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Señora Jefe
DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

SUPERINTENDENCIA Y COMERCIO
Radicación : 02005740 00000003 Folios: 2
Fecha (OIR): 2004-09-02 09:59:54
Tramite : 002 PATENTES D 1 REGISTRAR/ 530 PETICION
Remisión: PARA DIVISION DE NUEVAS CREACIONES

Re.: Expediente No. 02 5.740
Solicitud de Patente a nombre de
SMITHKLINE BEECHAM CORPORATION
Código 02 - 01 - 538

En relación con la solicitud contenida en el Expediente de la referencia y, en particular, con la publicación del extracto de la misma en la Gaceta de la Propiedad Industrial No. 539 de 30 de Abril de 2004, por medio del presente escrito muy respetuosamente me permito solicitarle se sirva proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Para tal efecto acompaño el comprobante de pago de las tasas correspondientes, por valor de \$ 353.000.00, Recibo No. 04.074.675

De Usted Atentamente,

GERMÁN CASTILLO GRAU
T.P. No. 2878 del C.S.J.

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NTT : 800174089-2

RECIBO OFICIAL DE CAJA : 4 - 74,675
FECHA : SEPTIEMBRE 21 DE 2004

SUPERINDUSTRIA Y COMERCIO
Radicación : 02005740 00000003 Folios: 2
Fecha (MD): 2004-09-22 09:59:54
Trámite : 002 PATENTES D I REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	23470739	21/09/2004	12,090,000.

CONCEPTO

CANT. CONTABILITICO	CONCEPTO	TOTAL CONCEPTO
1 90005-01-01 SOLICITUDES	05 EXAMEN DE PATENTABILIDAD DE INVEN	353,000.00
	TOTAL :	353,000.00

SON: TRESCIENTOS CINCUENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL ASUNTO Nº.

105

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 02-5740

**EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION
PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 539,
DE FECHA 30 DE ABRIL DE 2004, EL TERMINO HABIL SEÑALADO POR LA
LEY EXPIRA EL 02 DE AGOSTO DE 2004.**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO **X**

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 30 de agosto de 2008

Apoderado: Germán Castillo Grau

Oficio: 5 - 10446

REFERENCIA: Radicación No. 02-5740
Trámite 002
Evento 001
Actuación 430
Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- ◆Capítulo descriptivo, folios 12 a 66;
- ◆Capítulo reivindicatorio, folios 67 a 81;
- ◆1° examen de forma folios 85;
- ◆Respuesta técnica al primer examen de forma, folio 88;
- ◆No se reivindica prioridad.
- ◆2° examen de forma folio 101;
- ◆Solicitud del examen de patentabilidad, folios 103 y 104.

2. Objeto de la Invención:

La presente solicitud cuyo título es "RECEPTORE DE IL-8, DE BENZO-2-TRAZOL Y PREPARACIÓN"

El objeto de la solicitud es derivados de 1H-1,2,3-benzotriazol, 1H-benzimidazol, 2,3-dihidro-1H-benzimidazol y 2,3-dihidro-1H-1,2,3-benzotriazol, los cuales son útiles para el tratamiento de enfermedades mediadas por quimioquina que se une al receptor a ó b de IL-8.

El objeto de la invención se puede clasificar según la clasificación Internacional como A61K 31/4184

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Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: *"los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*.

Las reivindicaciones 8 y 9 reclama realmente un procedimiento para el tratamiento del cuerpo humano o animal, por lo tanto no son patentables de acuerdo con el artículo en referencia.

Evaluación de los requisitos de patentabilidad:

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

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial para las reivindicaciones, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio. Consultada la fuente de información con que cuenta este despacho se encontró el siguiente documento:

Item	Documento	Fecha de publicación	Título
D1	WO 9832439	30-JULIO-1998	IL-8 Receptor antagonists

Evaluación de la novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina dispone que: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*.

La solicitud en estudio reclama los derivados de 1H-1,2,3-benzotriazol, 1H-benzimidazol, 2,3-dihidro-1H-benzimidazol y 2,3-dihidro-1H-1,2,3-benzotriazol, que caen dentro de la fórmula Marckush I, II, III, IV.

-La anterioridad D1 enseña derivados de 1H-1,2,3-benzotriazol, 1H-benzimidazol, 2,3-dihidro-1H-benzimidazol y 2,3-dihidro-1H-1,2,3-benzotriazol compuestos de formulas I, II, III, IV, y todos los compuestos específicos que se reclaman como

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nuevos en la solicitud en estudio, toda vez que la anterioridad es igual a la presente solicitud, por lo tanto la solicitud en estudio no tiene novedad.

Tal como lo demuestra el antecedente citado, el compuesto y la composición farmacéutica que tienen como base dicho principio activo en referencia, no se considera nuevo.

No	Documento:	Reivindicaciones afectadas:	Requisito afectado
D1	WO9832439	1 a 30	NOVEDAD

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

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5° del título 1° de la Circular Única n°.10 de 2001.

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

El anterior requerimiento fue notificado por fijación en lista de fecha 14 SET. 2006

CONCEPTO TÉCNICO No. 1417	EXAMINADOR TÉCNICO Código: 202012
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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: A61K 31/41, 31/415, 31/53, 31/675, C07D 235/08, 235/26, 253/06, 285/14, C07F 9/6584	A1	(11) International Publication Number: WO 98/32439 (43) International Publication Date: 30 July 1998 (30.07.98)
(21) International Application Number: PCT/US98/01291 (22) International Filing Date: 23 January 1998 (23.01.98) (30) Priority Data: 60/035,991 23 January 1997 (23.01.97) US 60/042,829 8 April 1997 (08.04.97) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): WIDDOWSON, Kath- erine, L. [CA/US]; 1047 Old Valley Forge Road, King of Prussia, PA 19406 (US). RUTLEDGE, Melvin, C. [US/US]; 2148 Schultz Road, Lansdale, PA 19446 (US). (74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).		(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, DE, DK, ES, FI, FR, GB, GR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: IL-8 RECEPTOR ANTAGONISTS (57) Abstract This invention relates to novel compounds of Formula (I), and pharmaceutical compositions thereof, and methods of treatment of disease states mediated by the chemokine, Interleukin-8 (IL-8).		

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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, GRO α , GRO β , GRO γ 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); Donnelly 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, GRO α , GRO β , GRO γ 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 B-receptor. 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-8Ra, which binds only IL-8 with high affinity, and IL-8Rb, which has high affinity for IL-8 as well as for GRO α , GRO β , GRO γ 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 a or b 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

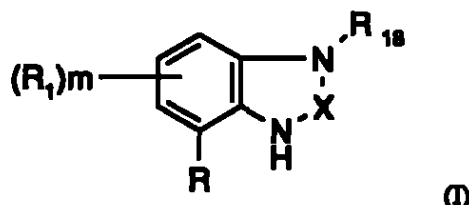
This invention provides for a method of treating a chemokine mediated disease, wherein the chemokine is one which binds to an IL-8 a or b receptor and

which method comprises administering an effective amount of a compound of Formula (I) or (II) 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) or (II).

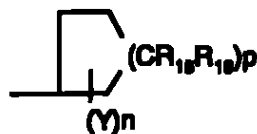
The present invention also provides for the novel compounds of Formula (I), and (II) and pharmaceutical compositions comprising a compound of Formula (I), and (II) and a pharmaceutical carrier or diluent.

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



wherein

R is $-\text{NH}-\text{C}(\text{X}_2)-\text{NH}-(\text{CR}_{13}\text{R}_{14})_v-\text{Z}$;



Z is W, HET, $(\text{Y})^n$, an optionally substituted C_{1-10} alkyl, an optionally substituted C_{2-10} alkenyl, or an optionally substituted C_{2-10} alkynyl;

X is $\text{C}(\text{X}_1)_2$, $\text{C}(\text{O})$, $\text{C}(\text{S})$, $\text{S}(\text{O})_2$, $\text{PO}(\text{OR}_4)$, or $\text{C}=\text{N}-\text{R}_{19}$;

X_1 is independently hydrogen, halogen, C_{1-10} alkyl, NR_4R_5 , C_{1-10} alkyl- NR_4R_5 , $\text{C}(\text{O})\text{NR}_4\text{R}_5$, optionally substituted C_{1-10} alkyl, C_{1-10} alkoxy, halosubstituted C_{1-10} alkoxy, hydroxy, aryl, aryl C_{1-4} alkyl, aryloxy, aryl C_{1-4} alkyloxy, heteroaryl, heteroarylalkyl, heterocyclic, heterocyclic C_{1-4} alkyl, or heteroaryl C_{1-4} alkyloxy;

X_2 is $=\text{O}$, or $=\text{S}$;

R_1 is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; azide; $(\text{CR}_g\text{R}_g)_q$ $\text{S}(\text{O})_t\text{R}_4$, hydroxy; hydroxy C_{1-4} alkyl; aryl; aryl C_{1-4} alkyl; aryloxy; aryl C_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C_{1-4} alkyl; heteroaryl C_{1-4} alkyloxy; aryl C_{2-10} alkenyl; heteroaryl C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(\text{CR}_g\text{R}_g)_q\text{NR}_4\text{R}_5$; C_{2-10} alkenyl $\text{C}(\text{O})\text{NR}_4\text{R}_5$; $(\text{CR}_g\text{R}_g)_q\text{C}(\text{O})\text{NR}_4\text{R}_5$; $(\text{CR}_g\text{R}_g)_q\text{C}(\text{O})\text{NR}_4\text{R}_{10}$; $\text{S}(\text{O})_3\text{R}_8$;

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- (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR_gR_g)_q C(O)OR₁₂; (CR_gR_g)_q OC(O) R₁₁; (CR_gR_g)_q NR₄C(O)R₁₁; (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q NHS(O)₂R₁₇; or (CR_gR_g)_q S(O)₂NR₄R₅; or two R₁ moieties together may form O-(CH₂)_sO or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may all be optionally substituted;
- n is an integer having a value of 1 to 3;
- m is an integer having a value of 1 to 3;
- 10 q is 0, or an integer having a value of 1 to 10;
- s is an integer having a value of 1 to 3;
- t is 0, or an integer having a value of 1 or 2;
- v is 0, or an integer having a value of 1 to 4;
- p is an integer having a value of 1 to 3;
- 15 HET is an optionally substituted heteroaryl;
- R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, or heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;
- 20 Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR_gR_g)_q S(O)_tR₄; hydroxy; hydroxyC₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR_gR_g)_q NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R_g; (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; (CR_gR_g)_q C(O)OR₁₂; (CR_gR_g)_q OC(O) R₁₁; (CR_gR_g)_q NR₄C(O)R₁₁; (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q NHS(O)₂R_g; or (CR_gR_g)_q S(O)₂NR₄R₅; or two Y moieties together may form O-(CH₂)_sO or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may all be optionally substituted;
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R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together with the nitrogen to which they are attached form a 5 to 7 member ring which ring may optionally contain an additional heteroatom which heteroatom is selected from oxygen, nitrogen or sulfur;

5 R₈ is independently hydrogen or C₁₋₄ alkyl;

R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;

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

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

R₁₃ and R₁₄ are independently hydrogen, or optionally substituted C₁₋₄ alkyl, or one of R₁₃ and R₁₄ may be optionally substituted aryl;

15 R₁₅ and R₁₆ are independently hydrogen, or an optionally substituted C₁₋₄ alkyl;

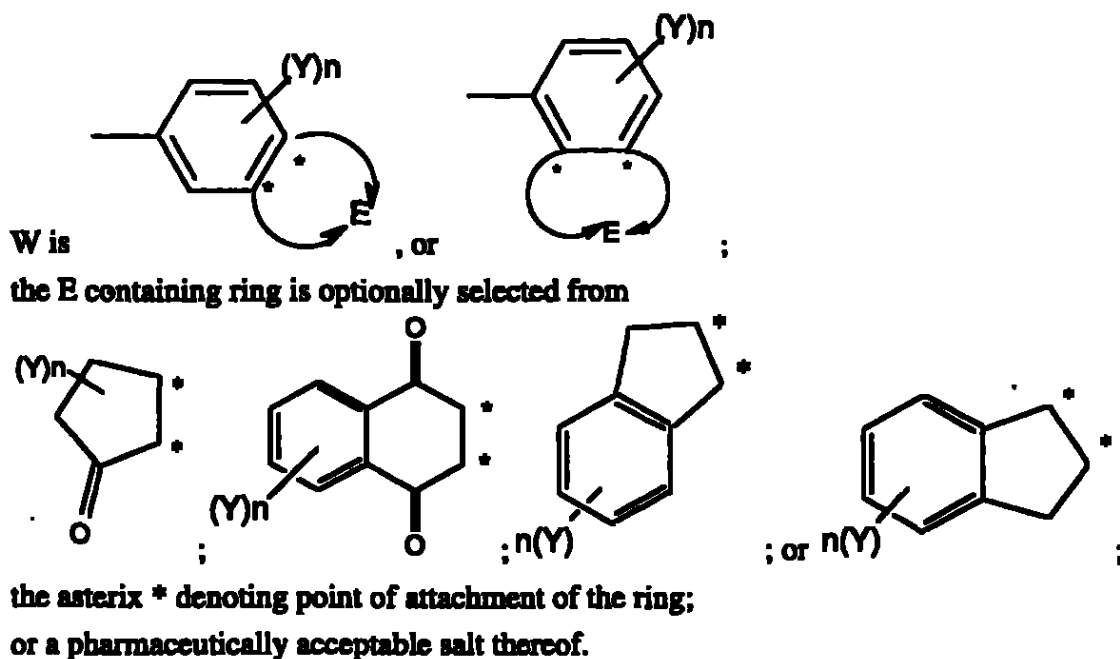
R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;

20 R₁₈ is hydrogen, optionally substituted C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halosubstituted C₁₋₁₀ alkoxy, hydroxy, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl, wherein the aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;

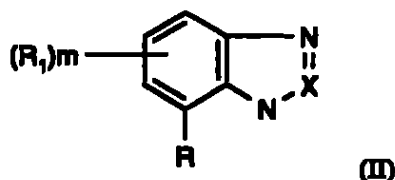
25 R₁₉ is cyano, nitro, S(O)₂NR₄R₅, S(O)₂R₁₇, alkyl, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl; and wherein the alkyl, aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;

30 R₂ is NR₆R₇, alkyl, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl; and wherein the aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;

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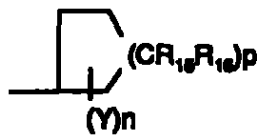


Compounds of Formula (II) useful in the present invention are represented by the structure:



wherein

R is -NH-C(X₂)-NH-(CR₁₃R₁₄)_v-Z;



Z is W, HET, , optionally substituted C₁₋₁₀ alkyl, optionally substituted C₂₋₁₀ alkenyl, or optionally substituted C₂₋₁₀ alkynyl;

X is N, or C(X₁);

X₁ is hydrogen, halogen, C₁₋₁₀ alkyl, NR₄R₅, C₁₋₁₀ alkyl-NR₄R₅, C(O)NR₄R₅,

C₁₋₁₀ alkylC(O)NR₄R₅, optionally substituted C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy,

halosubstituted C₁₋₁₀ alkoxy, hydroxy, aryl, aryl C₁₋₄ alkyl, aryloxy; aryl C₁₋₄

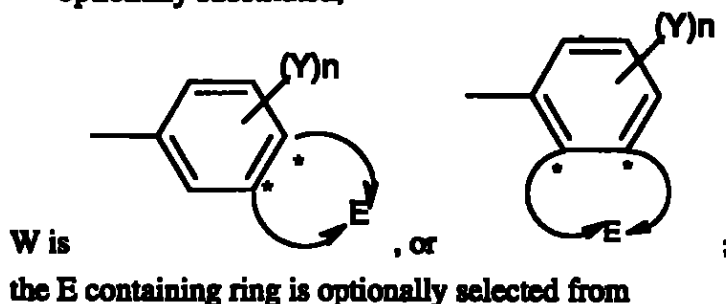
alkyloxy, heteroaryl, heteroarylalkyl, heterocyclic, heterocyclic C₁₋₄alkyl, or

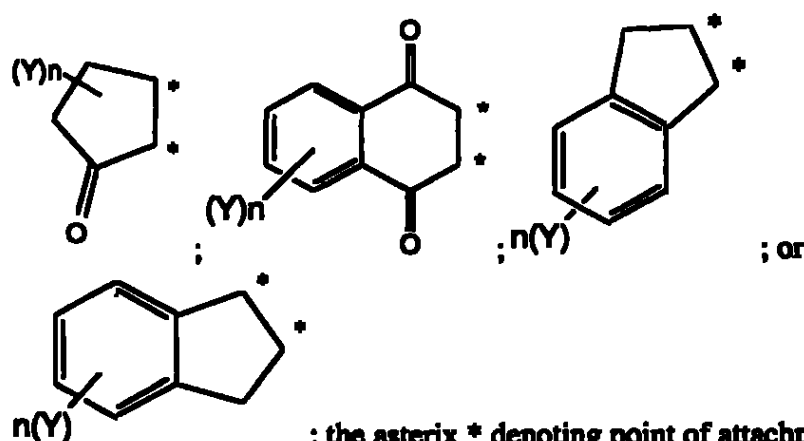
heteroaryl C₁₋₄ alkyloxy;

X₂ is =O, or =S;

- 105 H5
- R₁** is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR_gR_g)_q S(O)_tR₄; hydroxy; hydroxy C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic, heterocyclic C₁₋₄alkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR_gR_g)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R₈; (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR_gR_g)_q C(O)OR₁₂; (CR_gR_g)_q OC(O) R₁₁; (CR_gR_g)_qNR₄C(O)R₁₁; (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q NHS(O)₂R₁₇; (CR_gR_g)_q S(O)₂NR₄R₅; or two R₁ moieties together may form O-(CH₂)_s-O or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may all be optionally substituted;
- n** is an integer having a value of 1 to 3;
m is an integer having a value of 1 to 3;
q is 0, or an integer having a value of 1 to 10;
t is 0, or an integer having a value of 1 or 2;
s is an integer having a value of 1 to 3;
v is 0, or an integer having a value of 1 to 4;
p is an integer having a value of 1 to 3;
HET is an optionally substituted heteroaryl;
R₄ and **R₅** are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O/N/S;
- Y** is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR_gR_g)_q S(O)_tR₄; hydroxy; hydroxyC₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; arylC₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR_gR_g)_q NR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R₈; (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁;

- (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_q C(NR₄)NR₄R₅;
 (CR₈R₈)_q NR₄C(NR₅)R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁; (CR₈R₈)_q NHS(O)₂R₂;
 (CR₈R₈)_q S(O)₂NR₄R₅; or two Y moieties together may form O-(CH₂)₃-O or a
 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl,
 5 and heterocyclic containing moieties may all be optionally substituted;
 R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together
 with the nitrogen to which they are attached form a 5 to 7 member ring which ring
 may optionally contain an additional heteroatom which heteroatom is selected from
 oxygen, nitrogen or sulfur;
 10 R₈ is independently hydrogen or C₁₋₄ alkyl;
 R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;
 R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl
 C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted
 heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally
 15 substituted heterocyclicC₁₋₄alkyl;
 R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted
 arylalkyl;
 R₁₃ and R₁₄ are independently hydrogen, or optionally substituted C₁₋₄ alkyl, or
 one of R₁₃ and R₁₄ may be optionally substituted aryl;
 20 R₁₅ and R₁₆ are independently hydrogen, or an optionally substituted C₁₋₄ alkyl;
 R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or
 heterocyclicC₁₋₄alkyl; and wherein the aryl, heteroaryl and heterocyclic
 containing moieties may all be optionally substituted;
 R₈ is NR₆R₇, alkyl, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-
 25 C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl; and
 wherein the aryl, heteroaryl and heterocyclic containing moieties may all be
 optionally substituted;





; the asterisk * denoting point of attachment of the ring;
or a pharmaceutically acceptable salt thereof.

5 DETAILED DESCRIPTION OF THE INVENTION

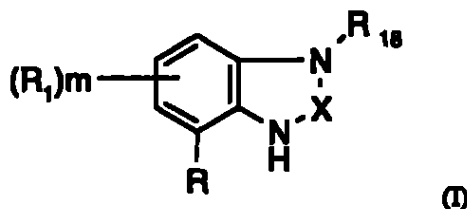
The compounds of Formula (I) and (II) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of IL-8 or other chemokines which bind to the IL-8 a and b receptors. Chemokine mediated diseases for treatment, therapeutically or prophylactically,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

As readily seen, the difference between compounds of Formula (I) and (II) lies in the unsaturation of the A containing ring, and hence the substitutions on the X moiety. The remaining terms, defined below, are the same for both compounds of Formula (I) and (II) unless otherwise indicated.

In compounds of Formula (I), suitably R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl, such as CF₃; C₁₋₁₀ alkyl, such as methyl, ethyl, isopropyl, or n-propyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy, such as methoxy, or ethoxy; halosubstituted C₁₋₁₀ alkoxy, such as trifluoromethoxy; azide; (CR_gR_g)_q S(O)_tR₄, wherein t is 0, 1 or 2; hydroxy; hydroxy C₁₋₄alkyl, such as methanol or ethanol; aryl, such as phenyl or naphthyl; aryl C₁₋₄ alkyl, such as benzyl; aryloxy, such as phenoxy; aryl C₁₋₄ alkyloxy, such as benzyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR_gR_g)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃H; S(O)₃R_g; (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR_gR_g)_q C(O)OR₁₂; (CR_gR_g)_q OC(O) R₁₁; (CR_gR_g)_q NR₄C(O)R₁₁; (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q

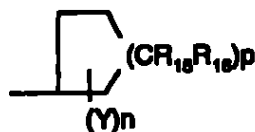
What is Claimed Is:

1. A compound of the formula:



wherein

R is -NH-C(X₂)-NH-(CR₁₃R₁₄)_v-Z;



Z is W, HET, $(Y)_n$, an optionally substituted C₁₋₁₀ alkyl, an optionally substituted C₂₋₁₀ alkenyl, or an optionally substituted C₂₋₁₀ alkynyl;

X is C(X₁)₂, C(O), C(S), S(O)₂, PO(OR₄), or C=N-R₁₉;

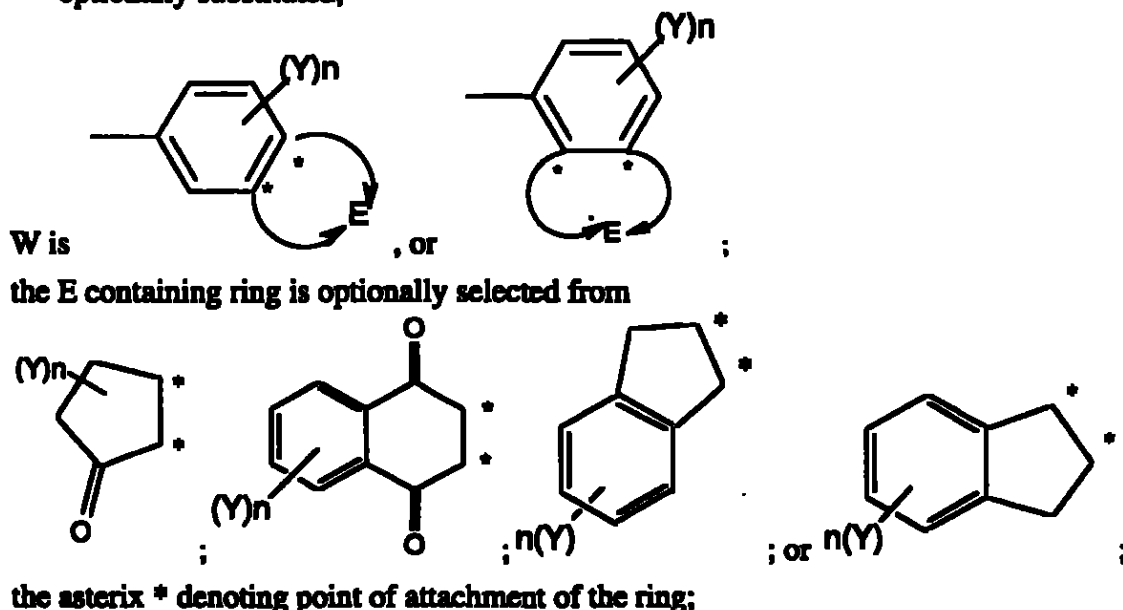
X₁ is independently hydrogen, halogen, C₁₋₁₀ alkyl, NR₄R₅, C₁₋₁₀ alkyl-NR₄R₅, C(O)NR₄R₅, optionally substituted C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halosubstituted C₁₋₁₀ alkoxy, hydroxy, aryl, aryl C₁₋₄ alkyl, aryloxy, aryl C₁₋₄ alkyloxy, heteroaryl, heteroarylalkyl, heterocyclic, heterocyclic C₁₋₄alkyl, or heteroaryl C₁₋₄ alkyloxy;

X₂ is =O, or =S;

R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄; hydroxy; hydroxy C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic; heterocyclic C₁₋₄alkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁; C(O)R₁₁; (CR₈R₈)_q C(O)OR₁₂; (CR₈R₈)_q OC(O) R₁₁; (CR₈R₈)_qC(NR₄)NR₄R₅; (CR₈R₈)_q NR₄C(NR₅)R₁₁; (CR₈R₈)_q NR₄C(O)R₁₁; (CR₈R₈)_q NHS(O)₂R₁₇; (CR₈R₈)_q S(O)₂NR₄R₅; or two R₁ moieties together may form O-(CH₂)₃O or a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl, and heterocyclic containing moieties may all be optionally substituted;

- n is an integer having a value of 1 to 3;
 m is an integer having a value of 1 to 3;
 q is 0, or an integer having a value of 1 to 10;
 s is an integer having a value of 1 to 3;
 5 t is 0, or an integer having a value of 1 or 2;
 v is 0, or an integer having a value of 1 to 4;
 p is an integer having a value of 1 to 3;
 HET is an optionally substituted heteroaryl;
 R₄ and R₅ are independently hydrogen, optionally substituted C₁₋₄ alkyl, optionally
 10 substituted aryl, optionally substituted aryl C₁₋₄alkyl, optionally substituted
 heteroaryl, optionally substituted heteroaryl C₁₋₄alkyl, heterocyclic, or
 heterocyclic C₁₋₄ alkyl, or R₄ and R₅ together with the nitrogen to which they
 are attached form a 5 to 7 member ring which may optionally comprise an
 additional heteroatom selected from O/N/S;
 15 Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted
 C₁₋₁₀ alkyl; C₁₋₁₀ alkenyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀
 alkoxy; azide; (CR_gR_g)_q S(O)_tR₄; hydroxy; hydroxyC₁₋₄alkyl; aryl; aryl C₁₋₄
 alkyl; aryloxy; arylC₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C₁₋₄
 alkyloxy; heterocyclic, heterocyclic C₁₋₄alkyl; aryl C₂₋₁₀ alkenyl; heteroaryl
 20 C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR_gR_g)_q NR₄R₅; C₂₋₁₀ alkenyl
 C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₅; (CR_gR_g)_q C(O)NR₄R₁₀; S(O)₃R₈;
 (CR_gR_g)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁;
 (CR_gR_g)_q C(O)OR₁₂; (CR_gR_g)_q OC(O) R₁₁; (CR_gR_g)_q NR₄C(O)R₁₁;
 (CR_gR_g)_qC(NR₄)NR₄R₅; (CR_gR_g)_q NR₄C(NR₅)R₁₁; (CR_gR_g)_q NHS(O)₂R₈;
 25 (CR_gR_g)_q S(O)₂NR₄R₅; or two Y moieties together may form O-(CH₂)₅O or a
 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl,
 and heterocyclic containing moieties may all be optionally substituted;
 R₆ and R₇ are independently hydrogen or a C₁₋₄ alkyl group, or R₆ and R₇ together
 with the nitrogen to which they are attached form a 5 to 7 member ring which ring
 30 may optionally contain an additional heteroatom which heteroatom is selected from
 oxygen, nitrogen or sulfur;
 R₈ is independently hydrogen or C₁₋₄ alkyl;
 R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;
 R₁₁ is hydrogen, C₁₋₄ alkyl, optionally substituted aryl, optionally substituted aryl
 35 C₁₋₄alkyl, optionally substituted heteroaryl, optionally substituted

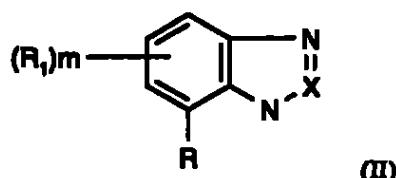
- heteroarylC₁₋₄alkyl, optionally substituted heterocyclic, or optionally substituted heterocyclicC₁₋₄alkyl;
- R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;
- 5 R₁₃ and R₁₄ are independently hydrogen, optionally substituted C₁₋₄ alkyl, or one of R₁₃ and R₁₄ may be optionally substituted aryl;
- R₁₅ and R₁₆ are independently hydrogen, or an optionally substituted C₁₋₄ alkyl;
- R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic moieties
- 10 may all be optionally substituted;
- R₁₈ is hydrogen, optionally substituted C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halosubstituted C₁₋₁₀ alkoxy, hydroxy, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl, wherein all the aryl, heteroaryl and heterocyclic containing moieties may all be
- 15 optionally substituted;
- R₁₉ is cyano, nitro, S(O)₂NR₄R₅, S(O)₂R₁₇, alkyl, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl, wherein the alkyl, aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;
- 20 R₂ is NR₆R₇, alkyl, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl, wherein the aryl, heteroaryl and heterocyclic containing moieties may all be optionally substituted;



- or a pharmaceutically acceptable salt thereof.
2. The compound according to Claim 1 wherein R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O)R₄R₁₀, alkenyl C(O)OR₁₂,
5 heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅.
3. The compound according to Claim 1 wherein X is C(O) or C(S).
4. The compound according to any of Claims 1 to 3 wherein Z is W.
10
5. The compound according to Claim 4 wherein Y is halogen, C₁₋₄ alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, methylene dioxy, NR₄R₅, thioC₁₋₄alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C₁₋₄alkyl, or hydroxy alkyl.
15
6. The compound according to Claim 1 which is:
N-4-(Benzimidazoline-2-one-N'-(2'-bromophenyl)urea;
N-4-(1H,3H-2,1,3-benzothiazole 2,2-dioxide)-N'-(2-bromophenyl) urea;
N-4-(7-Cyano-1-N-methyl-benzimidazoline-2-thione)-N'-(2,3-dichlorophenyl) urea;
20 N-4-(7-Cyano-benzimidazoline-2-thione)-N'-(2 bromophenyl) urea;
N-4-(7-Cyano-1-methyl-benzimidazoline-2-thione)-N'-(2 bromophenyl) urea;
N-(4-Cyano-2-oxo-3-methylbenzimidazol-7-yl)-N'-(2-bromophenyl) urea
N-4-(7-Cyano-benzimidazoline-2-one)-N'-(2-bromophenyl)urea;
N-4-(7-Cyano-benzimidazoline-2-thione)-N'-(2,3-dichlorophenyl) urea;
25 N-4-(7-Cyano benzimidazoline-2-imine)-N'-(2-bromophenyl) urea; or
a pharmaceutically acceptable salt thereof.
7. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1, and a pharmaceutically acceptable carrier or
30 diluent.
8. A method of treating a chemokine mediated disease in a mammal in need thereof, wherein the chemokine binds to an IL-8 a or b receptor, which method comprises administering to said mammal an effective amount of a compound
35 according to Claim 1.

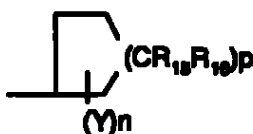
9. The method according to Claim 8 wherein the mammal is afflicted with a chemokine mediated disease selected from psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxemic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, or allograft rejections.

10. A compound of the formula:



wherein

R is -NH-C(X₂)-NH-(CR₁₃R₁₄)_v-Z;



- 15 Z is W, HET, (Y)_n, optionally substituted C₁₋₁₀ alkyl, optionally substituted C₂₋₁₀ alkenyl, or optionally substituted C₂₋₁₀ alkynyl;
 X is N, or C(X₁);
 X₁ is hydrogen, halogen, C₁₋₁₀ alkyl, NR₄R₅, C₁₋₁₀ alkyl-NR₄R₅, C(O)NR₄R₅, optionally substituted C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, halosubstituted C₁₋₁₀ alkoxy, hydroxy, aryl, aryl C₁₋₄ alkyl, aryloxy; aryl C₁₋₄ alkyloxy, heteroaryl, heteroarylalkyl, heterocyclic, heterocyclic C₁₋₄alkyl, or heteroaryl C₁₋₄ alkyloxy;
 20 X₂ is =O, or =S;
 R₁ is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted C₁₋₁₀ alkyl; C₁₋₁₀ alkyl; C₂₋₁₀ alkenyl; C₁₋₁₀ alkoxy; halosubstituted C₁₋₁₀ alkoxy; azide; (CR₈R₈)_q S(O)_tR₄, hydroxy; hydroxy C₁₋₄alkyl; aryl; aryl C₁₋₄ alkyl; aryloxy; aryl C₁₋₄ alkyloxy; heteroaryl; heteroarylalkyl; heterocyclic; heterocyclic C₁₋₄alkyl; heteroaryl C₁₋₄ alkyloxy; aryl C₂₋₁₀ alkenyl; heteroaryl C₂₋₁₀ alkenyl; heterocyclic C₂₋₁₀ alkenyl; (CR₈R₈)_qNR₄R₅; C₂₋₁₀ alkenyl C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₅; (CR₈R₈)_q C(O)NR₄R₁₀; S(O)₃R₈; (CR₈R₈)_q C(O)R₁₁; C₂₋₁₀ alkenyl C(O)R₁₁; C₂₋₁₀ alkenyl C(O)OR₁₁;

- $C(O)R_{11}$; $(CR_gR_g)_q C(O)OR_{12}$; $(CR_gR_g)_q OC(O)R_{11}$;
 $(CR_gR_g)_q C(NR_4)NR_4R_5$; $(CR_gR_g)_q NR_4C(NR_5)R_{11}$; $(CR_gR_g)_q$
 $NR_4C(O)R_{11}$; $(CR_gR_g)_q NHS(O)_2R_{17}$; or $(CR_gR_g)_q S(O)_2NR_4R_5$; or two R_1
 moieties together may form $O-(CH_2)_sO$ or a 5 to 6 membered saturated or
 5 unsaturated ring; and wherein the aryl, heteroaryl and heterocyclic containing
 moieties may all be optionally substituted;
 n is an integer having a value of 1 to 3;
 m is an integer having a value of 1 to 3;
 p is an integer having a value of 1 to 3;
 10 q is 0, or an integer having a value of 1 to 10;
 s is an integer having a value of 1 to 3;
 t is 0, or an integer having a value of 1 or 2;
 v is 0, or an integer having a value of 1 to 4;
 HET is an optionally substituted heteroaryl;
 15 R_4 and R_5 are independently hydrogen, optionally substituted C_{1-4} alkyl, optionally
 substituted aryl, optionally substituted aryl C_{1-4} alkyl, optionally substituted
 heteroaryl, optionally substituted heteroaryl C_{1-4} alkyl, heterocyclic, or
 heterocyclic C_{1-4} alkyl, or R_4 and R_5 together with the nitrogen to which they
 are attached form a 5 to 7 member ring which may optionally comprise an
 20 additional heteroatom selected from O/N/S;
 Y is independently selected from hydrogen; halogen; nitro; cyano; halosubstituted
 C_{1-10} alkyl; C_{1-10} alkyl; C_{2-10} alkenyl; C_{1-10} alkoxy; halosubstituted C_{1-10}
 alkoxy; azide; $(CR_gR_g)_q S(O)_tR_4$; hydroxy; hydroxy C_{1-4} alkyl; aryl; aryl C_{1-4}
 alkyl; aryloxy; aryl C_{1-4} alkyloxy; heteroaryl; heteroarylalkyl; heteroaryl C_{1-4}
 25 alkyloxy; heterocyclic, heterocyclic C_{1-4} alkyl; aryl C_{2-10} alkenyl; heteroaryl
 C_{2-10} alkenyl; heterocyclic C_{2-10} alkenyl; $(CR_gR_g)_q NR_4R_5$; C_{2-10} alkenyl
 $C(O)NR_4R_5$; $(CR_gR_g)_q C(O)NR_4R_5$; $(CR_gR_g)_q C(O)NR_4R_{10}$; $S(O)_3R_8$;
 $(CR_gR_g)_q C(O)R_{11}$; C_{2-10} alkenyl $C(O)R_{11}$; C_{2-10} alkenyl $C(O)OR_{11}$;
 $(CR_gR_g)_q C(O)OR_{12}$; $(CR_gR_g)_q OC(O)R_{11}$; $(CR_gR_g)_q NR_4C(O)R_{11}$;
 30 $(CR_gR_g)_q C(NR_4)NR_4R_5$; $(CR_gR_g)_q NR_4C(NR_5)R_{11}$; $(CR_gR_g)_q NHS(O)_2R_a$;
 or $(CR_gR_g)_q S(O)_2NR_4R_5$; or two Y moieties together may form $O-(CH_2)_sO$ or
 a 5 to 6 membered saturated or unsaturated ring; and wherein the aryl, heteroaryl
 and heterocyclic containing moieties may all be optionally substituted;
 R_6 and R_7 are independently hydrogen or a C_{1-4} alkyl group, or R_6 and R_7 together
 35 with the nitrogen to which they are attached form a 5 to 7 member ring which ring

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

R₈ is independently hydrogen or C₁₋₄ alkyl;

R₁₀ is C₁₋₁₀ alkyl C(O)₂R₈;

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

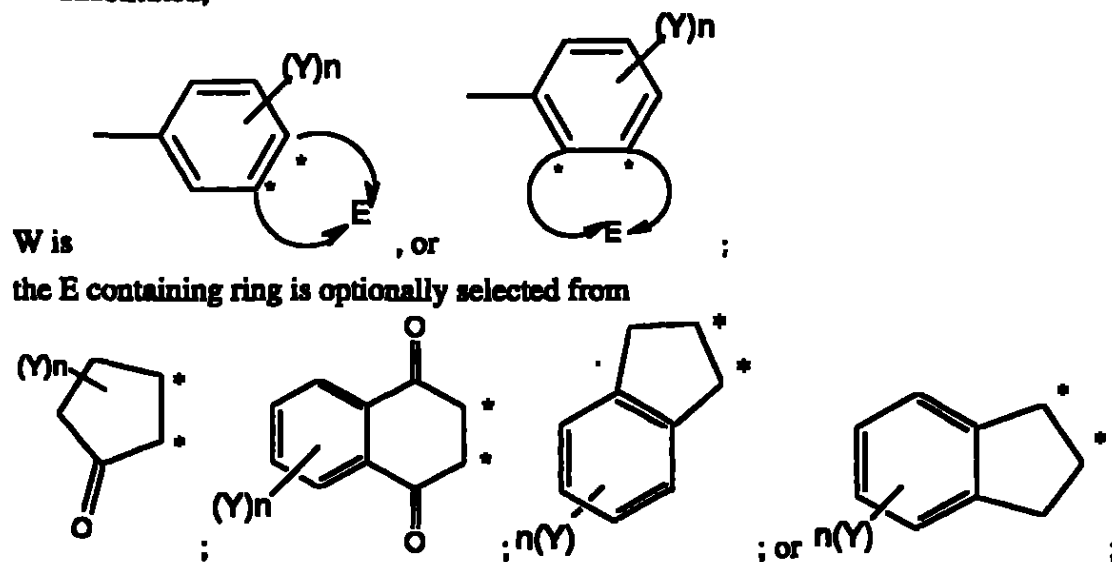
- 10 R₁₂ is hydrogen, C₁₋₁₀ alkyl, optionally substituted aryl or optionally substituted arylalkyl;

R₁₃ and R₁₄ are independently hydrogen, optionally substituted C₁₋₄ alkyl, or one of R₁₃ and R₁₄ may be optionally substituted aryl;

R₁₅ and R₁₆ are independently hydrogen, or an optionally substituted C₁₋₄ alkyl;

- 15 R₁₇ is C₁₋₄alkyl, aryl, arylalkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclicC₁₋₄alkyl, wherein the aryl, heteroaryl and heterocyclic moieties may all be optionally substituted;

20 R₂ is NR₆R₇, alkyl, arylC₁₋₄ alkyl, arylC₂₋₄ alkenyl, heteroaryl, heteroaryl-C₁₋₄alkyl, heteroarylC₂₋₄ alkenyl, heterocyclic, or heterocyclicC₁₋₄ alkyl, wherein the aryl, heteroaryl and heterocyclic moieties may all be optionally substituted;



the asterix * denoting point of attachment of the ring;

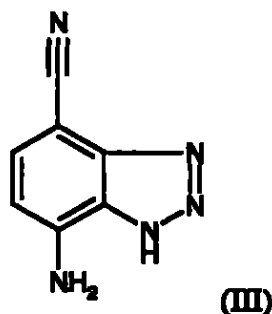
- 25 or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 10 wherein R₁ is halogen, cyano, nitro, CF₃, C(O)NR₄R₅, alkenyl C(O)NR₄R₅, C(O)R₄R₁₀, alkenyl C(O)OR₁₂, heteroaryl, heteroarylalkyl, heteroaryl alkenyl, or S(O)NR₄R₅.
- 5 12. The compound according to Claim 10 wherein X is N.
13. The compound according to any of Claims 10 to 12 wherein Z is W.
14. The compound according to Claim 13 wherein Y is halogen, C₁₋₄ alkoxy, optionally substituted aryl, optionally substituted arylalkoxy, methylene dioxy, NR₄R₅, thioC₁₋₄alkyl, thioaryl, halosubstituted alkoxy, optionally substituted C₁₋₄alkyl, or hydroxy alkyl.
- 10 15. The compound according to Claim 10 which is:
- 15 N-7-(Benzotriazole)-N'-(2-bromophenyl)urea;
N-7-(4-Bromobenzotriazole)-N'-(2,3-dichlorophenyl)urea;
N-7-(4-Bromo-2-trifluoromethyl-benzimidazolyl)-N'-(2-bromophenyl)urea;
N-4-(2-Trifluoromethyl-benzimidazolyl)-N'-(2-bromophenyl)urea;
N-7-(4-Cyano-benzotriazole)-N'-(2,3-dichlorophenyl) urea;
- 20 N-(2-Bromophenyl)-N'-7-(4-cyano-benzotriazole) urea;
N-7-(4-Cyano-2-trifluoromethyl-benzimidazolyl)-N'-(2-bromophenyl) urea;
N-7-(4-Cyano-benzimidazolyl)-N'-(2,3-dichlorophenyl) urea;
N-7-(4-Cyano-benzimidazolyl)-N'-(2-bromophenyl) urea;
N-7-(4-Cyano-benzotriazole)-N'-(2,3-dichlorophenyl)urea;
- 25 or a pharmaceutically acceptable salt thereof.
16. A pharmaceutical composition comprising an effective amount of a compound according to Claim 10, and a pharmaceutically acceptable carrier or diluent.
- 30 17. A method of treating a chemokine mediated disease in a mammal in need thereof, wherein the chemokine binds to an IL-8 a or b receptor, which method comprises administering to said mammal an effective amount of a compound according to Claim 10.
- 35

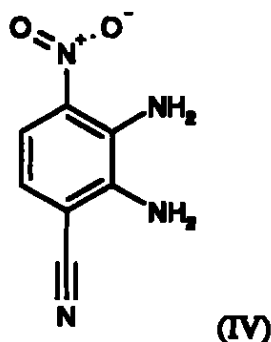
18. The method according to Claim 17 wherein the mammal is afflicted with a chemokine mediated disease selected from psoriasis, atopic dermatitis, asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, or allograft rejections.

19. A process for making a compound of the formula:

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by reacting a compound of the formula:



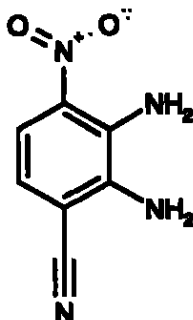
- 15 with sodium nitrite in a protic solvent, followed by reduction of the nitro group to yield a compound of Formula (III).

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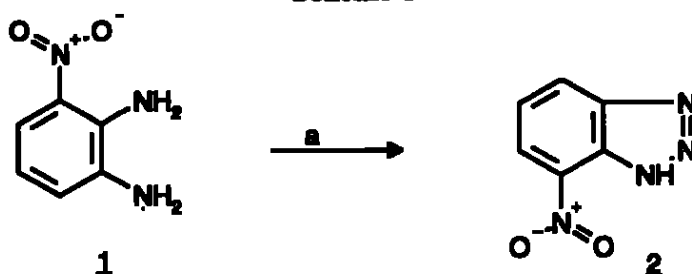
20. A process for making a compound of Formula (IV)



which process comprises reacting 2-cyano-5-nitroaniline with tetramethyl hydrazine
iodide, a strong hindered base, and an aprotic solvent to yield a compound of
5 Formula (IV).

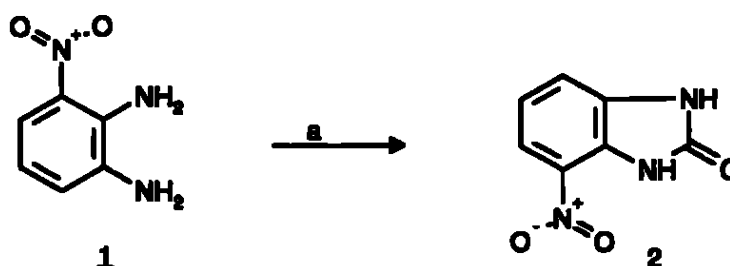
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Scheme 1

a) NaNO₂, HOAc

If the 2-nitro substituted heterocyclic compound 2-scheme 1 is not commercially available it can be made by treating the commercially available 3-nitrophenylenediamine 1-scheme 1 with sodium nitrite in a protic solvent such as HOAc.

Scheme 2

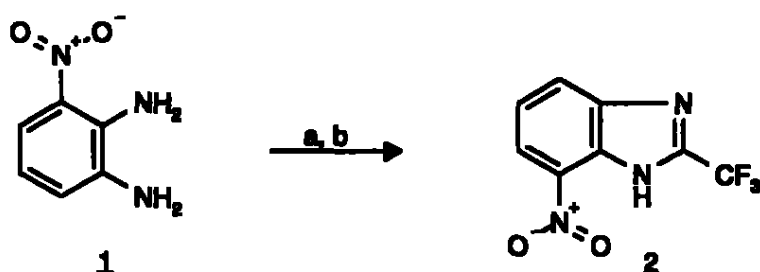
a) Triphosgene, Et₃N, DMF

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If the 2-nitro substituted heterocyclic compound 2-scheme 2 is not commercially available it can be made by treating the commercially available 3-nitrophenylenediamine 1-scheme 2 with triphosgene and triethylamine in DMF or the thiophosgene to form the thio urea.

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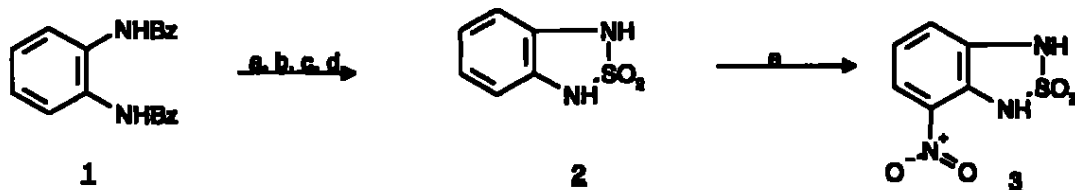
Scheme 3



a) Trifluoroacetic anhydride b) Toluene, reflux

If the 2-nitro substituted heterocyclic compound 2-scheme 3 is not commercially available it can be made by treating the commercially available 3-nitrophenylene diamine 1-scheme 3 with the corresponding anhydride then refluxing in toluene.

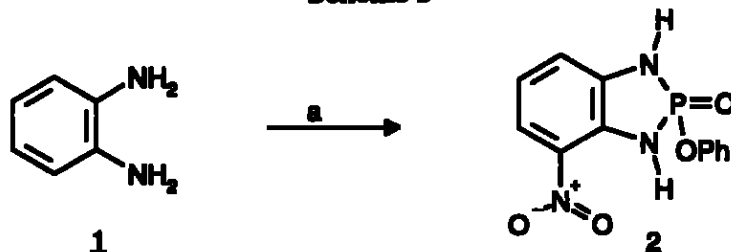
Scheme 4



a) Et_3N , THF, -70°C b) SOCl_2 c) m-CPBA d) H_2 , Pd/C e) NaNO_3 , 3M H_2SO_4

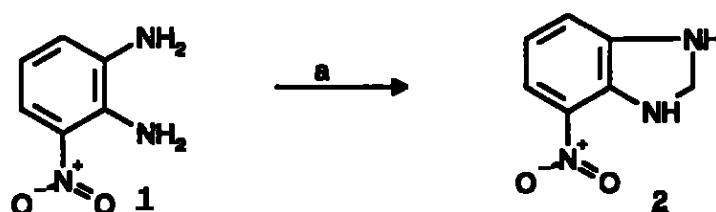
If the 2-nitro substituted heterocyclic compound 3-scheme 4 is not commercially available it can be made by treating compound 2-scheme 4, under standard nitrating conditions (using HNO_3 or NaNO_3) at 23°C . If heterocyclic compound 2-scheme 4 is not commercially available it can be made from the commercially available 1, 2-dibenzylamine 1-scheme 4 with triethylamine at -70°C , then thionyl chloride followed by oxidation with m-CPBA and reduction of the benzyl groups using H_2 / Pd in MeOH.

Scheme 5

a) PhOP(O)Cl_2 b) NaNO_3

- If the 2-nitro substituted heterocyclic compound 2-scheme 5 is not commercially available it can be made by treating the commercially available 1, 2-diamine 1-scheme 5 with PhOP(O)Cl_2 followed by standard nitrating conditions (using HNO_3 or NaNO_3) at 23°C .

Scheme 6

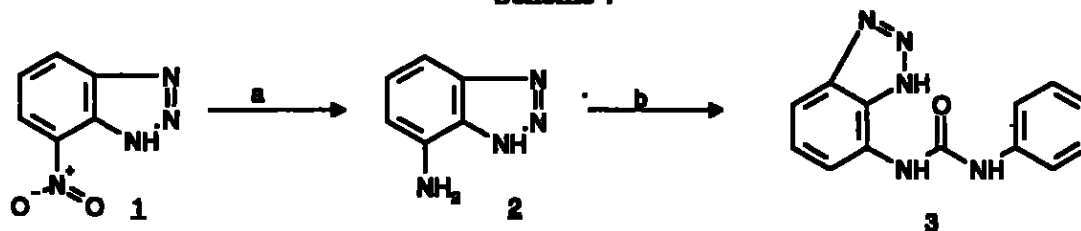


a) Formaldehyde, reflux

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If the heterocyclic compound 2-scheme 6 is not commercially available it can be made by treating the commercially available 1, 2-diamine 1-scheme 6 with formaldehyde at reflux.

Scheme 7

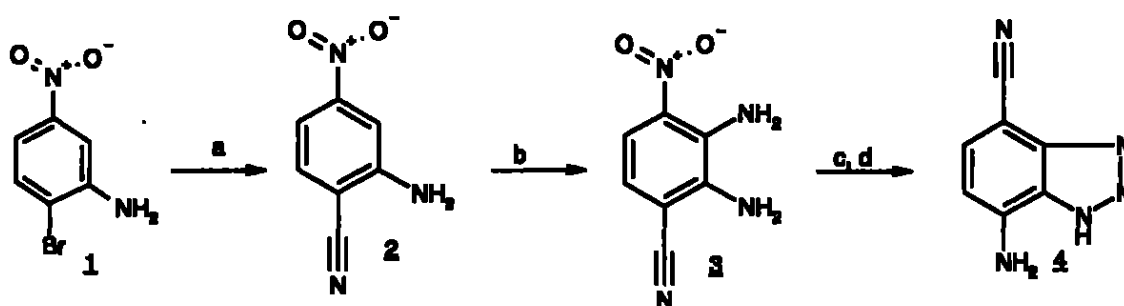
a) H_2 Pd/C, MeOH b) PhNCO , DMF, 80°C

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If the desired aniline 2-scheme 7 is not commercially available the corresponding nitro compound 1-scheme 4 is then reduced under standard condition (H_2 Pd/C or $SnCl_2$). The ortho substituted phenyl urea in 3-scheme 7 may be prepared by standard conditions involving the condensation of the commercially available substituted aryl isocyanate (Aldrich Chemical Co., Milwaukee, WI.) with the corresponding aniline 2-scheme 7 in an aprotic solvent such as (DMF or toluene).

Scheme 8



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a) CuCN, pyridine, DMF b) TMHI, DMSO, Na-t-pentoxide c) NaNO₂, HOAc d) Pd/C H₂ MeOH

If the 7-amino substituted heterocyclic compound 4-scheme 8 is not commercially available it can be made by treating the commercially available 2-bromo-5-nitroaniline 1-scheme 8 with copper (I) cyanide and pyridine in an aprotic solvent such as DMF to form the 2-cyano-5-nitroaniline 2-scheme 8. The diamine 3-scheme 8 can be formed by reacting 2-cyano-5-nitroaniline 2-scheme 8 with tetramethyl hydrazine iodide and a strong hindered base such as sodium t-pentoxide, in an aprotic solvent such as DMSO. The 7-amino-4-cyanobenzotriazole 4-scheme 8 can be made by reacting the diamine 3-scheme 8 with sodium nitrite, in a protic solvent such as HOAc, followed by reduction of the nitro group with a suitably reducing agent, such as Pd/C in MeOH.

20

The amino substituted heterocyclic compound 4-scheme-8 can then be converted to the corresponding urea by condensation with a commercially available isocyanate.

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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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

122

RADICACIÓN: 2-5740

EDICTO No. 2845

LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió Resolución No. 1223 de 28-ENE-2007. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "RECEPTORES DE IL-8, DE BENZO-2-TRIAZOL Y PREPARACION".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Germán Castillo Grau, o a quien haga sus veces, en su calidad de apoderado de Smithkline Beecham Corporation., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición Interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

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

29 ENE 2007

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIR RUBÉN ESCOBAR

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

Secretaría General Ad-Hoc 13-FEB-2007
Secretaría General Ad-Hoc
EDICTO No. 2845

Este edicto se desliza hoy 28-FEB-2007 a las 4:30 p.m.