloride (0.12 mL, 1.58 mmol) and triethylamine (0.22 mL, 1.58 mmol) were reacted to form the desired product (480 mg, crude). ^{1}H NMR ($CDCl_3$) δ 0.39 (s, 6H), 1.1 (s, 9H), 2.4 (m, 2H), 3.76 (t, 2H), 4.22 (t, 2H), 7.09 (m, 2H), 7.21 (d, 1H), 7.29 (m, 1H), 7.45 (d, 1H), 7.6 (d, 1H).

N-(2-,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] thiourea (355 mg, 0.59 mmol), methanesulfonyl chloride (0.09 mL, 1.18 mmol) and triethylamine (0.16 mL, 1.18 mmol) were reacted to form the desired product (355 mg, crude). ^{1}H NMR ($CDCl_3$) δ 0.38 (s, 6H), 1.03 (s, 9H), 2.4 (m, 2H), 3.77 (t, 2H), 4.22 (t, 2H), 7.12 (d, 1H), 7.16 (t, 1H), 7.26 (d, 1H), 7.31 (d, 1H), 7.40 (d, 1H).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine

Following the general procedure for cyanoguanidine formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] carbodiimide (480 mg, 0.84 mmol), cyanamide (142 mg, 3.36 mmol) and N,N-diisopropylethylamine (130 mg, 1.0 mmol) were reacted, followed by desilylation with Cesium fluoride (153.2 mg, 1.0 mmol) to form the desired product (150 mg, 36%). LC-MS m/z 500.

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine

Following the general procedure for cyanoguanidine formation outlined in example 1, N-(2-,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-isoxazolidinylaminosulfonylphenyl] carbodiimide (355 mg, 0.63 mmol), cyanamide (105 mg, 2.52 mmol) and N,N-diisopropylethylamine (100 mg, 1.26 mmol) were reacted, followed by desilylation with Cesium fluoride (115 mg, 0.76 mmol) to form the desired product (28 mg, 10%). LC-MS m/z 490.

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Example 10 & 11

Preparation of N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] cyanoguanidine and N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl) phenyl] cyanoguanidine

N-(Ethoxycarbonyl)tetrahydroisoxazine

To a solution of KOH (3.34g, 59.6mmol) and hydroxyurethane (6.1g, 58.5mmol) in ethanol (25mL) was added 1,4–dibromobutane (3.5mL, 29.3mmol). The resulting suspension was heated at reflux for 1 hour. After the mixture was cooled to room temperature, an additional portion of KOH (1.65g, 29.4mmol) and of dibromopropane (1.8mL, 15mmol) was added. The mixture was then refluxed for 1 hour, cooled to room temperature, and solvent was evaporated. The residue was suspended in boiling ether three times and filtered. The combined filtrates were dried over sodium sulfate, filtered, and evaporated. A portion of 4g of the crude product was purified by flash column chromatography (EtOAC/Hexane, gradient elution), yielding 1.85g of N-(ethoxycarbonyl)tetrahydroisoxazine. ^{1}H NMR ($CDCl_3$) δ 1.05 (q, 3H), 1.45 (dd, 2H), 1.55 (dd, 2H), 3.4 (t, 2H), 3.7 (t, 2H), 3.95 (q, 2H).

Tetrahydroisoxazine hydrochloride

N-(ethoxycarbonyl)tetrahydroisoxazine (1.85g, 11.6mmol) was dissolved in aqueous HCl (6N, 7.8mL)and heated at reflux for 7 hours. After being cooled to room temperature, this solution was washed with ether (3x) and then evaporated affording crude tetraisoxazine hydrochloride which was recrystalized from ethanol/ether yielding 0.74 g (52%) of tetrahydroisoxazine hydrochloride.^{1}H NMR (CH_3OD) δ 1,85 (dd, 2H), 1.95 (dd, 2H), 3.4 (t, 2H), 4.25 (t, 2H).

c) (N-Tetrahydroisoxazinyl)-2,6-dichloro-3-nitrobenzenesulfonamide

Following the general procedure for sulfonamide formation outlined in example 1, 2,6-dichloro-3-nitrobenzenesulfonyl chloride (1.75 g, 6.0 mmol), Tetrahydroisoxazine hydrochloride hydrochloride (0.63 g, 5.1 mmol) and triethylamine (2.2 mL, 15.5 mmol) were reacted to form the desired product (1.32 g, 75%). EI-MS m/z 341 (M^+).

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(N-Tetrahydroisoxazinyl)-2-hydroxy-6-chloro-3-nitrobenzenesulfonamide

Following the general hydrolysis procedure outlined in example 1, (N-Tetrahydroisoxazinyl)-2,6-dichloro-3-nitrobenzenesulfonamide (0.1 g, 0.29 mmol), 80% sodium hydride (26 mg, 0.88 mmol) and water (6.3 mg, 0.35 mmol) were reacted to form the desired product (50 mg, 53 %). EI-MS m/z 323 (M^+).

(N-Tetrahydroisoxazinyl)-2-hydroxy-3-amino-6-chlorobenzenesulfonamide

Following the general hydrogenation procedure outlined in example 1, (N-tetrahydroisoxazinyl)-2-hydroxy-6-chloro-3-nitrobenzenesulfonamide (0.76 g, 2.35 mmol) was reduced with hydrogen and Pd/C (760 mg) to form the desired product (890 mg, crude). EI-MS m/z 293 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydro isoxazyl amino sulfonyl)phenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, (N-tetrahydroisoxazinyl)-2-hydroxy-3-amino-6-chlorobenzenesulfonamide (620 mg, 2.12 mmol) and 2-bromophenylisothiocyanate (500 mg, 2.33 mmol) were coupled to form the desired thiourea (627 mg, 58%). EI-MS m/z 507 (M).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylamino sulfonyl)phenyl] thiourea

Following the general procedure for thiourea formation outlined in example 1, (N-tetrahydroisoxazinyl)-2-hydroxy-3-amino-6-chlorobenzenesulfonamide (888 mg, 3.04 mmol) and 2,3-dichlorophenylisothiocyanate (682 mg, 3.34 mmol) were coupled to form the desired thiourea (958 mg, 64%). EI-MS m/z 495.67 (M).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetra hydro isoxazylaminosulfonyl)phenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] thiourea

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(627 mg, 1.24 mmol), *tert*-butyldimethylsilyl chloride (934 mg, 6.2 mmol) and imidazole (169 mg, 2.48 mmol) were reacted to form the desired product (350 mg, 45%). EI-MS m/z 622 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] thiourea

Following the general procedure for protected phenyl thiourea formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] thiourea (898 mg, 1.81 mmol), *tert*-butyldimethylsilyl chloride (1.4 g, 9.05 mmol) and imidazole (246 mg, 3.62 mmol) were reacted to form the desired product (546 mg, 49%). EI-MS m/z 611.81 (M^+).

N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydro isoxazylaminosulfonyl)phenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] thiourea (385 mg, 0.74 mmol), methanesulfonyl chloride (0.12 mL, 1.48 mmol) and triethylamine (0.21 mL, 1.48 mmol) were reacted to form the desired product (385 mg, crude). ^{1}H NMR ($CDCl_3$) δ 0.35 (s, 6H), 1.02 (s, 9H), 1.68 (m, 2H), 1.9 (m, 2H), 3.04 (t, 2H), 4.0 (t, 2H), 7.09 (d, 1H), 7.12 (d, 1H), 7.2 (d, 1H), 7.3 (t, 1H), 7.42 (d, 1H), 7.6 (d, 1H).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] carbodiimide

Following the general procedure for carbodiimide formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] thiourea (547 mg, 0.897 mmol), methanesulfonyl chloride (0.14 mL, 1.79 mmol) and triethylamine (0.25 mL, 1.79 mmol) were reacted to form the desired product (547 mg, crude). ^{1}H NMR ($CDCl_3$) δ 0.36 (s, 6H), 1.03 (s, 9H), 1.68 (m, 2H), 1.9 (m, 2H), 3.53 (t, 2H), 4.0 (t, 2H), 7.11 (m, 2H), 7.14 (t, 1H), 7.2 (d, 1H), 7.3 (d, 1H), 7.39 (d, 1H).

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N-(2-Bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] cyanoguanidine

Following the general procedure for cyanoguanidine formation outlined in example 1, N-(2-bromophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] carbodiimide (385 mg, 0.79 mmol), cyanamide (133 mg, 3.16 mmol) and N,N-diisopropylethylamine (127 mg, 0.95 mmol) were reacted, followed by desilylation with Cesium fluoride (144 mg, 0.95 mmol) to form the desired product (100 mg, 26%). EI-MS m/z 515 (M^+).

N-(2,3-Dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] cyanoguanidine

Following the general procedure for cyanoguanidine formation outlined in example 1, N-(2,3-dichlorophenyl)-N'-[4-chloro-2-*tert*-butyldimethylsilyloxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] carbodiimide (547 mg, 0.95 mmol), cyanamide (159 mg, 3.8 mmol) and N,N-diisopropylethylamine (150 mg, 1.14 mmol) were reacted, followed by desilylation with Cesium fluoride (174 mg, 1.14 mmol) to form the desired product (190 mg, 40%). LC-MS m/z 504.

Example 12

Preparation of N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) propylguanidine

N, N-Dimethyl-3-amino-6-chloro-2-hydroxybenzenesulfonamide

To a solution of N, N-Dimethyl-6-chloro-2-hydroxy-3-nitrobenzenesulfonamide (550 mg, 1.96 mmol) in ethyl acetate, was added 10% Pd/C (550 mg). The mixture was flushed with argon, and then stirred under a hydrogen atmosphere at balloon pressure for 3 hours at room temperature. TLC showed the reaction was not complete. The mixture was filtered through celite and the celite was washed with methanol. The mixture was retreated under the same conditions as mentioned above. After 3 hours, the solvent was evaporated to give the desired product (480 mg, 98%). EI-MS (m/z) 250.82, 252.87 (M^+).

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N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) thiourea

A solution of N,N-dimethyl-3-amino-6-chloro-2-hydroxybenzenesulfonamide (480 mg, 3.58 mmol) and 2-bromophenylisothiocyanate (0.53 μL, 3.94 mmol) in 10 mL of ethanol was stirred at room temperature for overnight. Purification by column chromatography on silica gel, eluting with ethyl acetate/hexane (gradient elution) gave the desired product (368 mg, 22 %). EI-MS (m/z) 463.67, 465.66, 467.65, 468.64 (M⁺).

N-[4-chloro-2-tert-butyldimethylsiloxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) thiourea

To a solution of N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) thiourea (350 mg, 0.755 mmol) in THF (10 mL), tert-butyldimethylsilyl chloride (171 mg, 1.13 mmol) and imidazole (106mg, 1.56 mmol) were added. The reaction mixture was stirred at room temperature for overnight. Then it was partitioned between ethyl acetate and water. The combined organic phase was dried and concentrated. Chromatography of the residue on silica gel gave desired product (150 mg, 46 %) and recovered starting material (90 mg). EI-MS m/z 577.81, 579.66, 580.65, 581.46, 582.77 (M⁺).

N-[4-chloro-2-tert-butyldimethylsiloxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl)carbodiimide

To a solution of N-[4-chloro-2-tert-butyldimethylsiloxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) thiourea (150 mg, 0.26mmol) in dichloromethane (5 mL) at 0°C, methanesulfonyl chloride (40μL, 0.52 mmol), 4-Dimethylaminopyridine (10 mg) and triethylamine (0.11 mL, 0.77 mmol) were added. The reaction mixture was stirred at 0°C for 3 hours. Then it was partitioned between ethyl acetate and water. The combined organic phase was dried and concentrated to give the desired product (120 mg, 85%). IR: 2140 cm^{-1}

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N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) propylguanidine

To a solution of N-[4-chloro-2-tert-butyldimethylsiloxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl)carbodiimide (60 mg, 0.11 mmol) in tetrahydrofuran (2 mL) at room temperature, N,N-diisopropylethylamine (14 µL, 0.12 mmol) and n-propylamine (10 µL, 012 mmol) were added. The reaction mixture was stirred at room temperature for 15 minutes, then cooled to 0°C, and TBAF and methanol (1 mL) were added. After 30 minutes, the mixture was quenched with water, and extracted with ethylacetate. The organic layer was concentrated under reduced pressure. The residue was purified by Gilson HPLC to give the desired product (19 mg, 35 %). EI-MS m/z 488.7, 490.68, 492.67 (M^+).

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, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cells release and diseases caused by respiratory viruses, herpesviruses, and hepatitis viruses, meningitis, cystic fibrosis, pre-term labor, cough, pruritus, multi-organ dysfucntions, trauma, strains, sprains, contusions, psoriatic arthritis, 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, hyperoxia-induced inflammations, hypoxia, surgerical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertropy, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds and lupus.

These diseases are primarily characterized by massive neutrophil infiltration, T-cell infiltration, or neovascular growth, and are associated with increased IL-8,

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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.

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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 Vaisc & 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 include 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-ß).

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.

The present compounds are also useful in normalizing leukocyte counts as well as normalizing levels of circulating chemokines.

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

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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

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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 (Haour, *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% polyethylenimine/ 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 temporaparietal 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.

<u>CNS Injury model for IL-1β mRNA</u>

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

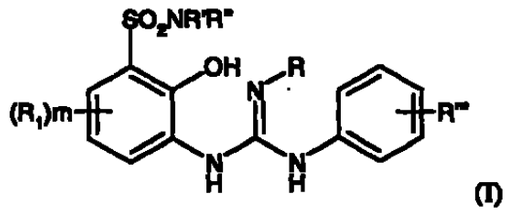
right hippocampus (RH) are prepared. Total RNA is isolated and Northern blot hybridization was performed and the quantity of brain tissue IL-1ß mRNA is presented as percent relative radioactivity of IL-1ß positive macrophage RNA which was loaded on the same gel. At 1 hr following brain injury, a marked and significant increase in expression of IL-1ß 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-1ß mRNA is observed in any of the respective brain areas. These results indicate that following TBI, the temporal expression of IL-1ß mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1ß 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 is selected from the group consisting of cyano, OR_{11}, $C(O)NR_{15}R_{16}$, R_{18}, $C(O)OR_{11}$, $C(O)R_{11}$, and $S(O)_2R_{17}$;

R'R'' is independently selected from the group consisting of hydrogen, NR_6R_7, OH, OR_a, C_{1-5}alkyl, aryl, arylC_{1-4}alkyl, aryl C_{2-4}alkenyl; cycloalkyl, cycloalkyl C_{1-5} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heteroarylC_{2-4} alkenyl, heterocyclic, heterocyclic C_{1-4}alkyl, and a heterocyclic C_{2-4}alkenyl moiety, all of which moieties may be optionally substituted one to three times independently by a substituent selected from the group consisting of halogen, nitro, halosubstituted C_{1-4} alkyl, C_{1-4} alkyl, amino, mono or di-C_{1-4} alkyl substituted amine, OR_a, $C(O)R_a$, $NR_aC(O)OR_a$, $OC(O)NR_6R_7$, hydroxy, $NR9C(O)R_a$, $S(O)_mR_a$, $C(O)NR_6R_7$, C(O)OH, $C(O)OR_a$, $S(O)_tNR_6R_7$, and $NHS(O)_tR_a$; or the two R_b substituents join to form a 3-10 membered ring, optionally substituted and containing, in addition to optionally substituted C_{1-4} alkyl, independently, 1 to 3 NR_a, O, S, SO, or SO_2 moieties, which moieties can be optionally unsaturated;

R''' is selected from the group consisting of Y 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, $(CR_8R_8)qS(O)_tR_a$, $(CR_8R_8)qOR_a$, 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$C(O)OR_{11}$, $(CR_8R_8)_qOC(O)R_{11}$, $(CR_8R_8)_qNR_4C(O)R_{11}$, $(CR_8R_8)_q$ $NHS(O)_tR_{13}$, $(CR_8R_8)_q$ $S(O)_tNR_4R_5$, $(CR_8R_8)_qC(NR_4)NR_4R_5$, and $(CR_8R_8)_q$ $NR_4C(NR_5)R_{11}$; or two Y moieties together form $O-(CH_2)_s-O$ or a 5 to 6 membered saturated or unsaturated ring, such that the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic, and heterocyclicalkyl groups may be optionally substituted;

R_1 is independently selected from the group consisting of 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 $C(O)OR_{11}$, $(CR_8R_8)_q$ $C(O)OR_{11}$, $(CR_8R_8)_q$ $OC(O)R_{11}$, $(CR_8R_8)_qNR_4C(O)R_{11}$, $(CR_8R_8)_q$ $C(NR_4)NR_4R_5$, $(CR_8R_8)_q$ $NR_4C(NR_5)R_{11}$, $(CR_8R_8)_q$ $NHS(O)_tR_{13}$, and $(CR_8R_8)_q$ $S(O)_tNR_4R_5$; or two R_1 moieties together form $O-(CH_2)_3O$ or a 5 to 6 membered saturated or unsaturated ring, wherein the alkyl, aryl, arylalkyl, heteroaryl, and heterocyclic moieties may be optionally substituted.

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.

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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 R_b is hydrogen, C_{1-4} alkyl, C_{1-4} alkyl substituted with C(O)OH, or $C(O)OR_a$.

10. The compound according to Claim 1 wherein Y is halogen, n is 1 or 2, R_1 is halogen, m is 1 or 2, and R_b is independently hydrogen, C_{1-4} alkyl, C_{1-4} alkyl substituted with C(O)OH, or $C(O)OR_a$.

11. The compound according to Claim 1 which is selected from the group consisting of:
N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N",N"dimethylaminosulfonyl)phenyl] cyanoguanidine;
N-[4-chloro-2-hydroxy-3- (N",N"-dimethylaminosulfonyl)phenyl]-N'-(2,3-dichlorophenyl) cyanoguanidine;
N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;
N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-phenyl-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-[R-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-[R-(2-methoxymethyl)pyrrolidin-1-yl]aminosulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-isoxazolidinylaminosulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-tetrahydroisoxazylaminosulfonyl)phenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(4-thiomorpholinylaminosulfonyl)phenyl] cyanoguanidine;

N-[4-chloro-2-hydroxy-3-[N",N"-dimethylaminosulfonyl]phenyl]-N'-(2-bromophenyl) propylguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(4-oxidothiomorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2,3-chlorophenyl)-N'-[4-chloro-2-hydroxy-3-(4-oxidothiomorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-methylpiperazino)amino sulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-methylpiperazino)amino sulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-ethylmorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-[4-chloro-2-hydroxy-3-(N"-ethylmorpholino)amino sulfonylphenyl] cyanoguanidine;

N-(2-bromophenyl)-N'-{4-chloro-2-hydroxy-3-[N"-ethyl-2-(2-ethylpyrrolidino)]amino sulfonylpheny} cyanoguanidine;

N-(2,3-dichlorophenyl)-N'-{4-chloro-2-hydroxy-3-[N"-ethyl-2-(2-ethylpyrrolidino)]amino sulfonylpheny} cyanoguanidine;
N-(2-bromophenyl)-N'-{4-chloro-2-hydroxy-3-[S-(+)-(2-carboxy)pyrrolidin-1-yl]amino sulfonylpheny} cyanoguanidine;
N-(2,3-dichlorophenyl)-N'-{4-chloro-2-hydroxy-3-[S-(+)-(2-carboxy)pyrrolidin-1-yl]amino sulfonylpheny} cyanoguanidine;
N-(2-bromo-3-fluorophenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] cyanoguanidine;
N-(2-phenoxyphenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] cyanoguanidine; and
N-(2-benzoxyphenyl)-N'-[4-chloro-2-hydroxy-3-[S-(+)-(2-methoxymethyl)pyrrolidin-1-yl]sulfonylphenyl] cyanoguanidine;
or a pharmaceutically acceptable salt thereof.

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

13. 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 11.

14. The method according to Claim 13 wherein the mammal is afflicted with a chemokine mediated disease selected from the group consisting of 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, restenosis, angiogenesis, atherosclerosis, osteoporosis, gingivitis and undesired hematopoietic stem cells release and diseases caused by respiratory viruses, herpesviruses, and hepatitis viruses, meningitis, cystic fibrosis, pre-term labor, cough, pruritus, multi-organ dysfucntions, trauma, strains, sprains,

contusions, psoriatic arthritis, 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, hyperoxia-induced inflammations, hypoxia, surgerical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertropy, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds and lupus.

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ABSTRACT

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

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SUPERINTENDENCIA

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 177

Radicación no 01-23845

Concepto Técnico no 1803 Clasificación Internacional de Patentes A61K31/17

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-I).
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
202050

Bogotá D. C., DICIEMBRE 12 DEL 2002

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Industria y Comercio
SUPERINTENDENCIA

Folio 178

2020
Bogotá DC

Doctor(a)
GERMAN CASTILLO GRAU
Apoderado(a)

REFERENCIA:	Radicación No.	01-23848
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	2327
	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 DC, a los 17 DIC. 2002

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

202050

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