CAVELIER
ABOGADOS

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EDIFIC
CARRERA
BOGOTA

(1) 347-1611
(1) 610-4995

00 85303
Tramite : 002
Dependencia: 250 DIVISION DE NUEVAS CREACIONES

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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D..

Referencia : Expediente No. 00.085.303
Solicitante : **NEUROGEN CORPORATION**
Asunt : Solicitud de patente para: **"ARILIMIDAZOLES, ARILPIRIDILOS, CICLOALQUILIMIDAZOLES SUSTITUIDOS CON ARILO, ARILPIRAZOLES, TETRAHIDRO ISOQUINOLINAS Y DERIVADOS DE CARBOXAMIDA, COMPUESTOS INTERMEDIOS Y COMPOSICIONES FARMACEUTICAS QUE LOS COMPRENDEN"**
Fecha de la solicitud : 9 de noviembre de 2000

TRAMITE: 002 - EVENTO: 001 - ACTUACION: 444

Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al auto número 4071, notificado por estado del 30 de noviembre de 2000. Para atender a la providencia anterior solicité un plazo por medio de mi memorial número 00085303 00000001 radicado el 15 de enero de 2001.

2. Mediante el auto número 4071 se puso en conocimient del s licitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

2.1. <u>Títul del invento.</u> Para atender a la observación

RESPUESTA AUTO No. 4071 DEL ESTADO
N.I.T. 860.041.367-3 DEL DIA 30 de noviembre de 2000,

hecha por su Despacho en relación al título, presento aquí nuevo título como sigue

ARILIMIDAZOLES, ARILPIRIDILOS, CICLOALQUILIMIDAZOLES SUSTITUIDOS CON ARILO, ARILPIRAZOLES, TETRAHIDROISOQUINOLINAS Y DERIVADOS DE CARBOXAMIDA, COMPUESTOS INTERMEDIOS Y COMPOSICIONES FARMACEUTICAS QUE LOS COMPRENDEN

Adicionalmente presento nuevo formato de solicitud en donde aparece el nuevo título que presento

2 2 **Extracto** Adjunto a este memorial presento nuevo extracto, nueva tarjeta temática y nueva tarjeta de archivo de propietarios (Formas P-103, P-104 y P-105), los cuales están en conformidad con las modificaciones hechas al título

2 3 **Arte Final** Adjunto a este memorial presento los artes finales de acuerdo con lo requerido

2 4 **Copia Certificada** Presento con este escrito copias certificadas de las solicitudes de patente estadounidenses números 60/202,749, 60/212,449, y 60/224,036 del 8 de mayo de 2000, 16 de junio de 2000, y 9 de agosto de 2000, respectivamente, junto con sus respectivas traducciones de sus reivindicaciones y carátula, en la cual se basa la reivindicación de la prioridad

Con relación a la copia certificada de la solicitud de patente estadounidense número 60/221,787 del 31 de julio de 2000, adjunto a este memorial una carta de la Oficina de Marcas y Patentes de los Estados Unidos donde informan las razones por las cuales no han podido expedir

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dicha copia certificada solicitada Desafortunadamente, dicha Oficina de Patentes no tiene aún disponible ni el expediente ni el microfilme de la solicitud 60/221,787 Por lo tanto, le ruego se sirva concederme un plazo prudencial para presentar la copia certificada de dicha solicitud estadounidense sin que el solicitante pierda el derecho a dicha prioridad

3 Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación

Bogotá, - 9 FEB 2001
Señora Jefe,

EMILIO FERRERO
T P A No 31 929

COLO 10611-801-006-0
MRE-51

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PETITORIO

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE SOLICITUD DE PATENTE
2000-3

1 SOLICITUD DE

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

2 SOLICITANTE (71)	Nombre **NEUROGEN CORPORATION** Dirección 35 Northeast Industrial Road, Branford, Connecticut 06405, EE UU Teléfono 546 09 70 E-mail clientes@camyp com Fax 249 40 70 Domicilio Branford Connecticut, EE.UU,	**IDENTIFICACION** C C ☐ NIT ☐ C E ☐ Otro ☐ Número _____
3 REPRESENTANTE O APODERADO (74)	Nombre Emilio Ferrero Dirección Carrera 4ª No 72-35 Teléfono 347 36 11 E-mail cavelier@cavelier com Fax 217 92 11 Domicilio Bogotá, Colombia	**IDENTIFICACI N** C C ☒ NIT ☐ C E ☐ Otro ☐ Número 438 019 TP 31 929
4 INVENTOR(ES) (72)	Nombre 1- Andrew THURKAUF 2- George MAYNARD 3- Xiao-shu HE 4- He ZHAO 5- John PETERSON 6- Xiaoyan ZHANG 7- Robert OHLIGER Dirección **VER HOJA ANEXA**	**IDENTIFICACION** C C ☐ NIT ☐ C E ☐ Otro ☐ Número _____

5 LO (54) ARILIMIDAZOLES, ARILPIRIDILOS, CICLOALQUILIMIDAZOLES SUSTITUIDOS CON ARILO, ARILPIRAZOLES, TETRAHIDRO ISOQUINOLINAS Y DERIVADOS DE CARBOXAMIDA, COMPUESTOS INTERMEDIOS Y COMPOSICIONES FARMACEUTICAS QUE LOS COMPRENDEN

6 Clasificación Internacional (51)

7 Prioridad SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	60/202 749	8-V-2000
US	60/212/449	16-VI-2000
US	60/221 787	31-VII-2000
US	60/224 036	9-VIII-2000

8 Para publicar a partir de la fecha de la presente solicitud a los

6 meses ☐ 12 meses ☐ 18 meses ☒ Otro ☐

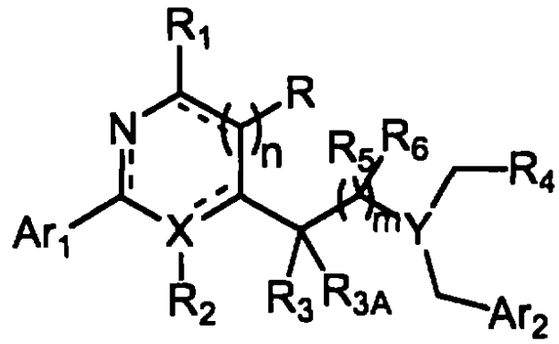
9 Comprobante de pago No _____ **Fecha** _____

4

10 **ANEXOS**

- ☐ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Certificado de existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, *si fuere el caso*
- ☐ Copia certificada de la primera solicitud, si se reivindica prioridad
- ☐ Traducción simple de la primera solicitud, si se reivindica prioridad
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Descripción de la invencion
- ☐ Una o más reivindicaciones
- ☐ Dibujos y/o planos necesarios
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12

11 **FIGURA CARACTERISTICA.**



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NOMBRE EMILIO FERRERO

FIRMA

C.C. 1.438.019 de Usaquén T.P. 31 929

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

R/arc -
20-2018

HOJA ANEXA DOMICILIOS INVENTORES

1 16 Fox Den Road, Danbury, Connecticut 06811, Estados Unidos
2 27 Glenwood Road, Clinton, Connecticut 06413, Estados Unidos
3 50 Foxbridge Village Road, Branford, Connecticut 06405, Estados Unidos
4 4 Stoneridge Lane, Branford, Connecticut 06405, Estados Unidos
5 28 Highland Terrace, Madison, Connecticut 06443, Estados Unidos
6 102 Wicklow Way, Bridgewater, New Jersey 08807, Estados Unidos
7 2115 Durham Road, Madison, Connecticut 06443, Estados Unidos

5 2

Sellos folios 6 / 2
6 / 3 y 6 / 4 para
tramites de ~~[illegible]~~ propietario
domestico y extracto de
publicación

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Royal Technologies S A

Item		Expediente No 0008838	No de Folio 610
		No de Unidades	√
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA	1	
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS		

Observaciones sobre oficio de Arte Final

b/3
610

Arte final
Neurogen Corporation

Equipe arte 12x12
202030 Sep 16 2002

UNITED STATES DEPARTMENT OF COMMER
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington D C 20231

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JANUARY 9, 2001

EDWARDS & ANGELL, LLP

Dear Customer

The purpose of this letter is to document the problems associated with filling your request for a certified copy of a provisional application 60/221,787

The original request, for the copies was dated, and received in our office December 18, 2000 Unfortunately, the paper file, nor the microfilm is not available Therefore, we have not been able to provide the certified copy in a timely manner When the media becomes available we will process your request as soon as possible

I apologize for any inconvenience resulting from the delay

Sincerely,

A Jones
Office of Public Records
Customer Service Representative
(703) 308-9726



PTO 248B12

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

December 26, 2000

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

APPLICATION NUMBER ***60/202,749***
FILING DATE ***May 08, 2000***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

E. Bornett

E. BORNETT
Certifying Officer

05-01-00 A/PROV

Customer Number 000959

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of

Attorney Docket No. N 2000.004

For

Assistant Commissioner For Patents
Box Provisional patent Application
Washington, DC 20231

CERTIFICATION UNDER 37 CFR 1 10

Date of Deposit 05/05/00 Mailing Label Number EJ898809998US

I hereby certify that this Cover Sheet for Filing Provisional Application (37 C.F.R. § 1.51(2)(1) and the documents referred to as attached therein are being deposited with the United States Postal Service on the date indicated above in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1 10 and addressed to the Assistant Commissioner for Patents, Box Provisional Patent Application Washington DC 20231

Leslie-Anne Horvath
Name of Person Mailing Paper

Signature of Person Mailing Paper

COVER SHEET FOR FILING PROVISIONAL PATENT APPLICATION

Dear Sir

The accompanying application, entitled ***Aryl Cycloalkyimidazoles***, is a provisional patent application under 37 C F R § 1.51 (a)(2) and § 1 53 (b)(2)

1 ☐ The names and addresses of the inventors of this application are as follows

	Last Name	First Name	Middle Initial	Residence
1	Thurkauf	Andrew		16 Fox Den Road Danbury, CT 06811
2	Zhao	He		4 Stonebridge Lane Branford, CT 06405
3	He	Xiao-shu		50 Foxbridge Village Road Branford, CT 06405
4				
5				
6				

Attorney Docket NGF-001

#9

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2 ☐ This invention was made by an agency of the United States Government or under contract with an agency of the United States Government The name of the U S Government agency and the Government contract number are

Agency _____

Contract No _____

3 ☒ The following documents are enclosed

☒ 109 pages of Applicationn (*includes Specification and Claims)*

☒ 1 page of abstract

4 ☒ A verified statement to establish small entity status under 37 CFR 1 9 and 1 27 is enclosed.

5 ☐ An Assignment of the invention to _____ is enclosed. A check in the amount of $40 00 for recording this assignment and a recordation form cover sheet (Form PTO 1595) are also enclosed.

6 ☒ The fee for filing this provisional application, as set forth in 37 CFR 1 16(k), is $75.000

a. ☐ **A check for this filing is enclosed.**

b ☒ Charge the filing fee to Deposit Account No 501116

c ☐ The filing fee is not being paid at this time.

7 ☐ Please charge any fee deficiencies associated with this filing to Deposit Account No 501116 *A duplicate copy of this sheet is enclosed.*

Please address all future communications to

Patent Department
Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405

and direct telephone calls to Leslie-Anne Horvath or Seth A Fidel

Respectfully submitted,

5/8/00
Date

Leslie-Anne Horvath
Registration No 44,778

Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

US Express Mailing No EL980050 • 6472020 US

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APPLICATION FOR UNITED STATES LETTERS PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ARYL CYCLOALKYLIMIDAZOLES

BACKGROUND OF THE INVENTION

008050-6h/20209

1 Field of the Invention

This invention relates to certain heterocyclic derivatives which when appropriately substituted, are modulators of human complement C5a receptors This invention also relates to pharmaceutical compositions comprising such compounds It further relates to the use of such compounds in treating a variety of inflammatory and immune system disorders Additionally, this invention relates to the use such compounds as probes for the localization of C5a receptors

2 Description of Related Art

Inflammation is the normal physiological response to cellular injury - microbial infection, physical or chemical trauma, or invasion of cancerous cells While necessary to remove infectious particles and damaged tissue, inflammation can also cause pain and further tissue damage Pathogenic

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inflammation is associated with various diseases, and is a hallmark of autoimmune disease

Proteins of the complement cascade play a key role in the mediation of inflammation This system of more than 20 interacting soluble and membrane-bound proteins undergoes a series of proteolytic reactions that set in motion a number of important immune functions including the recruitment of leukocytic cells to sites of injury and/or infection Additionally, proteins of the complement system mediate changes in vascular permeability and blood flow, target cells for opsonization, and effect formation of the membrane attack complex, which mediates the immune lysis of foreign cells

WO 95/08050 PCT/US94/10279

C5a, a 74 amino acid peptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement enzyme C5 convertase The anaphylatoxic effects of the C5a peptide are mediated through the C5a receptor, a 52 kD membrane bound G-coupled protein receptor C5a is a potent chemoattractant for polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to the site of cellular injury Additionally, C5a stimulates the release of inflammatory mediators (e g , histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes, C5a

also promotes the production of activated oxygen radicals and the contraction of smooth muscle

Considerable experimental evidence implicates increased levels of C5a in a number of autoimmune diseases and inflammatory and related disorders Such autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus, psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, and immunovasculitis Such inflammatory and related conditions include neutropenia, sepsis, septic shock, artherosclerosis, Alzheimer's disease, vascular occlusion, post-surgical vascular reocclusion, stroke, coronary thrombosis, and myocardial infarction lung injury, and acute respiratory distress syndrome (ARDS), tissue graft rejection, hyperacute rejection of transplanted organs, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephris and pulmonary hemorrhage), myasthenia gravis, pathologic sequellae associated with insulin-dependent diabetes mellitus, glomerulonephristis, ischemic heart disease, inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (e g , during hemodialysis or via a heart-lung machine, for example, in association with heart surgery such as coronary artery bypass grafting or heart valve replacement) such as extracorporeal post-dialysis syndrome or in

WO 02/074900 PCT/US02/08800

association with contact with other artificial vessel or container surfaces (e g , ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, and the like) Antagonists that block the binding of C5a to its receptor or which modulate signal transduction associated with C5a-receptor interactions can inhibit the pathogenic chemotaxis associated with such inflammatory and autoimmune conditions Indeed, certain modified C5a peptides have been identified as C5a antagonists and have been shown to block a number of C5a mediated actions including neutrophil chemotaxis, neutropenia and superoxide formation

SUMMARY OF THE INVENTION

The present invention provides novel substituted 1-alkyl-2-aryl-4,5-cycloalkylimidazoles The invention also provides novel compounds of Formula I, shown below, that bind specifically, and preferably with high affinity, to C5a receptors Preferred C5a receptors are mammalian receptors, including human C5a receptors and may either be cloned, recombinantly expressed receptors or naturally expressed receptors

Novel intermediates useful for synthesizing compounds of the invention are also provided

The invention also provides pharmaceutical compositions comprising compounds of Formula I The compounds are particularly useful in the treatment of C5a-mediated

inflammation, e g , inflammation associated with various inflammatory and immune system disorders The invention further comprises a method of treating a patient in need of such anti-inflammatory treatment with a sufficient concentration of a compound of the invention A preferred concentration is one sufficient to inhibit white blood cell chemotaxis in vitro Treatment of humans, domesticated companion animals (pets) or livestock animals suffering such conditions with an effective amount of a compound of the invention is contemplated by the invention

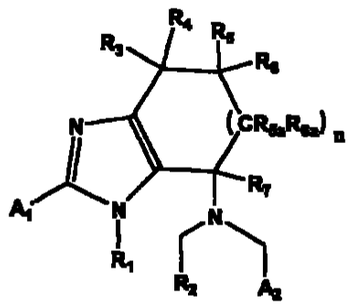
In a separate aspect, the invention provides methods of using compounds of this invention as positive controls in assays for receptor activity and using appropriately labeled compounds of the invention as probes for the localization of receptors, particularly C5a receptors in tissue sections

The invention provides compounds and compositions that are useful as inhibitors of C5a-mediated chemotaxis (e g , they may be used as standards in assays of such chemotaxis) The invention additionally comprises methods of inhibiting C5a-mediated chemotaxis, preferably leukocyte chemotaxis, the methods comprising contacting white blood cells with a chemotaxis-inhibitory concentration of a compound of the invention Preferably the concentration is sufficient to inhibit chemotaxis of white blood cells in an *in vitro* chemotaxis assay, so that the

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levels of chemotaxis observed in a control assay (e g , one to which a compound of the invention has not been added) are significantly higher (significantly here measured as $p<0.05$ using a conventional parametric statistical analysis method) than the levels observed in an assay to which one or more compounds of the invention have been added

Accordingly, a broad embodiment of the invention is directed to compounds of Formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3 and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl (i e cyclopentylmethyl), or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted

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heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

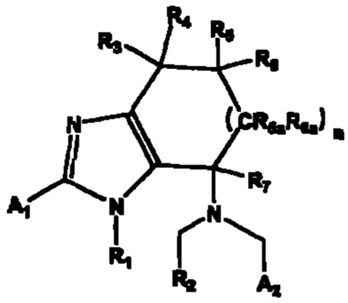
A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

WO 02/074900 PCT/US02/08800

DETAILED DESCRIPTION OF THE INVENTION

The invention provides novel compounds of Formula I, shown above that bind to specific cellular receptors Preferably the receptors are cell surface receptors, more preferably G-protein coupled receptors, and most preferably the receptors are C5a receptors Preferred compounds of the invention are those of Formula IA



Formula IA

or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

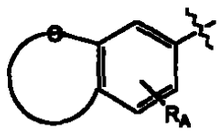
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each of which may be substituted or unsubstituted, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached may form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, alkyl, alkoxy, cyano, amino, mono- or

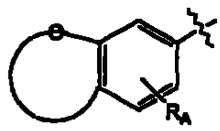
dialkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-trifluoromethyl, trifluoromethoxy or $-XR_B$, wherein X and R_B are as defined below, or

A_1 is thiophene or pyridine which is unsubstituted or may be substituted with alkyl, halogen, alkoxy, amino or mono or dialkylamino

A_2 is pheryl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from

halogen, alkyl, alkoxy, cyano, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy, or $-XR_B$, wherein X and R_B are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



EP0274849.050800

wherein R_A' is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

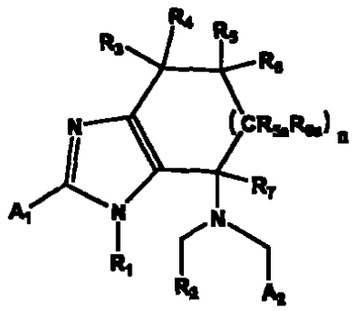
X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from

oxo, hydroxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_x$(alkyl), $-S(O)_x$(alkyl), $-S(O)_xNH$(alkyl), $-S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2)

Also preferred are compounds of Formula IB



Formula IB

or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

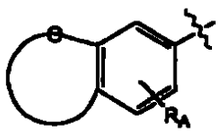
R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group (i e an oxygen containing small ring such as furan, dioxolane, dioxane or the like, fused to phenyl) of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, and C_1-C_7 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono

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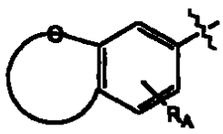
or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_8$, wherein X ard R_8 are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino, and

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cvano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NHC(O)($ C_1-C_4 alkyl), $-N(C_1$-C_4 alkyl)$C(O)($ C_1-C_4 alkyl), $-NHS(O)_x(C_1$-C_4 alkyl), $-S(O)_x(C_1$-C_6 alkyl), $-S(O)_xNH(C_1$-C_4 alkyl), $-S(O)_xN(C_1$-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

Particularly preferred compounds of Formula IB include those for which

R_3 and R_4 are the same or different and represent hydrogen or

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methyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are irdependently selected at each occurrence from hydrogen and methyl, and

n, R_1, R_2, R_7, A_1, and A_2 are as defined above for Formula IB

More preferred compounds of Formula IB include those wherein

R_3 and R_4 hydrogen,

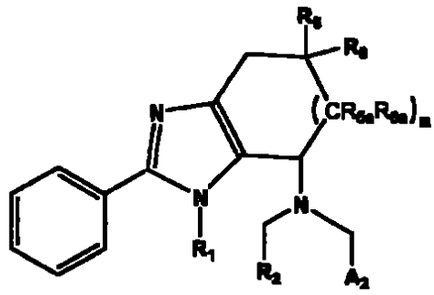
R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl, and

n, R_1, R_2, R_7, A_1, and A_2 are as defined above for Formula IB

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Other preferred compounds of the invention are compounds of Formula II



Formula II

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or a pharmaceutically acceptable salt thereof, wherein

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

R_1, R_2, A_2, and n are as defined above for Formula IB

Particularly preferred compounds of Formula II include those wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

R_2, A_2, and n are as defined above for Formula IB

Additional preferred compounds of Formula II include those wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

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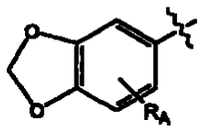
R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and A_2, and n are as defined above for Formula IB

Yet more preferred compounds of Formula II include those wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is phenyl, which may be unsubstituted or substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

A_2 is phenyl which is unsubstituted or substituted with up to four groups independently selected from

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halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined for Formula IB, above,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

n is as defined for Formula IB, above

Preferred compounds of Formula II also include those wherein

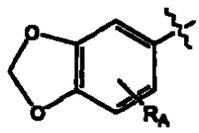
R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

A_2 is a bicyclic oxygen containing group of the formula

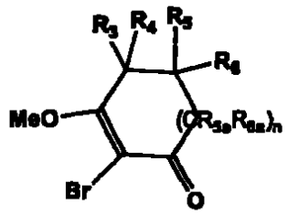


wherein R_A' is as defined above for Formula IB, and

n is as defined for Formula IB

For all preferred compounds of the invention the pharmaceutically acceptable salts thereof are included as part of the invention

Also provided are novel intermediates useful for synthesizing compounds of the invention and methods of synthesizing compounds of the invention using such intermediates Specifically provided are compounds of Formula III



Formula III

wherein

n is an integer from 0 to 3,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

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R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkoxy, or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring, and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, hydroxy, halogen, alkoxy, and alkyl

Preferred compounds of Formula III are those where

n is an integer from 0 to 3,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms, and

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen and C_1-C_7 alkyl Such compounds are known as compounds of Formula IIIA

More preferred compounds of Formula III are those where

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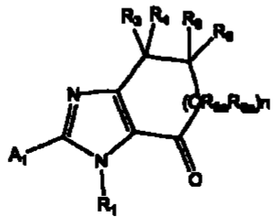
n is an integer from 0 to 3,

R_3 and R_4 are hydrogen, and

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurence represent hydrogen and methyl Such compounds are known as compounds of Formula IIIB

Also provided as intermediates are compounds of Formula IV



Formula IV

wherein

n is an integer from 0 to 3,

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl (i e cyclopentylmethyl), or haloalkyl, each of which may be substituted or unsubstituted,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, hydroxy, halogen, alkoxy or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, hydroxy, halogen, alkoxy and alkyl, and

A_- is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

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Preferred intermediates of Formula IV include those compounds in which

n is an integer from 0 to 3,

R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms, and

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen or C_1-C_7 alkyl, and

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_B$, wherein X and R_B are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of

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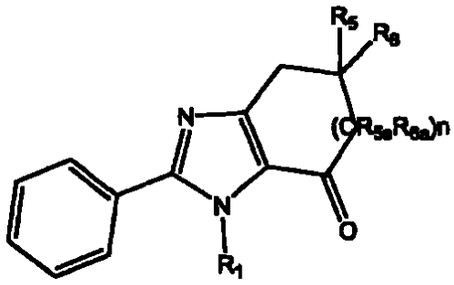
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hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, -O(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -NHS(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$NH(C_1-C_4 alkyl), -S(O)$_x$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

Such compounds are known as compounds of Formula IVA

Especially preferred intermediates of Formula IV are compounds of Formula IVB



Formula IVB

wherein

n is an integer from 0 to 3,

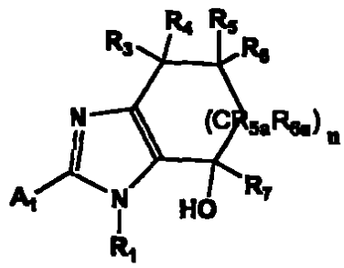
R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

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R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and C_1-C_7 alkyl,

Other intermediates included in the invention are those of Formula V



Formula V

wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3

rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, hydroxy, halogen, alkoxy or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, hydroxy, halogen, alkoxy and alkyl,

R_7 represents hydrogen or alkyl, and

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

Preferred intermediates of Formula V include those compounds in which

n is an integer from 0 to 3,

R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

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R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which tney are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and and are independently selected at each occurrence from hydrogen and C_1-C_7 alkyl,

R_7 represents hydrogen or alkyl, and

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from:

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_8$, wherein X and R_8 are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group

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consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

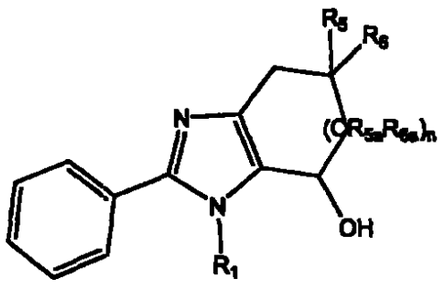
R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$(C_1-C_4$ alkyl), $-NHC(O)(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl$)C(O)(C_1-C_4$ alkyl), $-NHS(O)_x(C_1-C_4$ alkyl), $-S(O)_x(C_1-C_4$ alkyl), $-S(O)_xNH(C_1-C_4$ alkyl), $-S(O)_xN(C_1-C_4$ alkyl$)(C_1-C_4$ alkyl), (where x is 0, 1, or 2)

Such compounds are known as compounds of Formula VA

Especially preferred intermediates of Formula V are compounds of Formula VB



Formula VB

wherein

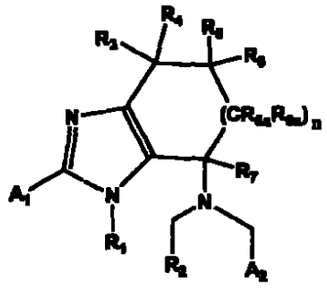
n is an integer from 0 to 3,

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl

The invention also includes a process for preparing a compound of the formula



wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or

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haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkoxy, or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, hydroxy, halogen, alkoxy, or alkyl,

R_7 represents hydrogen or alkyl,

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3

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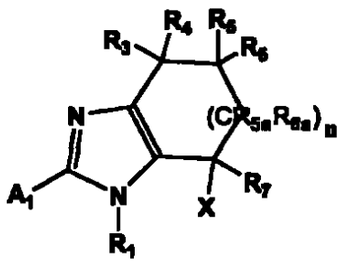
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hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

the process comprising

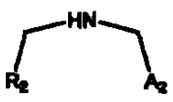
reacting a compound of the formula



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wherein X is halogen or sulfonate ester,

in a suitable solvent in the presence of a suitable base with a secondary amine of the formula



Suitable solvents include dimethyl chloride, tetrahydrofuran, 1,2-dichloroethane, dimethylformamide, and the like Suitable bases include potassium carbonate, sodium triacetoxyborohydride, triethylamine, N-methylmorpholine and the like

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In a preferred embodiment of the above process,

X is halogen or sulfonate ester,

and the variables n, A_1, A_2, R_1, R_2, R_3, R_4, R_5, R_6, R_{5a}, R_{6a}, and R_7 are defined as follows

n is an integer from 0 to 3, and

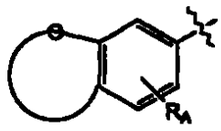
R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-

C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, and C_1-C_7 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_8$, wherein X and R_8 are as defined below, or

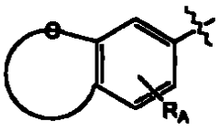
A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or

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mono or di(C_1-C_6)alkylamino, and

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_B$, wherein X and R_B are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

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$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)(C_1-C_4 alkyl), $-NHC(O)($ C_1-C_4 alkyl), $-N(C_1-C_4$ alkyl)$C(O)($ C_1-C_4 alkyl), $-NHS(O)_x(C_1-C_4$ alkyl), $-S(O)_x(C_1-C_4$ alkyl), $-S(O)_xNH(C_1-C_4$ alkyl), $-S(O)_xN(C_1-C_4$ alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

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In certain situations, the compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms These compounds can be, for example, racemates or optically active forms In these situations, the single enantiomers, i e , optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates Resolution of the racemates can be accomplished, for example, by conventional methods such as

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crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds of Table 1 and their pharmaceutically acceptable salts Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0 - 4, and the like Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts

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The present invention also encompasses the acylated prodrugs of the compounds of Formula I Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compound encompasses by Formula I

As indicated above, various substituents of the various formulae may be "substituted or unsubstituted", including A_1, A_2, R_1, and R_2 of Formula I, and such substituents as recited in the sub-formulae such as Formulae II and the like When substituted, those substituents (A_1, A_2, R_1, and R_2) may be substituted by other than hydrogen at one or more available positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as

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those disclosed herein Suitable groups that may be present on a "substituted" A_1, A_2, R_1, and R_2 group or other substituent include e g halogen such as fluoro, chloro, bromo and iodo, cyano, hydroxyl, nitro, azido, alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like, carboxamido, alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms, alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, aryloxy such as phenoxy, alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, carbocyclic aryl having 6 or more carbons, particularly phenyl (e g an Ar group being a substituted or unsubstituted biphenyl moiety), aralkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred

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group, aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group, or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e g coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl

When "araalkyl" is specified in the present invention the point of attachment is the alkyl group

By the term "C_1-C_x alkyl" in the present invention is meant straight or branched chain alkyl groups having 1 to x carbon atoms, generally up to 6 or 7 carbon atoms, such as, for example, methyl, ethyl, propyl, iscpropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl Preferred C_1-C_6 alkyl groups are methyl, ethyl, propyl, butyl, pentyl and cyclopentyl

By the term "alkyloxy" is meant the group -O-R wherein R is alkyl as defined above

The term "C_1-C_x alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-

butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy

The term "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl

The term "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl

The term "Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl

In the term "(C_{3-x} cycloalkyl)C_{1-y} alkyl the point of attachment is on the alkyl group This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl, cyclohexylmethyl

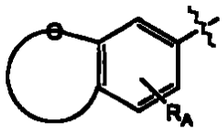
The term "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w =1 to (2v+1) Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl

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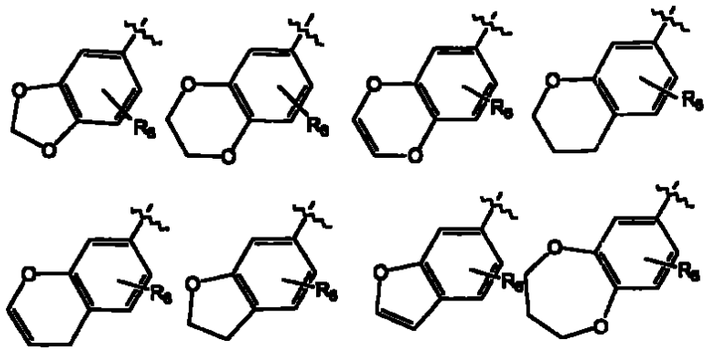
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By the term "halogen" is meant fluorine, chlorine, bromine or iodine

Examples of bicyclic oxygen containing groups of the formula



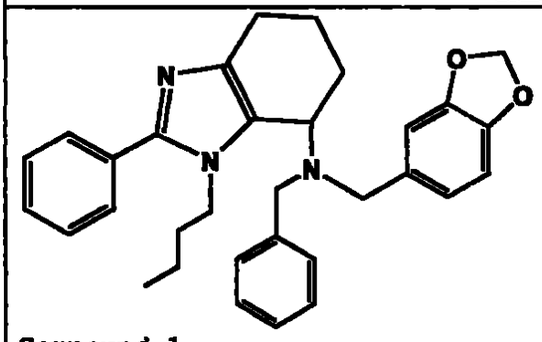
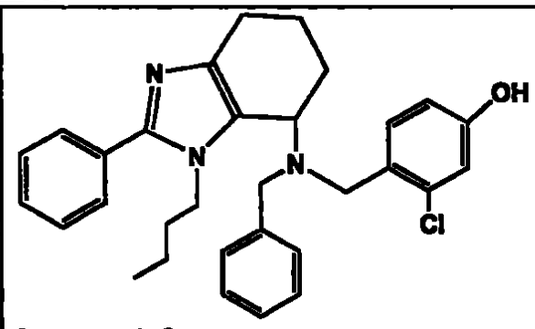
include the following



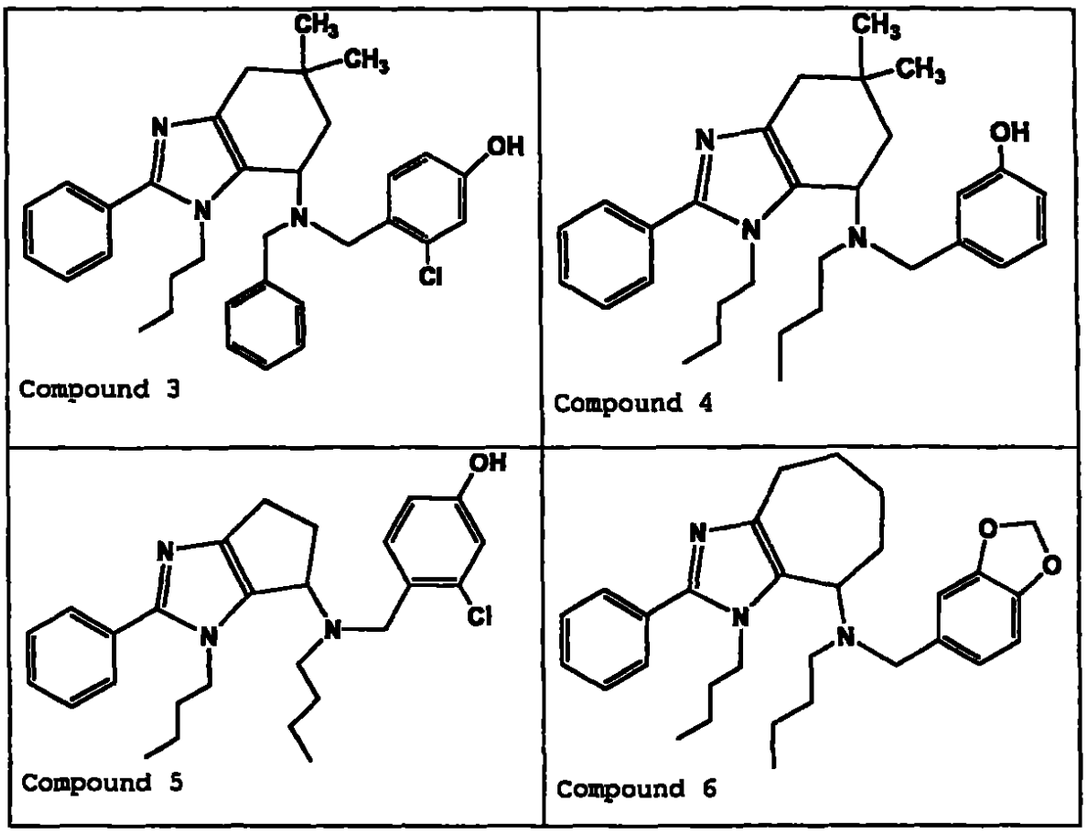
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Representative compounds of the invention are shown in Table 1

TABLE 1

 Compound 1	 Compound 2

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The invention also includes methods for the treatment or prevention of various inflammatory and immune system disorders, such as for example rheumatoid arthritis and Crohn's disease, which comprises administering to a patient in need of such treatment a compound of the invention The interaction of compounds of the invention with C5a receptors is shown by the inhibition of C5a-mediated chemotaxis e g , as described in Example 5 While not wishing to be bound by any particular theory of operation, it is believed that this interaction results

in the pharmacological activity of these compounds This invention includes compounds that inhibit C5a mediated chemotaxis Preferred compounds exhibit EC_{50} values of less than 1 μM in an assay of C5a mediated chemotaxis, more preferred compounds exhibit EC_{50} values of less than 500 nM, and most preferred compounds exhibit EC_{50} values of less than 250 nM

This invention also includes compounds that act as are selective modulators of G-coupled protein receptors, especially the C5a receptor Preferably, compounds of this invention do not bind to dopamine receptors Most preferably compounds of this invention do not exhibit binding constants less than 1 μM at dopamine receptors in a standard radioligand binding assay for dopamine binding activity (US patent no 5,159,083 is hereby incorporated by reference for its teachings in regard to such assays at col 8)

The present invention also pertains to methods of inhibiting the binding of C5a to C5a receptors which methods involve contacting a compound of the invention with cells expressing C5a receptors, wherein the compound is present at a concentration sufficient to inhibit C5a binding to C5a receptors *in vitro* This method includes inhibiting the binding of C5a to C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of C5a to C5a receptors *in vitro* In one embodiment, such methods are useful in

treating physiological disorders associated with excess concentrations of C5a The amount of a compound that would be sufficient to inhibit the binding of a C5a to the C5a receptor may be readily determined via a C5a receptor binding assay, or from the EC_{50} of a C5a receptor functional assay, such as the standard assay of C5a receptor mediated chemotaxis described in Example 5 The C5a receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of leukocytes or from cells expressing cloned human C5a receptors, e g human promonocytic U937 cells

The present invention also pertains to methods for altering the activity of C5a receptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white blood cells *in vitro* This method includes altering the activity of C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I that would be sufficient to alter the chemotactic responses to C5a of white blood cells *in vitro* The amount of a compound that would be sufficient to alter the chemotactic activity of C5a receptors may be determined via an assay of C5a receptor mediated chemotaxis, such as the standard assay described in Example 5

The C5a receptor ligands provided by this invention and

labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the C5a receptor

Labeled derivatives the C5a receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT)

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred The term parenteral as used herein includes injections and the like, such as subcutaneous, intradermal, intravascular (e g , intravenous), intramuscular, intrasternal, spinal, intrathecal, and like injection or infusion techniques, with subcutaneous, intramuscular and intravascular injections or infusions being preferred In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients The pharmaceutical compositions containing

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compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, corn starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed

Formulations for oral use may also be presented as hard

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gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin

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Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparatiors These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above Additional excipients, for example sweetening, flavoring and coloring agents, may also be present

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example

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sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides In addition, fatty acids such as oleic acid find use in the preparation of injectables

The compounds of general Formula I may also be administered in the form of suppositories e g , for rectal administration of the drug These compositions can be prepared by mixing the drug

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with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug Such materials are cocoa butter and polyethylene glycols

Compounds of general Formula I may be administered parenterally, preferably in a sterile non-toxic, pyrogen-free medium The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle

Dosage levels of the order of from about 0 1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0 5 mg to about 7 g per patient per day) The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient

Frequency of dosage may also vary depending on the compound used and the particular disease treated However, for treatment of most disorders, a dosage regimen of 4 times daily, three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred

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It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i e , other drugs being administered to the patient), the severity of the particular disease undergoing therapy, and other factors, including the judgment of the prescribing medical practitioner

Preferred compounds of the invention will have favorable pharmacological properties Such properties include, but are not limited to bioavailability (e g , oral bioavailibilty), low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lifes Distribution in the body to sites of complement activity is also desirable, e g , compounds to treat compounds used to treat CNS disorders will preferably penetrate the blood brain barrier, while low brain levels of compounds used to treat periphereal disorders are often preferred

Assays may be used to predict these desirable pharmacological properties Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers Toxicity to cultured hepatocyctes may be used to predict compound toxicity Penetration of the blood brain barrier of a compound in humans

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may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously

Serum protein binding may be predicted from albumin binding assays Such assays are described in a review by Oravcová, et al (Journal of Chromatography B (1996) volume 677, pages 1-27)

Compound half-life is inversely proportional to the frequency of dosage required for the effective administration of a compound *In vitro* half-lifes of compounds may be predicted, e g , from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127)

The present invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to C5a receptor modulation, e g , any of the inflammatory or autoimmune disorders discussed above as the "background of the invention" including but not limited to arthritis, ARDS, and Alzheimer's Disease The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one C5a receptor modulator as described supra and instructions for its use for the treatment of a disorder responsive to C5a receptor modulation

An illustration of the preparation of compounds of the present invention is given in Scheme 1 Those having skill in the art will recognize that the starting materials may be varied

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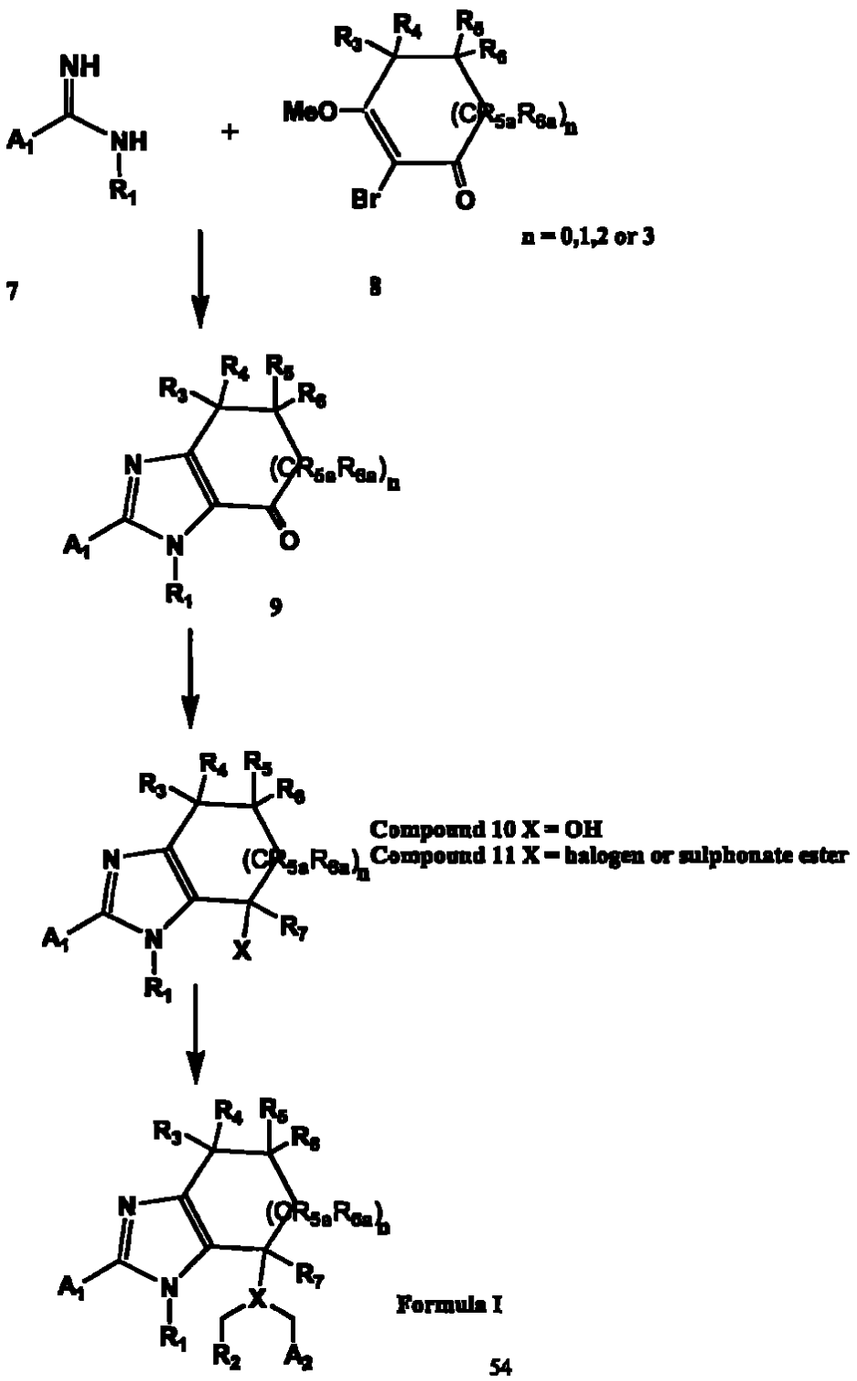
and additional steps employed to produce compounds encompassed by the present invention Within Scheme 1 the variables n, A_1, A_2, R_1, R_2, R_3, R_4, R_5, R_6, R_{5a}, R_{6a}, and R_7 are defined as previously described for Formula I

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Scheme 1. Preparation of Compounds of Formula I



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As shown in Scheme 1, an appropriately substituted arylamidine 7 is condensed with an appropriately substituted 2-halo-3-alkoxyenone 8 to provide a 2-aryl-4,5-cycloalkylimidazole 9 The ketone functionality of 9 can be either reduced (R_7 = H) or treated with the appropriate by treatment with the appropriate organometallic (for cases where R_7 is alkyl) to give the cyclic alcohol 10 Compounds of general formula 11 can be prepared from 10 by one of several methods described in the chemical literature, for instance, by treatment with thionyl chloride or by treatment with an alkyl or arylsulphonyl chloride in the presence of base

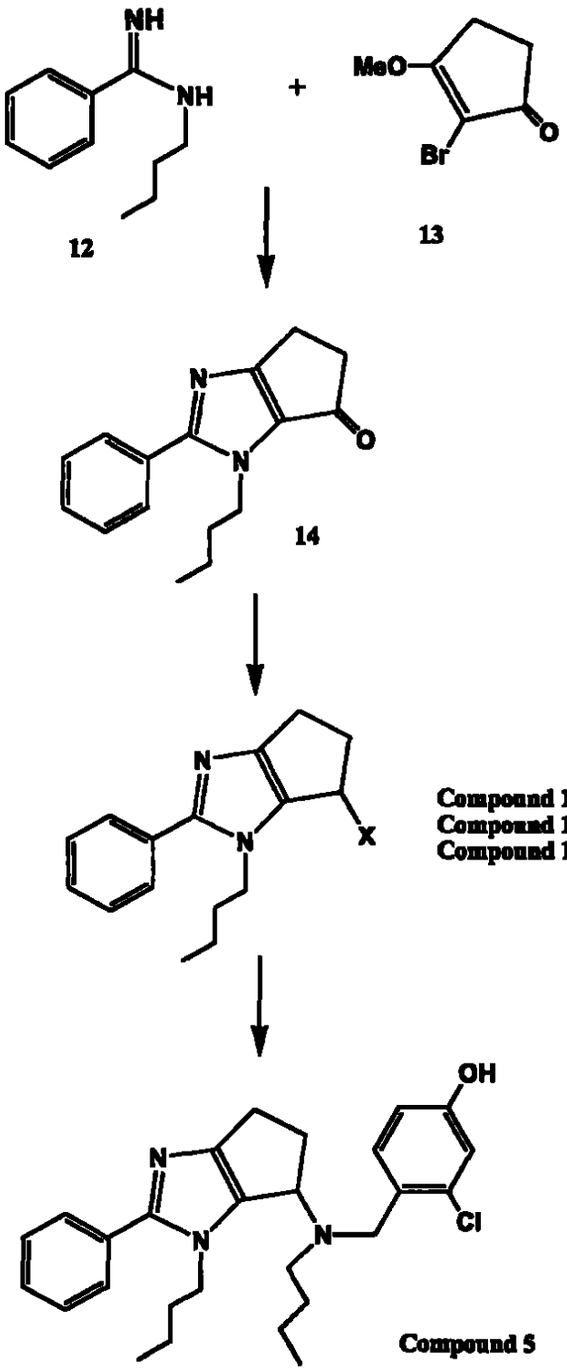
Compounds of formula 11 can then be transformed into compounds of general Formula I by direct treatment with the appropriate secondary amine Alternatively, the X functionality of 11 may be transformed into a tertiary amine in a stepwise manner In this case, 11 would be treated with a primary amine to provide an intermediate secondary amine This, in turn, could be alkylated to give compounds of general Formula I

Scheme 2 is a graphical representation of the preparation of a specific compound of this invention (Compound 5) according to the general route described graphically in Scheme 1 The preparation of Compound 5 and the subsequent demonstration of

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670

its ability to inhibit C5a mediated chemotaxis represents a reduction to practice of the described invention

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0080502 .4720209

The invention is further illustrated by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them

EXAMPLE I

Preparation of 4-{[butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol (Compound 5, Table 1)

N-(n-butyl)-benzamidine (12) To a solution of methyl benzimidate hydrochloride (12 g, 0 07 mole) in dimethylformamide (DMF, 20 mL) was added 7 ml of triethylamine at 0 °C After 2 h the reaction was filtered to remove triethylamine hydrochloride To the filtrate was added 3 68 g of 1-butylamine and the mixture heated to 60 °C for 6 h After cooling the mixture was partitioned between ethyl acetate and water The organic layer was washed with brine, dried over sodium sulfate and concentrated to provide 13 28 g of the amidine as a yellow oil ^{1}H NMR ($CDCl_3$) 7 55 (m, 2H), 7 4 (m, 3H), 3 37 (bm, 2H), 1 62 (m, 2H), 1 42 (m, 2H), 0 95 (t, J = 7 Hz, 3H)

2-Bromo-3-methoxycyclopentenone (13) was prepared via the method of Curran et al JACS, vol 112, page 5601 To a suspension of 1,3-cyclopentanedione (10 g) in chloroform (700 ml) was added

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a N-bromosuccinimide (18 2 g) The mixture was refluxed for 2 h, cooled and concentrated Methanol (700 mL) and p-toluenesulfonic acid (1 g) were added and the solution was refluxed overnight The mixture was concentrated to 100 ml, diluted with methylene chloride (500 mL) and poured into water The aqueous layer was discarded and the organic layer was washed with water (3 X 100 mL), dried (Na_2SO_4) and concentrated The residue was crystallized from ethyl acetate to give 13 as tan crystals (1 67 g)

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1-Butyl-2-phenyl-4,5-dihydrocyclopenty[1,2-d]imidazol-6-one (Compound 14, Scheme 2) To a mixture of amidine 12 (3 52 g, 20 mmol) and enone 13 (4 58 g, 24 mmol) in chloroform (40 mL) and water (5 mL) was added solid potassium carbonate (3 32 g, 24 mmol) The resulting mixture was refluxed overnight After cooling, the mixture was washed with water, dried (Na_2SO_4) and concentrated Purification on silica gel eluting with 25% ethyl acetate/hexane gave the desired product **14** (3 0 g)

LC-MS (M^++1) 255

^{1}H-NMR (δ, $CDCl_3$) 0 84 (t, J = 7 6 Hz, 3H), 1 23 (dt, J = 7 0, 7 6 Hz, 2H), 1 81 (m, 2H), 2 95 (m, 4H), 4 13 (t, J = 7 6 Hz, 2H) 7 5-7 45 (m, 3H), 7 76-7 6 (m, 2H) ppm

1-Butyl-2-phenyl-4,5-dihydrocyclopenty[1,2-d]imidazol-6-ol (Compound 15, Scheme 2) To a solution of 14 (2 68 g) in methanol (20 mL) was added sodium borohydride (1 5 equiv) and the mixture stirred overnight The mixture was concentrated, diluted with chloroform and washed with 0 5 N NH_4Cl solution The organic layer was dried (Na_2SO_4) and concentrated to provide the desired product 15

LC-MS (M + 1) 257

Butyl(1-butyl-2-phenyl-4,5,6-trihydrocyclopentyl[3,2-d]imidazol-6-yl))amine (Compound 17, Scheme 2) Compound 15 (2 g) was dissolved in chloroform (20 mL) and thionyl chloride (5 mL) and the resulting solution was stirred at room temperature overnight The solvent and excess thionyl chloride was evaporated and the crude chloride 16 was dissolved in n-butylamine (10 mL) After 2 h, the excess butylamine was evaporated, the residue dissolved in ethyl acetate and the organic solution washed with 5% NaOH solution and water The organic layer was dried and concentrated The organic residue was purified by column chromatography on silaica gel eluting with 10% CH_3OH in $CHCl_3$ to provide the desired secondary amine 17 in 82% yield

LC-MS (M+1) 312

^{1}H-NMR (chemical shift, $CDCl_3$) 0 83 (t, J = 7 2 Hz, 3H), 0 9 (t, J = 7 2 Hz, 3H), 1 23 (q, J = 7 2 Hz, 2H), 1 35 (q, J = 7 2 Hz,

2H), 1 46 (m, 2H), 1 70 (m, 2H), 2 24 (m, 1H), 2 55-2 66 (m, 4H), 2 73-2 80 (m, 2H), 3 97-4 04 (m, 2H), 4 30 (d, J = 5 6 Hz, 1H), 7 37-7 44 (m, 3H), 7 55-7 57 (m, 2H)

4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol (Compound 5, Table 1) To a solution of compound 17 (50 mg) in 1,2-dichloroethane (2 mL) and 2-chloro-4-hydroxybenzaldehyde (30 mg) was added sodium triacetoxyborohydride (100 mg) The resulting mixture was allowed to stir overnight After washing with 0 5 ammonium chloride solution, the organic layer was dried (Na_2SO_4) and concentrated Purification using preparative thin layer chromatography eluting with 5% $CH_3OH/CHCl_3$ provided the desired product 5 as an oil (21 mg)

LC-MS (M+1) 452, (M-1) 450

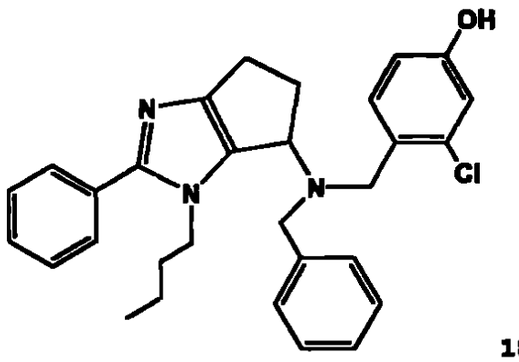
^{1}H-NMR (chemical shift, $CDCl_3$) 0 74 (t, J = 7 2 Hz, 3H), 0 83 (t, J = 7 2 Hz, 3H), 1 11 (q, J = 7 2 Hz, 2H), 1 21-1 33 (m, 2H), 1 41-1 51 (m, 4H), 2 34-2 44 (m, 3H), 2 51-2 57 (m, 1H), 2 60-2 67 (m, 1H), 2 69-2 75 (m, 1H), 3 38 (d, J = 7 6 Hz, 1H), 3 47 (d, J = 13 6 Hz, 1H), 3 65 (d, J = 13 6 Hz, 1H), 3 78-3 96 (m, 1H), 6 62 (dd, J = 8,2 Hz, 1H), 6 78 (d, J = 2 Hz, 1H), 7 07 (d, J = 8 Hz, 1H), 7 35-7 41 (m, 3H), 7 45-7 48 (m, 2H)

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Example II

2-Aryl-4,5-cycloalkylimidazoles

The following compounds were prepared essentially according to the procedures described in Example I

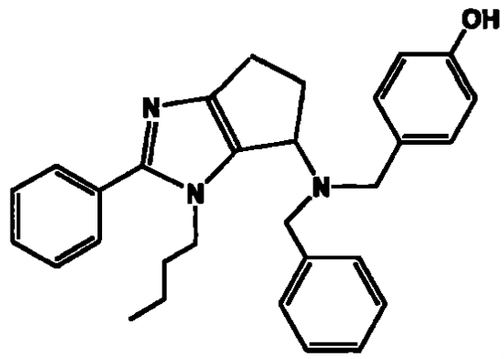


18

4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino]methyl}-3-chlorophenol (compound 18)

LC-MS (M^++1) 486 (M-1) 484

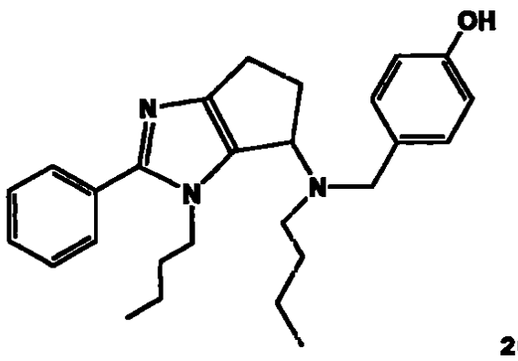
^{1}H-NMR (chemical shift, $CDCl_3$) 0 69 (t, J = 7 Hz, 3H), 1 02-1 08 (m, 2H), 1 32-1 40 (m, 2H), 2 38-2 43 (m, 1H), 2 63-2 69 (m, 2H), 2 75-2 80 (m, 1H), 3 21 (d, J = 13 6 Hz, 1H), 3 60 (s, 2H), 3 69-3 76 (m, 2H), 3 81-3 88 (m, 1H), 4 36 (d, J = 8 Hz, 1H), 6 61 (dd, J = 8 8, 2 4 Hz, 1H), 6 79 (d, J = 2 4 Hz, 1H), 7 04 (d, J = 8 8 Hz, 1H), 7 19-7 23 (m, 1H), 7 25-7 26 (m, 4H), 7 32-7 41 (m, 5H) ppm



19

4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino] methyl}phenol (compound **19**)

^{1}H-NMR (chemical shift, $CDCl_3$) 0 75 (t, J = 7 Hz, 3H), 1 12-1 16 (m, 2H), 1 43-1 51 (m, 2H), 2 34-2 43 (m, 1H), 2 59-2 69 (m, 2H), 2 75-2 79 (m, 1H), 3 30 (d, J = 13 6 Hz, 1H), 3 38 (d, J = 13 6 Hz, 1H), 3 65 (d, J = 13 6 Hz, 1H), 3 74 (d, J = 13 6 Hz, 1H), 3 81-3 96 (m, 1H), 4 42 (d, J = 7 Hz, 1H), 6 73 (d, J = 8 Hz, 2H), 7 09 (d, J = 8 0 Hz, 2H), 7 19-7 47 (m, 10H) ppm

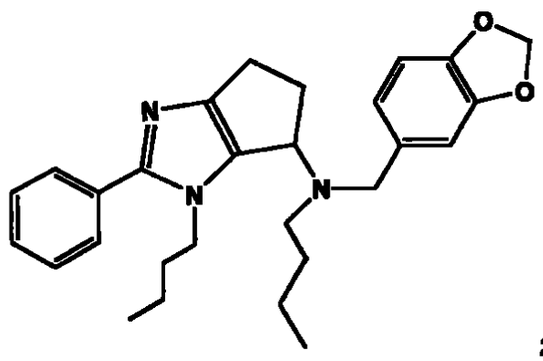


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4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}phenol (Compound 20)

^{1}H-NMR (chemical shift, $CDCl_3$) 0 79 (t, J = 7 2 Hz, 3H), 0 84 (t, J = 7 2 Hz, 3H), 1 74 (q, J = 7 2 Hz, 2H), 1 30-1 38 (m, 2H), 1 43-1 58 (m, 4H), 2 31-2 40 (m, 2H), 2 43-2 53 (m, 2H), 2 60-2 73 (m, 2H), 3 26 (d, J = 13 6 Hz, 1H), 3 64 (d, J = 13 6 Hz, 1H), 3 79-3 95 (m, 2H), 4 42 (d, J = 8 Hz, 1H), 6 71 (d, J = 8 4 Hz, 1H), 6 77 (d, J = 8 4 Hz, 1H), 7 05 (d, 8 4 Hz, 1H), 7 15 (d, J = 8 4 Hz, 1H), 7 34-7 41 (m, 3H), 7 46-7 49 (m, 2H)



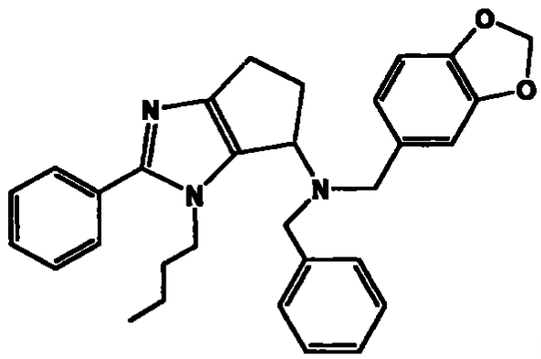
21

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))amine (Compound 21)

LC-MS (M^++1) 446

^{1}H-NMR (chemical shift, $CDCl_3$) 0 82 (t, J = 7 Hz, 3H), 0 85 (t, J = 7 2 Hz, 3H), 1 21-1 26 (m, 3H), 1 28-1 37 (m, 1H), 1 41-1 48 (m, 2H), 1 55-1 61 (m, 2H), 2 31-2 53 (m, 4H), 2 60-2 75 (m, 2H), 3 26 (d, J = 14 Hz, 1H), 3 67 (d, J = 13 5 Hz, 1H), 3 88-4 01 (m,

2H), 4 31 (dt, J = 7, 2 Hz, 1H), 5 90 (dd, J = 7, 2 Hz, 2H), 6 72 (s, 2H), 6 82 (s, 1H), 7 34-7 43(m, 3H), 7 52-7 55 (m, 2H)



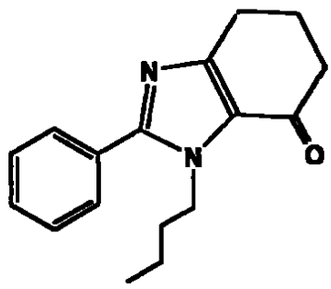
22

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))benzylamine (Compound 22)

LC-MS (M^++1) 480

^{1}H-NMR (chemical shift, $CDCl_3$) 0 79 (t, J = 7 Hz, 3H), 1 14-1 21 (m, 2H), 1 49-1 53 (m, 2H), 2 34-2 44 (m, 1H), 2 60-2 72 (m, 2H), 2 76-2 84 (m, 1H), 3 31 (d, J = 14 Hz, 1H), 3 37 (d, J = 13 6 Hz, 1H), 3 67 (d, J = 13 6 Hz, 1H), 3 76 (d, J = 14 Hz, 1H), 3 88-4 02 (m, 2H), 4 44 (dt, J = 7, 2 Hz, 1H), 5 92 (dd, J = 4, 2 Hz, 2H), 6 76 (s, 2H) 6 84 (d, J = 2 Hz, 1H), 7 22-7 42 (m, 8H), 7 48-7 52 (m, 2H)

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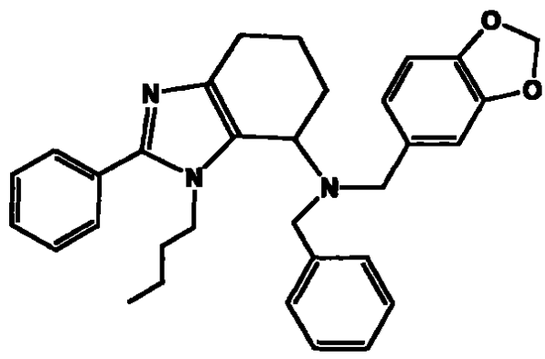


23

3-Butyl-2-phenyl-3, 5, 6, 7-tetrahydrobenzimidazol-4-one

(Compound 23)

^{1}H-NMR (chemical shift, $CDCl_3$) 0 83(t, J = 7 2 Hz, 3H), 1 23 (q, J = 7 Hz, 2H), 1 66-1 74 (m, 2H), 2 14-2 20 (m, 2H), 2 54-2 57 (m, 2H), 2 87-2 92 (m, 2H), 4 29 (d, J = 8 Hz, 2H), 7 46-7 50 (m, 3H), 7 58-7 60 (m, 2H)



1

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(3-butyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))benzylamine

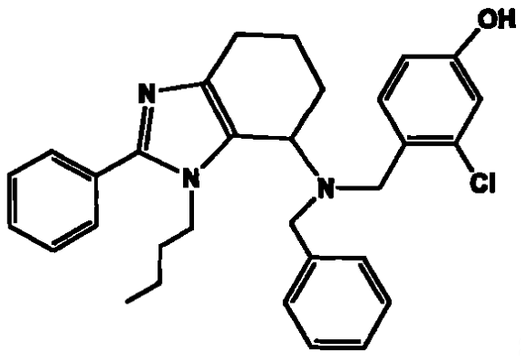
(Compound 1, Table 1)

LC-MS (M^++1) 494

631

^{1}H-NMR (chemical shift, $CDCl_3$) 0 60 (t, J = 7 Hz, 3H), 0 80-0 90 (m, 2H), 1 03-1 13 (m, 2H), 1 83-1 87 (m, 1H), 1 93-1 99 (m, 1H), 2 20-2 27 (m, 1H), 2 56-2 62 (m, 1H), 2 69-2 76 (m, 1H), 3 38 (d, J = 13 2 Hz, 1H), 3 42 (d, J = 13 2 Hz, 1H), 3 78 (d, J = 12 8 Hz, 1H), 3 88 (d, J = 12 8 Hz, 1H), 3 95-4 07 (m, 2H), 4 47-4 54 (m, 1H), 5 29 (s, 1H), 5 92 (s, 2H), 6 73 (s, 2H), 6 75 (s, 1H), 7 24-7 44 (m, 8H), 7 52-7 54 (m, 2H)

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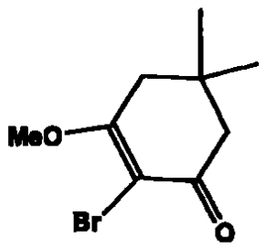


2

4-{[(3-Butyl-2-phenyl(3,4,5,6,7-pentahydrobenzımıdazoly-4-yl))benzylamino]methyl}-3-chlorophenol (Compound 2, Table 1)

LC-MS (M^++1) 500, (M^+-1) 498

^{1}H-NMR (chemical shift, $CDCl_3$) 0 52 (t, J = 7 Hz, 3H), 0 68-0 76 (m, 2H), 1 01-1 14 (m, 2H), 1 67-1 72 (m, 1H), 1 88-2 00 (m, 2H), 2 53-2 82 (m, 2H), 3 46-3 49 (m, 1H), 3 65-3 74 (m, 2H), 3 79-4 02 (m, 4H), 4 40-4 46 (m, 1H), 6 58 (dd, J = 12, 3 Hz, 1H), 6 74 (d, J = 3 Hz, 1H), 6 98 (d, J = 12 Hz, 1H), 7 24-7 44 (m, 8H), 7 54-7 58 (m, 2H)



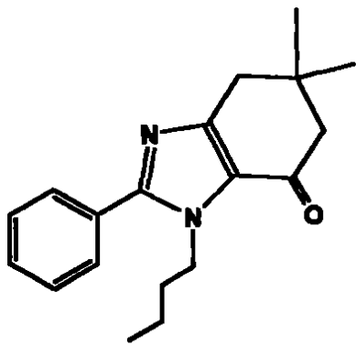
24

2-Bromo-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (Compound **24**)

LC-MS (M+1) 234 8,

^{1}H-NMR (chemical shift, $CDCl_3$) 1 14 (6H, s), 2 42 (2H, s), 2 57 (2H, s), 3 95 (3H, s)

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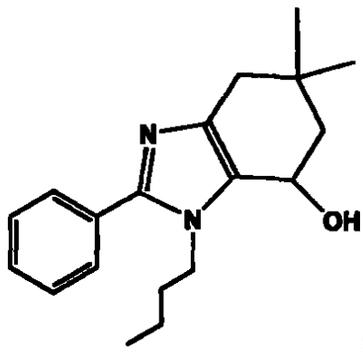
25

3-Butyl-6,6-dimethyl-2-phenyl-3,5,6,7-tetrahydrobenzimidazol-4-one (Compound **25**)

LC-MS (M+1) 297 3,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 82 (3H, t, J = 7 6 Hz), 1 16 (6H, s), 1 21 (2H, m, J = 7 6 Hz), 2 42 (2H, s), 2 77 (2H, s), 4 29 (2H, t, J = 7 6 Hz), 7 45-7 50 (3H, m), 7 57-7 61 (2H, m) ppm

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683



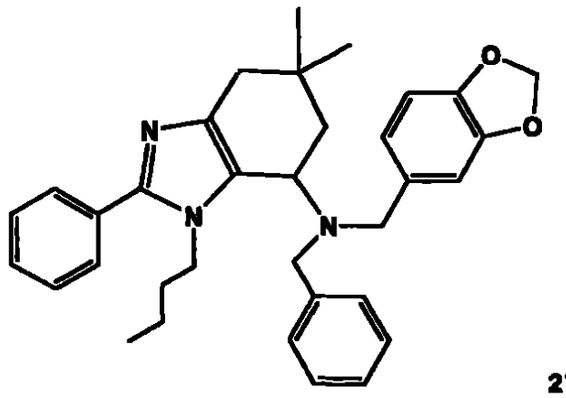
26

3-Butyl-6,6-dimethyl-2-phenyl-3,4,5,6,7-pentahydrobenzimidazol-4-ol (Compound **26**)

LC-MS (M+1) 299 3

^{1}H-NMR (chemical shift, $CDCl_3$) 0 76 (3H, t, J = 7 2 Hz), 0 92 (3H, s), 1 07 (3H, s), 1 12 (2H, m, J = 7 2 Hz), 1 58 (3H, m), 1 86 (1H, dd, J = 13 2, 6 8 Hz), 2 34 (1H, d, J = 16 Hz), 2 47 (1H, d, J = 16 Hz), 3 96 (1H, m), 4 20 (1H, m), 4 81 (1H, t, J = 6 8 Hz), 7 35-7 42 (3H, m), 7 49-7 52 (2H, m) ppm

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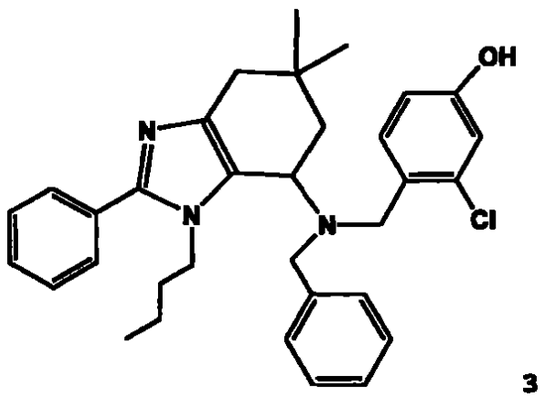


27

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzımıdazol-4-yl))(2H-benzo[3,4-d]1,3-dıoxolan-5-ylmethyl)benzylamıne (Compound 27)

LC-MS (M+1) 522 4,

^{1}H-NMR (chemıcal shift, $CDCl_3$) 0 58 (3H, m), 0 81 (5H, m), 0 98-1 20 (5H, m), 1 68-1 84(2H, m), 2 38 (1H, d, J = 16 Hz), 2 55 (1H, d, J = 16 Hz), 3 26-3 49 (2H, m), 3 67-3 80 (2H, m), 3 96-4 10 (2H, m), 4 70 (1H, br), 5 93 (2H, br), 6 76 (3H, m), 7 24-7 43 (8H, m), 7 53 (2H, d, J = 6 8 Hz) ppm

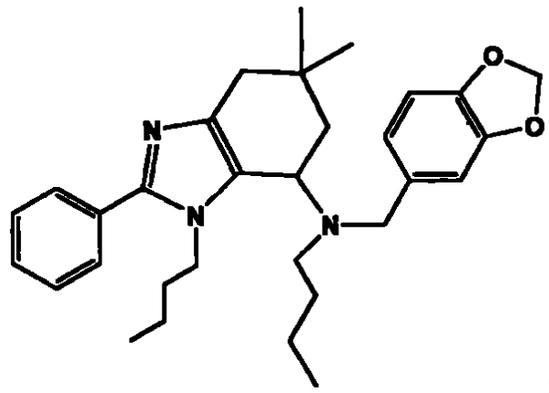


3

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4-hydroxybenzyl)benzylamine (Compound 3, Table 1)

LC-MS (M+1) 528 4,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 49-1 26 (11H, m), 1 76-2 50 (6H, m), 3 33-4 69 (7H, m), 6 30-6 76 (3H, m), 7 09-7 45 (10H, m) ppm



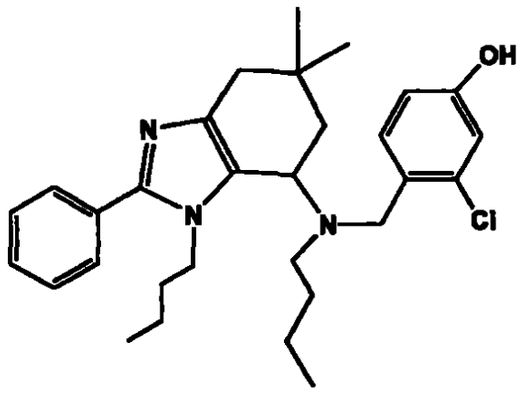
28

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2H-benzo[d]1,3-dioxolen-5-ylmethyl)butylamine (Compound 28)

LC-MS (M+1) 488 5,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 60-1 14 (14H, m), 1 23-1 33 (2H, m), 1 34-1 57 (3H, m), 1 71-1 82 (2H, m), 2 21-2 54 (4H, m), 3 17-4 81 (6H, m), 5 93 (2H, m), 6 5-6 88 (3H, m), 7 34-7 43 (3H, m), 7 53 (2H, d, J = 7 2 Hz) ppm

LGD
686



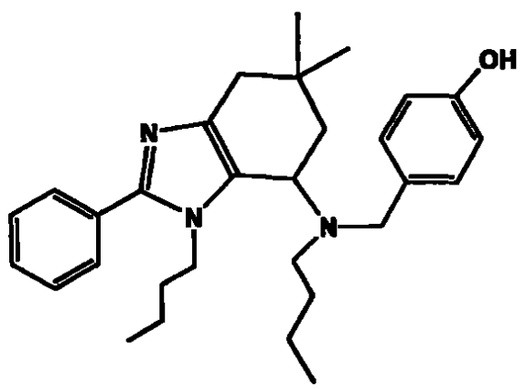
29

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4-hydroxybenzyl)butylamine (Compound 29)

LC-MS (M+1) 494 5,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 48-0 92 (11H, m), 1 10 (3H, m), 1 24-1 34 (3H, m), 1 55 (3H, m), 1 85 (1H, m), 2 30-2 65 (4H, m), 3 56-4 19 (5H, m), 4 68 (1H, m, J = 7 2 Hz), 6 43-7 13 (3H, m), 7 35 (3H, m), 7 46 (2H, m) ppm

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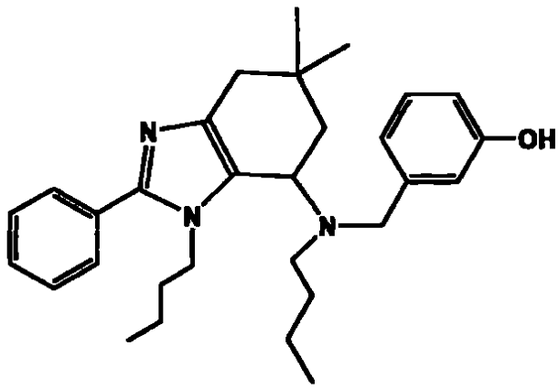


30

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(4- hydroxybenzyl)butylamine (Compound 30)

LC-MS (M+1) 460 5,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 57-1 11 (14H, m), 1 25-1 69 (7H, m), 2 24-2 57 (4H, m), 3 20-4 78 (6H, m), 6 66-6 76 (2H, m), 6 94 (1H, m), 7 16 (1H, m), 7 36 (3H, m), 7 49 (2H, m) ppm

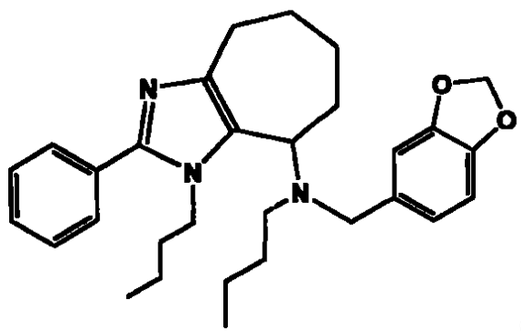


4

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(3-hydroxybenzyl)butylamine (Compound 4, Table 1)

LC-MS (M+1) 460 7,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 53-1 13 (14H, m), 1 25-1 74 (7H, m), 2 22-2 56 (4H, m), 3 09-4 78 (6H, m), 6 49-6 84 (3H, m), 7 06 (1H, t, J = 7 6 Hz), 7 34 (3H, m), 7 47 (2H, m) ppm



6

(1-Butyl-2-phenyl-4,5,6,7,8-pentahydrocyclonepta[3,2-d]imidazol-8-yl)(2H-benzo[d]1,3-dioxolen-5-ylmethyl)butylamine (Compound 6, Table 1)

LC-MS (M+1) 474 5,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 73 (3H, t, J = 7 6 Hz), 0 79 (3H, t, J = 7 6 Hz), 1 02 (2H, m), 1 15 (2H, m), 1 25-1 48 (6H, m), 1 72 (2H, m), 1 89 (2H, m), 2 48-2 63 (2H, m), 2 89 (2H, br), 3 42 (1H, d, J = 13 2 Hz), 3 73 (1H, d, J = 13 2 Hz), 3 83-3 91 (1H, m), 3 95 (1H, m), 4 17 (1H, m), 5 92 (2H, s), 6 68-6 75 (3H, m), 7 38-7 44 (3H, m), 7 52 (2H, d, J = 8 0 Hz) ppm

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Example 3

Assay for C5a Receptor Mediated Chemotaxis

This assay is a standard assay of C5a receptor mediated chemotaxis

Human promonocytic U937 cells are treated with dibutyryl cAMP for 48 hours prior to performing the assay The cells are pelleted and resuspended in culture media containing 0 1% fetal bovine serum (FBS) and 10 ug/ml calcein AM (a fluorescent dye) This suspension is then incubated at 37 °C for 30 minutes such that the cells take up the fluorescent dye The suspension is then centrifuged briefly to pellet the cells, which are then resuspended in culture media containing 0 1% FBS at a concentration of approximately 3 x 10^6 cells/mL Aliquots of this cell suspension are transferred to clean test tubes, which

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639

contain vehicle (1% DMSO) or varying concentrations of a compound of interest, and incubated at room temperature for at least 30 minutes The chemotaxis assay is performed in ChemoTx 101-8, 96 well plates The bottom wells of the plate are filled with varying concentrations of human C5a (0-10 nM) The top wells of the plate are filled with cell suspensions (compound or vehicle-treated) The plate is then placed in a tissue culture incubator for 60 minutes The top surface of the plate is washed with PBS to remove excess cell suspension The number of cells that have migrated into the bottom well is then determined using a fluorescence reader Chemotaxis index (the ratio of migrated cells to total number of cells loaded) is then calculated for each compound concentration to determine an EC_{50} value

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As a control to insure that cells retain chemotactic ability in the presence of the compound of interest, the bottom wells of the plate may be filled with varying concentrations chemoattractants that do not mediate chemotaxis via the C5a receptor, e g zymosan-activated serum (ZAS), N-formylmethionyl-leucyl-phenylalanine (FMLP) or leukotriene B4(LTB4)

Compounds of the accompanying Examples exhibit EC_{50} values of less than 1 μM in the above assay for C5a mediated chemotaxis Data is shown for several representative compounds of this invention in Table 2

TABLE 2	
Compound Number	EC_{50}
1	642 nM
2	22 nM
5	450 nM
6	148 nM

Example 4
Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I) Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds Such suppliers include Amersham Corporation, Arlington Heights, IL, Cambridge Isotope Laboratories, Inc Andover, MA, SRI International, Menlo Park, CA, Wizard Laboratories, West Sacramento, CA, ChemSyn Laboratories, Lexena, KS, American Radiolabeled Chemicals, Inc , St Louis, MO, and Moravek Biochemicals Inc , Brea, CA

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in

tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate

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Example 5

Use of compounds of the invention as probes for C5a receptors in cultured cells and tissue samples

Receptor autoradiography (receptor mapping) of NK-3 receptors in cultured cells or tissue samples is carried out in vitro as described by Kuhar in sections 8 1 1 to 8 1 9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference

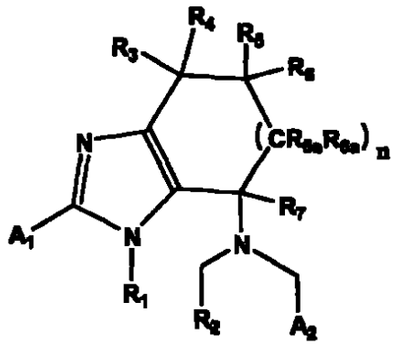
The invention and the manner and process of making and using it are now described in such full, clear, concise and exact terms

as to enable any person skilled in the art to which it pertains, to make and use the same It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims To particularly point out and distinctly claim the subject matter regarded as the invention, the following claims conclude the specification

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What is claimed is

1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

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R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

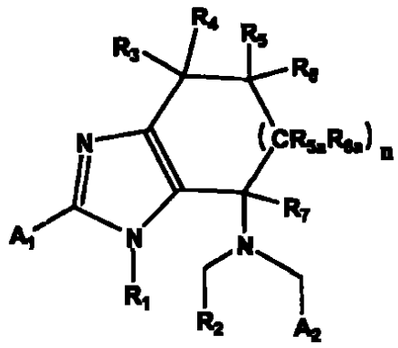
R_{5a} and R_{6b} are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

2 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

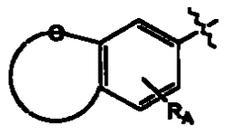
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each of which may be substituted or unsubstituted, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached may form a cycloalkyl ring,

R_{5a} and R_{6b} are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

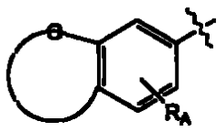
halogen, alkyl, alkoxy, cyano, amino, mono- or dialkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-trifluoromethyl, trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined below, or

A_1 is thiophene or pyridine which is unsubstituted or may be substituted with alkyl, halogen, alkoxy, amino or mono or dialkylamino,

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A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from halogen, alkyl, alkoxy, cyano, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy, or $-XR_B$, wherein X and R_B are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

X is independentec at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

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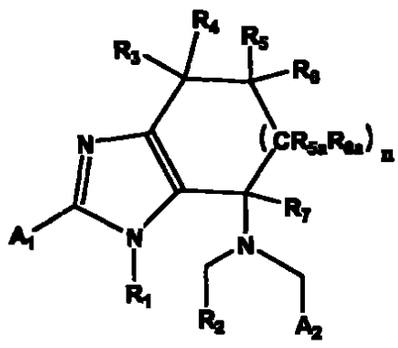
R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from

oxo, hydroxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_x$(alkyl), $-S(O)_x$(alkyl), $-S(O)_xNH$(alkyl), $-S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2)

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3 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

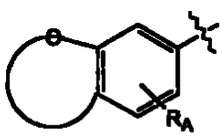
R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy, or

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R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, and C_1-C_7 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or -XR_8, wherein X and R_8 are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino, and

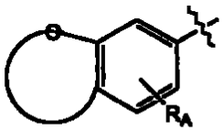
A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or

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dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_B$, wherein X and R_B are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

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oxo, hydroxy, -O(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -NHS(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$NH(C_1-C_4 alkyl), -S(O)$_x$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

4 A compound according to Claim 3 wherein

R_3 and R_4 are the same or different and represent hydrogen or methyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen and methyl

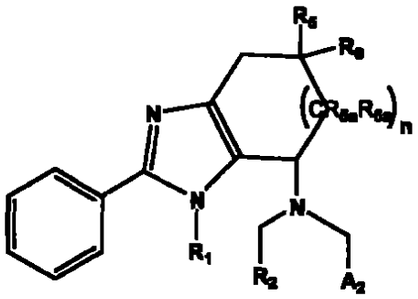
5 A compound according to Claim 3 wherein

R_3 and R_4 are hydrogen,

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen and methyl

6 A compound according to Claim 3 of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are independently chosen at each occurrence from hydrogen and methyl, and

R_1, R_2, A_2, and n are as defined for Claim 3

7 A compound according to Claim 6,

or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

R_2, A_2, and n are as defined for Claim 6

8 A compound according to Claim 6,

or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

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R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

A_2, and n are as defined for Claim 6

9 A compound according to Claim 6,

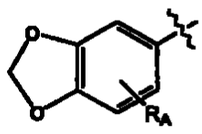
or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is phenyl, which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

A_2 is phenyl which is unsubstituted or substituted with up to four groups independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of

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carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined for Claim 6, and

n is as defined in Claim 6

10 A compound according to Claim 6,

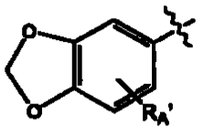
or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is as defined for Claim 6, and

n is as defined for Claim 6

11 A compound according to claim 1, which is selected from

4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol,

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4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino]methyl}-3-chlorophenol,

4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino] methyl}phenol,

4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}phenol,

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))amine,

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))benzylamine,

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(3-butyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))benzylamine,

4-{[(3-Butyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazoly-4-yl))benzylamino]methyl}-3-chlorophenol,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2H- benzo[3,4-d]1,3-dioxolan-5-ylmethyl)benzylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4-hydroxybenzyl) benzylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2H-benzo[d]1,3-dioxolen-5-ylmethyl)butylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4- hydroxybenzyl) butylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(4- hydroxybenzyl)butylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(3-hydroxybenzyl)butylamine, and

(1-Butyl-2-phenyl-4,5,6,7,8-pentahydrocyclohepta[3,2-d]imidazol-8-yl)(2H-benzo[d]1,3-dioxolen-5-ylmethyl)butylamine

12 A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient

13 A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 12 in a container and comprising instructions for using the composition to treat a patient in need of anti-inflammatory treatment

14 The packaged pharmaceutical composition of claim 13, wherein said patient is suffering from rheumatoid arthritis, Crohn's disease, irritable bowel syndrome, ARDS, extracorporeal post-dialysis syndrome, systemic lupus erythematosus, psoriasis or bronchial asthma

15 The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory diseases

16 A method of treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory disorders which comprises administering to patient in need of such treatment a C5a receptor-modulatory effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof

17 A method of inhibiting leukocyte chemotaxis, which comprises
contacting a compound of Claim 1 with white blood cells, wherein the compound is present at a concentration sufficient to inhibit chemotaxis of white blood cells *in vitro*

18 A method for the treatment of physiological disorders associated with localized excess concentrations of C5a, which method comprises administration to a patient in need of such treatment a compound according Claim 1, wherein the compound is

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administered in an amount sufficient to yield, at a site of localized excess concentrations of C5a, a concentration of the compound sufficient to inhibit chemotaxis of white blood cells *in vitro*

19 A method for localizing C5a receptors in tissue section samples comprising

contacting with a sample of tissue a detectably-labelled compound of claim 1 under conditions that permit binding of the compound to the sample of tissue,

washing the tissue sample to remove unbound compound, and

detecting the bound compound

20 A method of inhibiting the binding of C5a to C5a receptors, which method comprises contacting a solution comprising the compound of Claim 1 with C5a receptors, wherein the compound is present in the solution at a concentration sufficient to inhibit C5a binding to C5a receptors *in vitro*

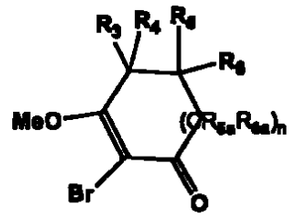
21 A method for altering the activity of cell surface C5a receptors, said method comprising contacting cells expressing such receptors with a solution comprising the compound of Claim 1, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic

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responses to C5a of white blood cells in vitro

22 A compound according to claim 1 wherein in an assay of C5a mediated chemotaxis the compound exhibits an IC_{50} of 1 micromolar or less

23 A compound of the formula



wherein

n is an integer from 0 to 3,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkoxy, or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkoxy, and alkyl

24 A compound according to Claim 23, wherein

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkoxy, or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms, and

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkoxy, or C_1-C_7 alkyl

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25 A compound according to Claim 23, wherein

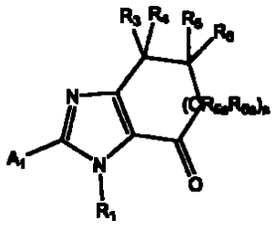
R_3 and R_4 are hydrogen,

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen and methyl

26 A compound of the formula

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wherein

n is an integer from 0 to 3,

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl (i e cyclopentylmethyl), or haloalkyl, each of which may be substituted or unsubstituted,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkoxy, or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkoxy, and alkyl, and

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

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27 A compound according to Claim 26 in which

R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms, and

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkoxy or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are independently selected from hydrogen, halogen, hydroxy, C_1-C_7 alkoxy or C_1-C_7 alkyl, and

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or

$-XR_8$, wherein X and R_8 are as defined below, or

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A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino,

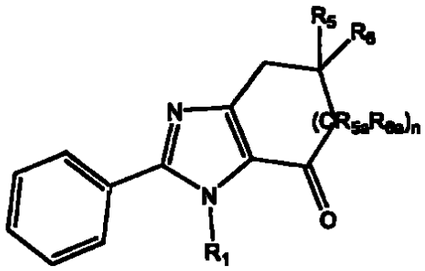
X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_c-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_c-$, $-C(=O)NH-$, $-C(=O)NR_c-$, $-S(O)_mNH-$, $-S(O)_mNR_c-$, $-NHC(=O)-$, $-NR_cC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_cS(O)_m-$ (where m is 0, 1, or 2), and

R_b and R_c, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)(C_1-C_4 alkyl), $-NHC(O)$(C_1-C_4 alkyl), $-N(C_1-C_4$ alkyl)$C(O)$(C_1-C_4 alkyl), $-NHS(O)_x(C_1-C_4$ alkyl), $-S(O)_x(C_1-C_4$ alkyl), $-S(O)_xNH(C_1-C_4$ alkyl), $-S(O)_xN(C_1-C_4$ alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

28 A compound according to Claim 26 of the formula



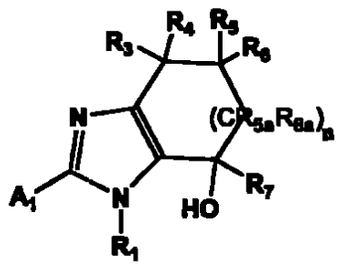
wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen and methyl

29 A compound of the formula



wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

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R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkoxy, or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

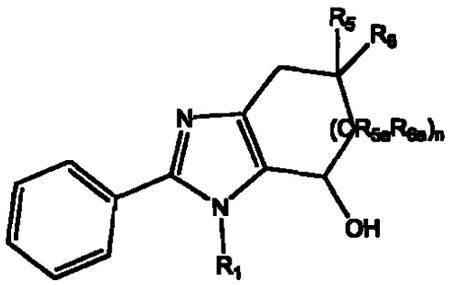
R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkoxy, and alkyl,

R_7 represents hydrogen or alkyl, and

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

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30 A compound according to Claim 30, of the formula



wherein

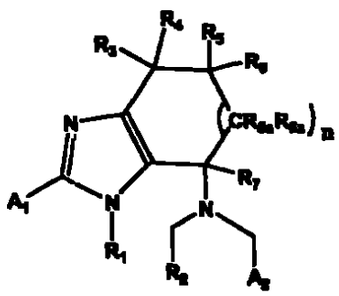
n is an integer from 0 to 3,

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen and methyl

31 A process for preparing a compound of the formula



wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, or alkoxy,

R_7 represents hydrogen or alkyl,

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having

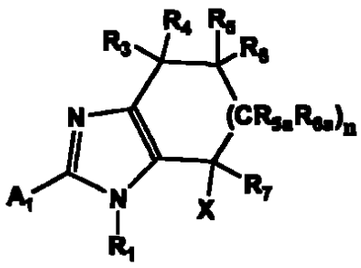
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from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or unsubstituted heteroarcmatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

the process comprising

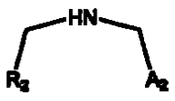
reacting a compound of the formula



wherein X halogen or sulfonate ester,

in a suitable solvent in the presence of a suitable base,

with a secondary amine of the formula



32 A process for preparing a compound of the formula of Claim 31,

wherein, in said formula

n is an integer from 0 to 3, and

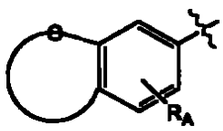
R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_8$, wherein X and R_8 are as defined below, or

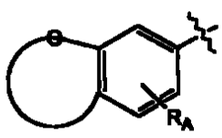
A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino, and

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from

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halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_B$, wherein X and R_B are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds,

each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, -O(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -NHS(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$NH(C_1-C_4 alkyl), -S(O)$_x$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

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ABSTRACT OF THE DISCLOSURE

Disclosed are aryl cycloalkylimidazoles that act as selective modulators of human complement C5a receptors that are, therefore, useful in the treatment of a variety of immune system and inflammatory disorders

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(Attorney's Docket No N 2000.004)

Applicant or Patentee. Andrew Thurkauf, et al

Serial or Patent No Not yet assigned Filed Herewith

Title Aryl Cycloalkylimidazoles

US Express Mailing No EJ080850 4/20209

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS
(37 C.F.R. § 1.9(f) AND § 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am an official of the small business concern empowered to act on behalf of the concern identified below

NAME OF SMALL BUSINESS CONCERN NEUROGEN CORPORATION

ADDRESS OF SMALL BUSINESS CONCERN 35 NORTHEAST INDUSTRIAL ROAD
BRANFORD CT 06405

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 C F R § 121 and referenced in 37 C.F R. § 1.9(d) for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year and (2) concerns are affiliates of each other when either directly or indirectly one concern controls or has the power to control the other or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention entitled Aryl Cycloalkylimidazoles by inventor(s) Andrew Thurkauf, et al

described in

☒ the specification filed herewith
☐ Application Serial No _____ filed _____
☐ Patent No. _____ issued _____

Patent Department
NEUROGEN CORPORATION
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

TBD
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☒ the specification filed herewith.
☐ Application Serial No. _____ filed _____
☐ Patent No _____ issued _____

If the rights held by the above identified small business concern are not exclusive, each individual concern or organization having rights in the invention must file verified statements averring to their status as small entities, and no rights to the invention are held by any person other than the inventor who would not qualify as an independent inventor under 37 CFR § 1 9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR § 1 9(d), or a nonprofit organization under 37 CFR § 1 9(e)

Each person concern or organization having any rights to the invention is listed below

☒ No such person concern or organization exists.
☐ Each such person, concern or organization is listed below

FULL NAME _____

ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____

ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

Separate verified statements are required from each named person, concern or organization having rights in the invention averring to their status as small entities. (37 CFR § 1 27)

I acknowledge the duty to file in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F R. § 1 28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing therein, or any patent to which this verified statement is directed.

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NEUROGEN CORPORATION
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

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727

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TITLE IN ORGANIZATION PRESIDENT AND CHIEF EXECUTIVE OFFICER

ADDRESS OF PERSON SIGNING 35 NORTHEAST INDUSTRIAL ROAD
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Signature

Date. May 5, 2000

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Patent Department
NEUROGEN CORPORATION
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

LOS ESTADOS UNIDOS DE AMÉRICA

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26 de diciembre de 2000

LA PRESENTE ES PARA CERTIFICAR QUE ADJUNTA A LA MISMA HAY UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA EN LO QUE SIGUE, QUE CUMPLEN LOS REQUISITOS PARA OTORGARLE UNA FECHA DE PRESENTACION BAJO 35 USC 111

NÚMERO DE SOLICITUD 60/202,749
FECHA DE PRESENTACIÓN 08 de mayo de 2000

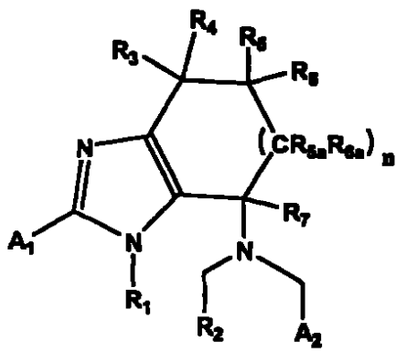
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E BORNETT

Oficial certificador

Lo que se reivindica es

1 Un compuesto de la fórmula



o una sal farmacéuticamente aceptable del mismo, en la cual

n es un número entero de 0 a 3, y

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o

R_2 es arilo carbocíclico sustituido o no sustituido, aralquil sustituido o no sustituido, o un grupo heteroaromático heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo, o alcoxi, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

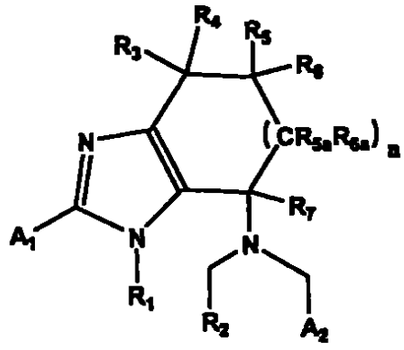
R_{5a} y R_{6b} se seleccionan independientemente cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo, y alcoxi,

R_7 representa hidrógeno o alquilo,

A_1 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido o un grupo heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos, y

A_2 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido o un grupo heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos

2 Un compuesto de la fórmula



o una sal farmacéuticamente aceptable del mismo, en la cual

n es un número entero de 0 a 3, y

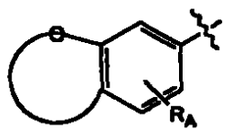
R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o

R_2 es fenilo, naftaleno, tiofeno o piridina cada uno de los cuales puede estar o no sustituido con

alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino, o

R_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo, o alcoxi, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_{5a} y R_{6b} se seleccionan independientemente cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo, y alcoxi,

R_7 representa hidrógeno o alquilo,

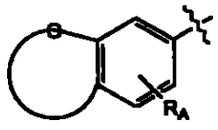
A_1 es fenilo el cual puede estar o no sustituido con hasta 4 sustituyentes seleccionados independientemente de halógeno, alquilo, alcoxi, ciano, amino, mono- o dialquilamino, hidroxi,

acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo, trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_1 es tiofeno o piridina que puede estar o no sustituido con alquilo, halógeno, alcoxi, amino o mono o dialquilamino,

A_2 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar o no sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, alquilo, alcoxi, ciano, amino, mono- o dialquilamino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, alquilo (cicloalquilo), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

X está independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_C-$, $-O-$, $-S(0)_m-$, $-NH-$, $-NR_C-$, $-C(=0)NH$, $-C(=0)NR_C-$, $-S(0)_mNH-$, $-S(0)_mNR_C-$, -

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NHC(=O)-, $-NR_cC(=O)$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$ y $NR_cS(O)_m-$ (donde m es 0, 1 ó 2),

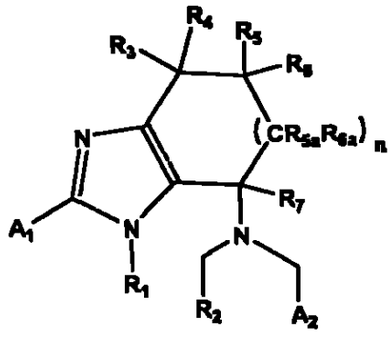
y

R_a y R_c pueden ser iguales o diferentes y están seleccionados independientemente cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada, que pueden contener uno o más dobles o triples enlaces, cada uno de los cuales puede estar no sustituido o puede estar sustituido con uno o más sustituyente(s) seleccionados de

Oxo, hidroxi, -O(alquilo), -NH(alquilo), N-(alquil)(alquilo), -NHC(O)alquilo, -N(alquilo)C(O) (alquilo), -NHS(O)x(alquilo), -S(O)x(alquilo), -S(O)xNH(alquilo), -S(O)xN(alquilo)(alquilo), (donde x es 0, 1 ó 2)

3 Un compuesto de la fórmula



O una sal farmacéuticamente aceptable del mismo, en donde

n es un número entero de 0 a 3, y

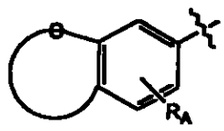
R_1 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 o alquilo C_3-C_8(cicloalquilo) o haloalquilo C_1-C_8,

R_2 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8 cicloalquilo C_1-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8, o

R_2 es fenilo, naftaleno, tiofeno o piridina cada uno de los cuales puede estar o no sustituido con

alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, mono- o dialquil(C_1-C_6)amino, o

R_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo C_3-C_6,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 o alcoxi C_1-C_7, o

R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo C_3-C_6,

R_{5a} y R_{6a} y están independientemente seleccionados cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 y alcoxi C_1-C_7,

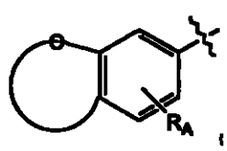
R_7 representa hidrógeno o alquilo C_1-C_7,

A_1 es fenilo el cual puede estar o no sustituido con hasta 4 sustituyentes seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, hidroxi, acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo o trifluorometoxi, o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_1 es tiofeno o piridina que puede estar o no sustituido con alquilo C_1-C_7, halógeno, alcoxi C_1-C_7, amino o mono o dialquil(C_1-C_6)amino, y

A_2 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar o no sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo

C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquil(C_1-C_6)amino,

X está independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_c-$, -O-, $-S(0)_m-$, -NH-, $-NR_c-$, -C(=0)NH, $-C(=0)NR_c-$, $-S(0)_mNH-$, $-S(0)_mNR_c-$, -NHC(=0)-, $-NR_cC(=0)$, $-NHS(0)_m-$, $-C(=0)NHS(0)_m-$ y $NR_cS(0)_m-$ (donde m es 0, 1 ó 2),

y

R_B y R_C pueden ser iguales o diferentes y están seleccionados independientemente cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada, que pueden contener uno o más dobles o triples enlaces, cada uno de los cuales puede estar no sustituido o puede estar sustituido con uno o más sustituyente(s) seleccionados de

Oxo, hidroxi, -O(alquilo C_1-C_4), -NH(alquilo C_1-C_4), N-(alquil C_1-C_4) (alquilo C_1-C_4), -NHC(O)(alquilo C_1-C_4) -N(alquiloC_1-C_4)C(O)(alquilo C_1-C_4), -NHS(O)x(alquilo C_1-C_4), -S(O)x(alquilo C_1-C_4), -S(O)xNH(alquilo C_1-C_4), -S(O)xN(alquilo C_1-C_4)(alquilo C_1-C_4), (donde x es 0, 1 ó 2)

4 Un compuesto de acuerdo con la reivindicación 3 en donde

R_3 y R_4 son iguales o diferentes y representan hidrógeno o metilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurren de hidrógeno y metilo

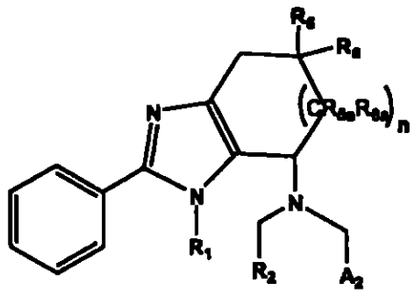
5 Un compuesto de acuerdo con la reivindicación 3, en donde

R_3 y R_4 son hidrógeno,

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurren de hidrógeno y metilo

6 Un compuesto de acuerdo con la reivindicación 3 que tiene la fórmula



o una sal farmacéuticamente aceptable del mismo, en el cual

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo,

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurre de hidrógeno y metilo, y

R_1, R_2 A_2, y n son como se definieron en la reivindicación 3

7 Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, en el cual

R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8 o alquinilo C_2-C_8, y

R_2 A_2, y n son como se definieron en la reivindicación 6

8 Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, donde

R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8, y

R_2 es alquilo C_1-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8, y

A_2, y n son como se definieron en la reivindicación 6

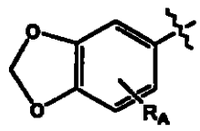
9 Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, donde

R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8,

R_2 es fenilo, que puede estar no sustituido o puede estar sustituido con

Alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 (cicloalquilo C_3-C_8)alquilo C_1-C_6, haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di alquil(C_1-C_6)amino, o

R_2 es un grupo bicíclico que contiene oxígeno que tiene la fórmula



Donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 (cicloalquilo C_3-C_8)alquilo C_1-C_6, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquil(C_1-C_6)amino,

A_2 es fenilo que está no sustituido o sustituido con hasta cuatro grupos independientemente seleccionados de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluormetilo, y trifluormetoxi, o $-XR_B$ donde X y R_B son tal como se han definido para la reivindicación 6, y

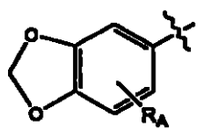
n es tal como se ha definido en la reivindicación 6

10 Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, en donde

R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_2 es alquilo C_1-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

A_2 es un grupo bicíclico que contiene oxígeno que tiene la fórmula



Donde R_A es como se definió para la reivindicación 6, y n es tal como se ha definido en la reivindicación 6

11 Un compuesto de acuerdo con la reivindicación 1, el cual se selecciona de

4-{[butil(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))amino]metil}-3-clorofenol,

4-{[(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))bencilamino]metil}-3-clorofenol,

4-{[(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))bencilamino]metil}fenol,

4-{[butil(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))amino]metil}fenol,

(2H-benzo[3,4-d]1,3-dioxolan-5-ilmetil)butil(1-butil-2-fenil (4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))amina,

(2H-benzo[3,4-d]1,3-dioxolan-5-ilmetil)(1-butil-2-fenil (4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))bencilamina,

(2H-benzo[3,4-d]1,3-dioxolan-5-ilmetil)(3-butil-2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il))bencilamina,

4-{[(3-butil-2-fenil(3,4,5,6,7-pentahidrobencimidazol-4-il))bencilamino]metil}-3-clorofenol,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il))(2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil)bencilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (2-cloro-4-hidroxibencil) bencilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (2H-benzo[d]1,3-dioxolan-5-ilmetil) butilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (2-cloro-4-hidroxibencil) butilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (4-hidroxibencil) butilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (3-hidroxibencil) butilamina, y

(1-butil-2-fenil-4,5,6,7,8-pentahidrociclohepta[3,2-d] imidazol-8-il)(2H-benzo[d]1,3-dioxolen-5-ilmetil) butilamina

12 Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, junto con al menos un adyuvante o excipiente farmacéuticamente aceptable

13 Una composición farmacéutica empacada que comprende la composición farmacéutica de la reivindicación 12 en un envase y que comprende instrucciones para el uso de la composición para tratar un paciente que necesita un tratamiento anti inflamatorio

14 La composición farmacéutica empacada de la reivindicación 13 en donde dicho paciente sufre de artritis reumatoide, enfermedad de Chron, síndrome de intestino irritable, ARDS, síndrome post-diálisis extracorpóreo, lupus sistémico eritematoso, soriasis o asma bronquial

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15 El uso de un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en la manufactura de un medicamento para el tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes

16 Un método de tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes, el cual comprende administrar a un paciente que necesita dicho tratamiento una cantidad efectiva C5a receptor-moduladora de un compuesto de acuerdo con la reivindicación 1 o una sal farmacéuticamente aceptable del mismo

17 Un método para inhibir la quimiotaxia de leucocitos, el cual comprende

Poner en contacto un compuesto de la reivindicación 1 con glóbulos blancos, en donde el compuesto está presente en una cantidad suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

18 Un método para el tratamiento de desórdenes fisiológicos asociados con el exceso de concentraciones de C5a localizadas, en donde dicho método comprende la administración a un paciente que necesita dicho tratamiento de un compuesto de acuerdo con la reivindicación 1, en donde el compuesto se administra en cantidad suficiente para producir, en un sitio del exces de concentraciones de C5a localizadas, una concentración del

compuesto suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

19 Un método para localizar receptores C5a en muestras de secciones de tejido que comprende

Poner en contacto una muestra de tejido con un compuesto de la reivindicación 1, detectable etiquetado, bajo condiciones que permiten el ligamiento del compuesto a la muestra de tejido,

Lavar la muestra de tejido para remover el compuesto no ligado, y

Detectar el compuesto ligado

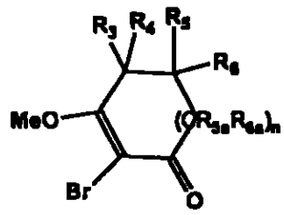
20 Un método para inhibir el ligamiento de C5a a receptores C5a, en donde dicho método comprende poner en contacto una solución que comprende el compuesto de la reivindicación 1 con receptores C5a, en donde el compuesto está presente en la solución a una concentración suficiente para inhibir el ligamiento de C5a a receptores C5a *in vitro*

21 Un método para alterar la actividad de receptores C5a de superficie de célula, en donde dicho método comprende poner en contacto células que expresan dichos receptores con una solución que comprende el compuesto de la reivindicación 1, en donde el compuesto está presente en la solución a una concentración suficiente para alterar específicamente las respuestas quimiotácticas de C5a de glóbulos blancos in vitro

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22 Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de quimiotaxia mediada por C5a, el compuesto exhibe un IC_{50} de 1 micromolar o menos

23 Un compuesto de la fórmula



donde

n es un número entero de 0 a 3,

R_3 y R_4 son iguales o diferentes y representan hidrógeno, o alquilo, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo o alcoxi, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo, y

R_{5a} y R_{6a} se seleccionan independientemente en cada ocurrencia de hidrógeno, halógeno, hidroxi, alquilo, o alcoxi

24 Un compuesto de acuerdo con la reivindicación 23, donde

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo de 3 a 6 átomos de carbono,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo C_1-C_7, o alcoxi C_1-C_7, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo de 3 a 6 átomos de carbono, y

R_{5a} y R_{6A} se seleccionan independientemente en cada ocurrencia de hidrógeno, halógeno, hidroxi, alquilo C_1-C_7, o alcoxi C_1-C_7

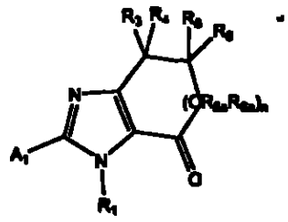
25 Un compuesto de acuerdo con la reivindicación 23, en donde

R_3 y R_4 son hidrógeno, y

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} se seleccionan independientemente en cada ocurrencia de hidrógeno y metilo

26 Un compuesto de la fórmula



en la cual

n es un número entero de 0 a 3,

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo (por ejemplo, ciclopentilmetilo), o

haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo,

R_5 y R_6, son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alcoxi, o alquilo, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo,

R_{5a} y R_{6a} se seleccionan independientemente en cada ocurrencia de hidrógeno, halógeno, hidroxi, alcoxi, o alquilo, y

A_1 es arilo carbobocíclico no sustituido o sustituido, aralquilo no sustituido o sustituido o un grupo heteroaromático o heteroalicíclico no sustituido o sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos

27 Un compuesto de acuerdo con la reivindicación 26 en donde

R_1 es alquilo C_1-C_8 de cadena recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_3-C_8 (cicloalquilo),o haloalquilo C_1-C_8,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo de tres a seis átomos de carbono, y

R_5 y R_6, son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alcoxi C_1-C_7, o alquilo C_1-C_7, o

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R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo de tres a seis átomos de carbono,

R_{5a} y R_{6a} se seleccionan independientemente de hidrógeno, halógeno, hidroxi, alcoxi C_1-C_7, o alquilo C_1-C_7, y

A_1 es fenilo el cual está no sustituido o está sustituido con hasta cuatro sustituyentes independientemente seleccionados de

Halógeno, alquilo C_1-C_7 alcoxi C_1-C_7, ciano, amino, mono- o di(C_1-C_6)alquilamino, hidroxi, acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo o trifluorometoxi, o $-XR_B$, donde X y R_B son tal como se definen a continuación, o

A_1 es tiofeno o piridina cada uno de los cuales está o no sustituido con alquilo C_1-C_7 halógeno, alcoxi C_1-C_7, amino, o mono- o dialquil(C_1-C_6)amino,

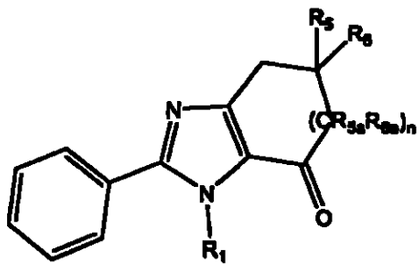
X es independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C$, $-C(=O)NH-$, $-C(O=)NR_C$ $-S(O)_mNH-$, $S(O)_mNR_c-$, $-NHC(=O)-NR_cC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, y $-NR_cS(O)_m-$ (donde m es 0, 1, ó 2), y

R_B y R_C pueden ser iguales o diferentes y están independientemente seleccionados cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada que pueden contener uno o más dobles o triples enlaces, ceda uno de los cuales puede estar no sustituido o sustituido con uno o más sustituyentes seleccionados de

Oxo, hidroxi, -O(alquilo C_1-C_4), -NH(alquilo C_1-C_4), -N(alquilo C_1-C_4)(alquilo C_1-C_4), -NHC(O)(alquilo C_1-C_4), -N(alquilo C_1-C_4)C(O)(alquilo C_1-C_4), -NHS(O)$_x$(alquilo C_{1-4}), -S(O)$_x$(alquilo C_1-C_4), -S(O)$_x$NH(alquilo C_1-C_4), -S(O)$_x$N(alquilo C_1-C_4) (alquilo C_1-C_4), (donde x es 0, 1, ó 2)

28 Un compuesto de acuerdo con la reivindicación 26 de la fórmula



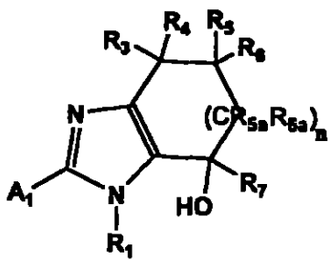
en la cual

R_2 es alquilo C_3-C_8 de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_5 y R_6, son iguales o diferentes y representan hidrógeno o metilo, y

R_{5A} y R_{6A} se seleccionan independientemente en cada ocurrencia de hidrógeno o metilo

29 Un compuesto que tiene la fórmula



en donde

n es un número entero de 0 a 3, y

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquíl) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o

R_2 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido, o un grupo heteroaromático o heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alcoxi, o alquilo, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

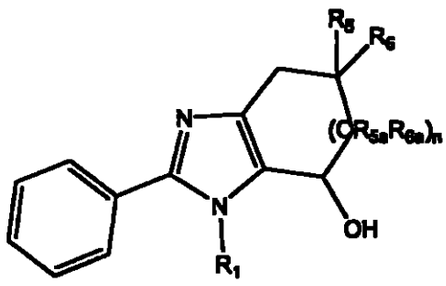
R_{5a} y R_{6b} se seleccionan independientemente cada vez que ocurren de hidrógeno, halógeno, hidroxi, alcoxi, y alquilo,

R_7 representa hidrógeno o alquilo, y

A_1 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido o un grupo heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que

tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos

30 Un compuesto de acuerdo con la reivindicación 30, de la fórmula



En donde

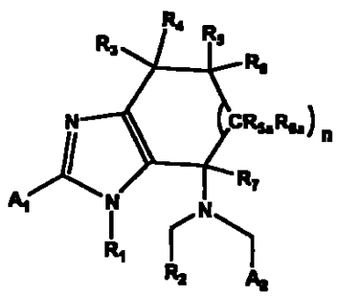
n es un número entero de 0 a 3,

R_1 es alquilo C_3-C_8 de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} son iguales o diferentes y representan hidrógeno o metilo

31 Un procedimiento para preparar un compuesto que tiene la fórmula



en la cual

n es un número entero de 0 a 3, y

R_1 alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o

R_2 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido, o un grupo heteroaromático o heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo, o alcoxi, o

R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurren entre hidrógeno, halógeno, hidroxi, alquilo, o alcoxi,

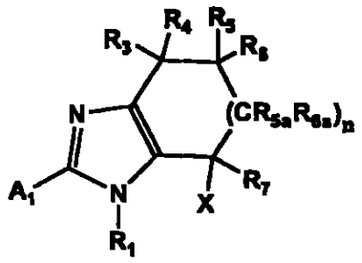
R_7 representa hidrógeno o alquilo,

A_1 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido, o un grupo heteroarilo o heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos, y

A_2 es arilo carbocíclico sustituido o no sustituido, arilalquilo sustituido o no sustituido, o un heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

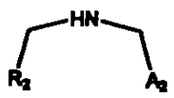
Comprendido dicho procedimiento

Hacer reaccionar un compuesto que tiene la fórmula



en la cual X es halógeno o un éster sulfonato,

en un solvente apropiado en presencia de una base apropiada, con una amina secundaria que tiene la fórmula



32 Un procedimiento para preparar un compuesto de la fórmula de la reivindicación 31, en donde en dicha fórmula

n es un número entero de 0 a 3, y

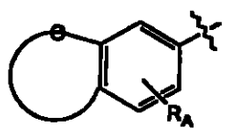
R_1 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_3-C_8(cicloalquilo) o haloalquilo C_1-C_8,

R_2 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8 cicloalquilo C_1-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8, o

R_2 es fenilo, naftaleno, tiofeno o piridina cada uno de los cuales puede estar o no sustituido con

alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, mono- o dialquil(C_1-C_6)amino, o

R_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo C_3-C_6,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 o alcoxi C_1-C_7, o

R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo C_3-C_6,

R_{5a} y R_{6a} son iguales o diferentes, y están independientemente seleccionados cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 y alcoxi C_1-C_7,

R_7 representa hidrógeno o alquilo C_1-C_7,

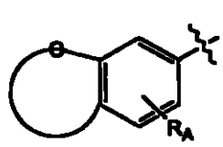
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A_1 es fenilo el cual puede estar o no sustituido con hasta 4 sustituyentes seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, hidroxi, acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo o trifluorometoxi, o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_1 es tiofeno o piridina que puede estar o no sustituido con alquilo C_1-C_7, halógeno, alcoxi C_1-C_7, amino o mono o dialquil(C_1-C_6)amino, y

A_2 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar o no sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquil(C_1-C_6)amino,

X está independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_C-$, -O-, $-S(0)_m-$, -NH-, $-NR_C-$, $-C(=0)NH$, $-C(=0)NR_C-$, $-S(0)_mNH-$, $-S(0)_mNR_C-$, $-NHC(=0)-$, $-NR_CC(=0)$, $-NHS(0)_m-$, $-C(=0)NHS(0)_m-$ y $NR_CS(0)_m-$ (donde m es 0, 1 ó 2),

y

R_B y R_C pueden ser iguales o diferentes y están seleccionados independientemente cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada, que pueden contener uno o más dobles o triples enlaces, cada uno de los cuales puede estar no sustituido o puede estar sustituido con uno o más sustituyente(s) seleccionados de

Oxo, hidroxi, -O(alquilo C_1-C_4), -NH(alquilo C_1-C_4), N-(alquilo C_1-C_4) (alquilo C_1-C_4), $-NHC(O)$(alquilo C_1-C_4) - N(alquilo C_1-C_4)$C(O)$(alquilo C_1-C_4), $-NHS(O)_x$(alquilo C_1-C_4), $-S(O)_x$(alquilo C_1-C_4), $-S(O)_xNH$(alquilo C_1-C_4), - $S(O)_xN$(alquilo C_1-C_4)(alquilo C_1-C_4), (donde x es 0, 1 ó 2)

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PTO 346086

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December 26, 2000

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

APPLICATION NUMBER. *60/212,449*
FILING DATE *June 16, 2000*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

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Certifying Officer

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Customer Number 00098

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney
In re the application of Andrew Thurkauf, et. al. Docket No. N2000.006

For

Assistant Commissioner For Patents
Box Provisional patent Application
Washington, DC 20231

CERTIFICATION UNDER 37 CFR 1.10

Date of Deposit: 06/16/00 Mailing Label Number EJ898809953US

I hereby certify that this Cover Sheet for Filing Provisional Application (37 C.F.R. § 1.51(2)(i) and the documents referred to as attached therein are being deposited with the United States Postal Service on the date indicated above in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10 and addressed to the Assistant Commissioner for Patents, Box Provisional Patent Application, Washington, DC 20231

Leslie-Anne Horvath
Name of Person Mailing Paper

Leslie-Anne Horvath
Signature of Person Mailing Paper

COVER SHEET FOR FILING PROVISIONAL PATENT APPLICATION

Dear Sir

The accompanying application, entitled 2-Phenyl-4-aminomethylpyridines, is a provisional patent application under 37 C.F.R § 1.51 (a)(2) and § 1.53 (b)(2)

1 ☒ The names and addresses of the inventors of this application are as follows

	Last Name	First Name	Middle Initial	Residence
1	Thurkauf	Andrew		16 Fox Den Road Danbury, CT 06811
2	He	Xiao-shu		50 Foxbridge Village Road Branford, CT 06405
3	Zhao	He		4 Stoneridge Lane Barnford, CT 06405
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5				
6.				

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2. ☐ This invention was made by an agency of the United States Government or under contract with an agency of the United States Government. The name of the U S Government agency and the Government contract number are.

Agency _____
Contract No _____

3 ☒ The following documents are enclosed.

☒ 79 pages of Specification and Claims

☒ 1 page of abstract

4. ☒ A verified statement to establish small entity status under 37 CFR 1 9 and 1.27 is enclosed

5 ☐ An Assignment of the invention to _____ is enclosed. A check in the amount of $40 00 for recording this assignment and a recordation form cover sheet (Form PTO 1595) are also enclosed.

6 ☒ The fee for filing this provisional application, as set forth in 37 CFR 1 16(k), is $75 000.

a. ☐ A check for this filing is enclosed.

b ☒ Charge the filing fee to Deposit Account No 501116

c. ☐ The filing fee is not being paid at this time

7 ☒ Please charge any fee deficiencies associated with this filing to Deposit Account No 501116
A duplicate copy of this sheet is enclosed.

Please address all future communications to

Patent Department
Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405

and direct telephone calls to Leslie-Anne Horvath or Seth A. Fidel.

Respectfully submitted,

Leslie-Anne Horvath
Date

Leslie-Anne Horvath
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Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

US PTO 60/212,498 06/19/00

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APPLICATION FOR UNITED STATES LETTERS PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Title **2-PHENYL-4-AMINOMETHYLPYRIDINES**

Inventors Andrew Thurkauf, 16 Fox Den Road, Danbury, CT 06811, Xiao-shu He, 50 Foxbridge Village Road, Branford, CT 06405, and He Zhao, 4 Stoneridge Lane, Branford, CT 06405

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BACKGROUND

Field of the Invention

This invention relates to certain 2-Phenyl-4-aminomethyl pyridines which when appropriately substituted, are modulators of human complement C5a receptors This invention also relates to pharmaceutical compositions comprising such compounds It further relates to the use of such compounds in treating a variety of inflammatory and immune system disorders Additionally, this invention relates to the use such compounds as probes for the localization of C5a receptors

Background of the Invention

Inflammation is the normal physiological response to cellular injury - microbial infection, physical or chemical trauma, or invasion of cancerous cells While necessary to remove infectious particles and damaged tissue, inflammation can also cause pain and further tissue damage Pathogenic

inflammation is associated with various diseases, and is a hallmark of autoimmune disease

Proteins of the complement cascade play a key role in the mediation of inflammation This system of more than 20 interacting soluble and membrane-bound proteins undergoes a series of proteolytic reactions that set in motion a number of important immune functions including the recruitment of leukocytic cells to sites of injury and/or infection Additionally, proteins of the complement system mediate changes in vascular permeability and blood flow, target cells for opsonization, and effect formation of the membrane attack complex, which mediates the immune lysis of foreign cells

C5a, a 74 amino acid peptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement enzyme C5 convertase The anaphylatoxic effects of the C5a peptide are mediated through its interation with the C5a receptor, a 52 kD membrane bound G-protein coupled receptor C5a is a potent chemoattractant for polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to sites of inflammation and/or cellular injury Additionally, C5a stimulates the release of inflammatory mediators (e g , histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes, C5a also promotes the

production of activated oxygen radicals and the contraction of smooth muscle

Considerable experimental evidence implicates increased levels of C5a in a number of autoimmune diseases and inflammatory and related disorders Such autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus (and associated glomerulonephritis), psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, and immunovasculitis Such inflammatory and related conditions include neutropenia, sepsis, septic shock, Alzheimer's disease, stroke, inflammation associated with severe burns, lung injury, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, artherosclerosis and ischemic heart disease, as well as acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), tissue graft rejection, hyperacute rejection of transplanted organs, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), myasthenia gravis, pathologic sequellae associated with insulin-dependent diabetes mellitus (including diabetic retinopathy), Heyman nephritis (and other forms of glomerulonephritis), inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for

example, during extracorporeal circulation of blood (e g , during hemodialysis or via a heart-lung machine, for example, in association with heart surgery such as coronary artery bypass grafting or heart valve replacement) such as extracorporeal post-dialysis syndrome or in association with contact with other artificial vessel or container surfaces (e g , ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, and the like) Antagonists that block the binding of C5a to its receptor or which modulate signal transduction associated with C5a-receptor interactions can inhibit the pathogenic chemotaxis associated with such inflammatory and autoimmune conditions Indeed, certain modified C5a peptides have been identified as C5a antagonists and have been shown to block a number of C5a mediated actions including neutrophil chemotaxis, neutropenia and superoxide formation

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Despite many attempts, no one has previously been able to provide any small molecule (less than 500 Daltons MW) non-peptide, amino acid free, C5a antagonist that is free of agonist activity at the C5a receptor and that exhibits a K_i at the C5a receptor of less than 1 micromolar

SUMMARY OF THE INVENTION

The present invention provides novel compounds that are small molecule C5a receptor antagonists that are non-peptide, amino acid free, and free of C5a receptor agonist activity, which

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compounds exhibit a K_i at the C5a receptor of less than 1 micromolar Preferred C5a receptors are mammalian receptors, including human C5a receptors and may either be cloned, recombinantly expressed receptors or naturally expressed receptors

In certain embodiments these compounds also possess one or more, and preferably two or more, three or more, four or more, five or more, or all of the following properties in that they are 1) multi-aryl in structure (having a plurality of un-fused or fused aryl groups), 2) heteroaryl in structure, 3) orally available in vivo (such that a sub-lethal or pharmaceutically acceptable oral dose can provide a detectable in vitro effect such as a reduction of C5a-induced neutropenia), 4) without amide bonds, and 5) capable of inhibiting leukocyte chemotaxis at nanomolar concentrations or 6) is capable of inhibiting leukocyte chemotaxis at sub-nanomolar concentrations

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In one of its aspects, the invention provides substituted 2-phenyl-4-methylaminopyridines The invention also provides novel compounds of Formula I, shown below, that bind specifically, and preferably with high affinity, to C5a receptors

Novel intermediates useful for synthesizing compounds of the invention are also provided

The invention also provides pharmaceutical compositions comprising compounds of Formula I The compounds are particularly useful in the treatment of C5a-mediated

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inflammation, e g , inflammation associated with various inflammatory and immune system disorders The invention further comprises a method of treating a patient in need of such anti-inflammatory treatment with a sufficient concentration of a compound of the invention A preferred concentration is one sufficient to inhibit white blood cell chemotaxis in vitro Treatment of humans, domesticated companion animals (pets) or livestock animals suffering such conditions with an effective amount of a compound of the invention is contemplated by the invention

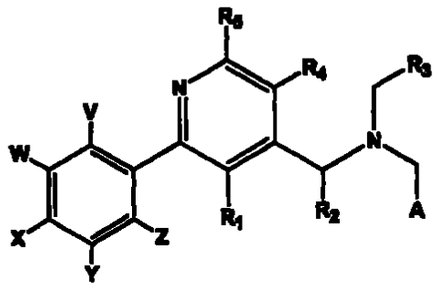
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In a separate aspect, the invention provides methods of using compounds of this invention as positive controls in assays for receptor activity and using appropriately labeled compounds of the invention as probes for the localization of receptors, particularly C5a receptors, in tissue sections

The invention provides compounds and compositions that are useful as inhibitors of C5a-mediated chemotaxis (e g , they may be used as standards in assays of such chemotaxis) The invention additionally comprises methods of inhibiting C5a-mediated chemotaxis, preferably leukocyte chemotaxis, the methods comprising contacting white blood cells with a chemotaxis-inhibitory concentration of a compound of the invention Preferably the concentration is sufficient to inhibit chemotaxis of white blood cells in an *in vitro* chemotaxis assay, so that the levels of chemotaxis observed in a control assay (e g , one to

which a compound of the invention has not been added) are significantly higher (significantly here measured as $p \leq 0.05$ using a conventional parametric statistical analysis method) than the levels observed in an assay to which one or more compounds of the invention have been added

Accordingly, a broad embodiment of the invention is directed to compounds of Formula I



Formula I

and the pharmaceutically acceptable salts thereof, wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

A represents optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

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DETAILED DESCRIPTION OF THE INVENTION

In addition to the compounds of general Formula I, described above, the invention provides compounds of the same general

Formula I, and the pharmaceutically acceptable salts thereof, wherein the variables R_1, R_2, R_3, R_4, R_5, A, V, W, X, Y, and Z are defined as follows

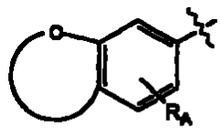
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, or

R_3 is a phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl or indolyl group, each of which is optionally susbstituted with up to four groups independently selected from halogen, nitro, trifluorotheyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

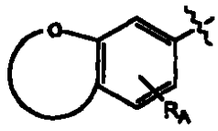
R_4 is hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl or alkoxy, or

R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono or dialkyl sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cyclolalkyl)alkyl or haloalkyl, each of which may be substituted or unsubstituted,

A is a phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, or indolyl group, each of which is optionally substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or dialkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl or

A is a bicyclic oxygen containing group of the formula



wherein R_A, represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl,

haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or dialkylamino, alkyl, alkoxy, akenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of General Formula IA

Alternatively, the invention includes compounds of general Formula I, described above, and the pharmaceutically acceptable salts thereof, wherein the variables R_1, R_2, R_3, R_4, R_5, A, V, W, X, Y, and Z are defined as follows

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

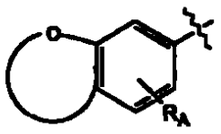
R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl,

C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

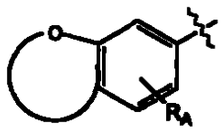
R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2-

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or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

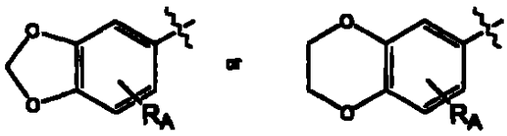
A is a bicyclic oxygen containing group of the formula



wherein R_A, represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

Such compounds will be referred to as compounds of General Formula IB Preferred bicyclic oxygen containing groups for formula IB include



for the variable R_3 or the same groups substituted by R_A, for the variable A

Preferred compounds of General Formula IB are those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of Formula IC

Other preferred compounds of General Formula IB are those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of Formula ID

More preferred compounds of General Formula IB are those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

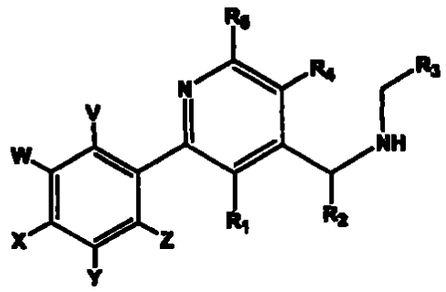
V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of Formula IE

For all preferred compounds of the invention the pharmaceutically acceptable salts thereof are included as part of the invention

Also provided are novel intermediates useful for synthesizing compounds of the invention and methods of synthesizing compounds of the invention using such intermediates

Specifically provided, as intermediates, are compounds of Formula II



Formula II

wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl,

optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

Preferred intermediates of Formula II, are those compounds wherein

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8

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alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy Such compounds are referred to as compounds of Formula IIA

A more preferred class of compounds of Formula II, includes those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy Such compounds are referred to as compounds of Formula IIB

Preferred compounds of Formula II also include those compounds wherein

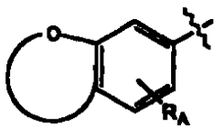
R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of

which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, carboxylic acid esters, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

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R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

Such compounds are referred to as compounds of Formula IIC

Epecially preferred compounds of Formula IIC includes those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds are referred to as compounds of Formula IIC

In certain situations, the compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms These compounds can be, for example, racemates or optically active forms In these situations, the single enantiomers, i e , optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column

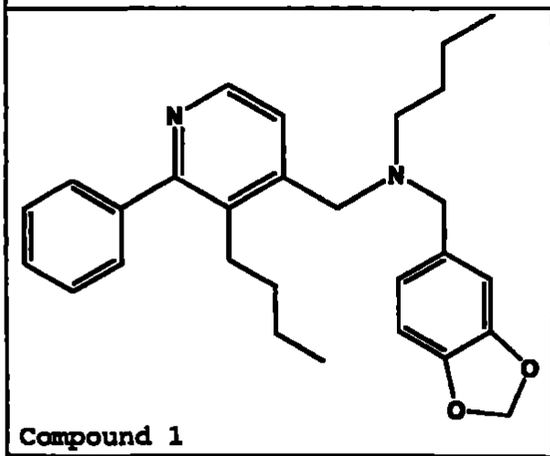
Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds of Table 1 and their pharmaceutically acceptable salts Pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0 - 4, and the like Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts

The present invention also encompasses the acylated prodrugs of the compounds of Formula I Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I

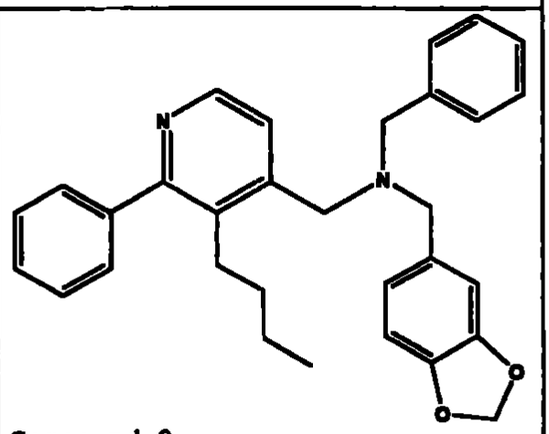
Representative compounds of the invention are shown in Table 1

TABLE 1

Representative 2-Phenyl-4-aminomethylpyridines

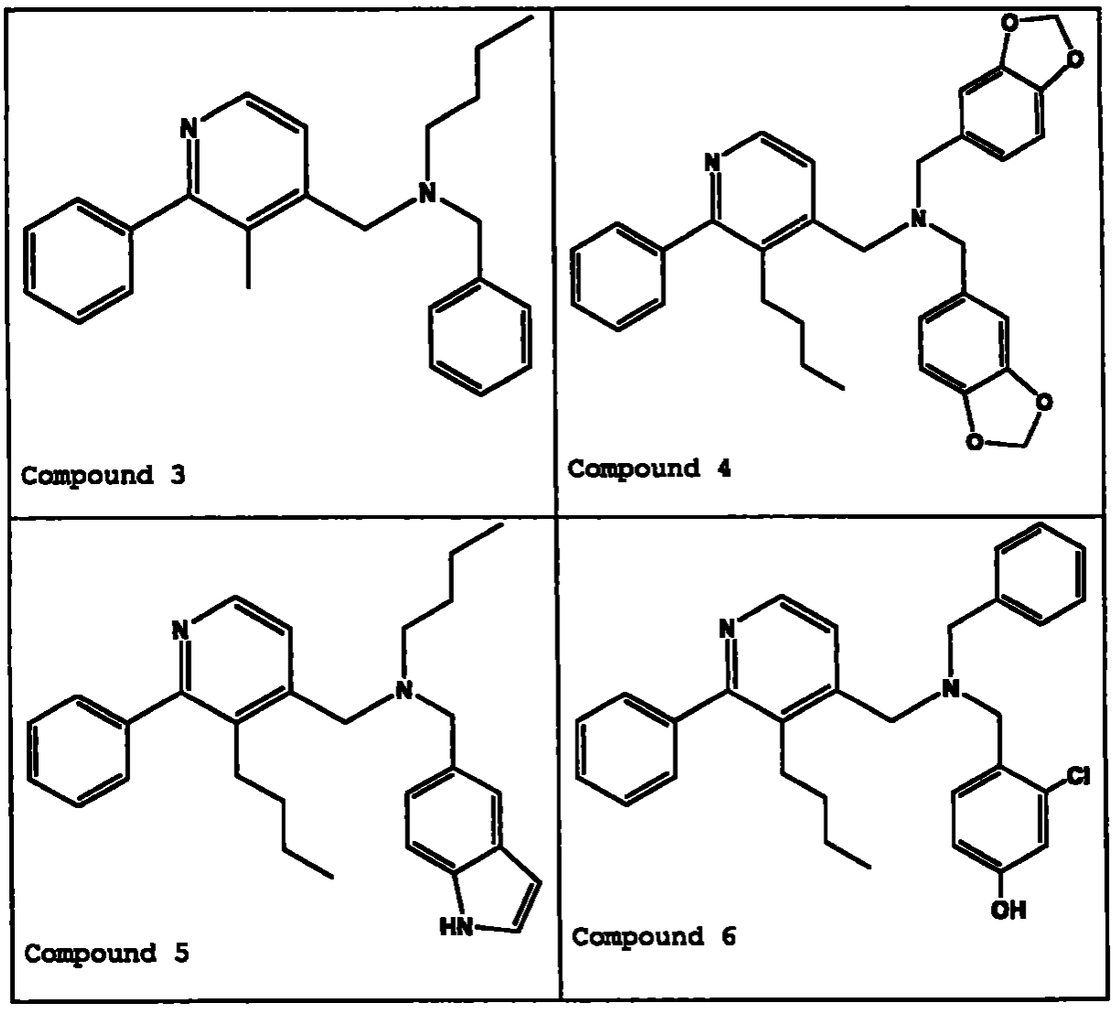


Compound 1



Compound 2

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This invention provides 2-phenyl-4-aminomethylpyridine compounds that bind with high affinity to C5a receptors, particularly human C5a receptors This invention also comprises such compounds that bind with high selectivity to C5a receptors, particularly human C5a receptors The ınteractıon of compounds of the invention with C5a receptors is shown by the inhibition of C5a-mediated chemotaxis e g , as descrıbed ın Example 3 Whıle

not wishing to be bound by any particular theory of operation, it is believed that this interaction results in the pharmacological activity of these compounds This invention includes compounds that inhibit C5a mediated chemotaxis Preferred compounds exhibit EC_{50} values of less than 1 μM in an assay of C5a mediated chemotaxis, more preferred compounds exhibit EC_{50} values of less than 500 nM, and most preferred compounds exhibit EC_{50} values of less than 250 nM

The invention includes methods for the treatment or prevention of disorders responsive to C5a receptor modulation, including but not limited to all of the inflammatory or autoimmune disorders involving pathogenic C5a activity discussed above in the "background of the invention" section, which comprise administering to a patient in need of such treatment an effective amount of compound of the invention

The present invention furthermore provides pharmaceutical compositions comprising a compound or compounds of the invention together with at least one pharmaceutically acceptable carrier or excipient The invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to C5a receptor modulation, e g , any of the inflammatory or autoimmune disorders discussed above as the "background of the invention" including but not limited to arthritis, ARDS, and Alzheimer's Disease The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one C5a receptor

modulator as described supra and instructions for its use for the treatment of a disorder responsive to C5a receptor modulation

This invention also includes compounds that act as selective modulators of G-coupled protein receptors, especially the C5a receptor Preferably, compounds of this invention do not bind to dopamine receptors Most preferably compounds of this invention do not exhibit binding constants less than 1 μM at dopamine receptors in a standard radioligand binding assay for dopamine binding activity (US patent no 5,159,083 is hereby incorporated by reference for its teachings in regard to such assays at col 8)

The present invention also pertains to methods of inhibiting the binding of C5a to C5a receptors which methods involve contacting a compound of the invention with cells expressing C5a receptors, wherein the compound is present at a concentration sufficient to inhibit C5a binding to C5a receptors *in vitro* This method includes inhibiting the binding of C5a to C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I sufficient to produce a body fluid concentration capable of altering the chemotactic responses to C5a of white blood cells *in vitro* In one embodiment, such methods are useful in treating physiological disorders associated with excess concentrations of C5a The amount of a compound that would be sufficient to inhibit the binding of a C5a to the C5a receptor may be readily determined via a C5a receptor binding assay, or from the EC_{50}

obtained via a C5a receptor functional assay, such as the standard assay of C5a receptor mediated chemotaxis described in Example 3 The C5a receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of leukocytes or from cells expressing cloned human C5a receptors, e g human promonocytic U937 cells

The present invention also pertains to methods for altering the activity of C5a receptors, said method comprising exposing cells expressing such receptors to a solution comprising an effective amount of a compound of the invention, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white blood cells *in vitro* This method includes altering the activity of C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I sufficient to produce a body fluid concentration capable of altering the chemotactic responses to C5a of white blood cells *in vitro* The amount of a compound that would be sufficient to alter the chemotactic activity of C5a receptors may be determined via an assay of C5a receptor mediated chemotaxis, such as the standard assay described in Example 5

The C5a receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a compound to interact with the C5a receptor

Labeled derivatives the C5a receptor ligands provided by

this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT)

Definitions

As indicated above, various substituents of the various formulae may be "substituted or unsubstituted" or "optionally substituted" including A, R_1, R_2, R_3, R_4, R_5, V, W, X, Y, and Z or Formula I, and such substituents as recited in the sub-formulae such as Formulae II and the like When substituted, those substituents (A, R_1, R_2, R_3, R_4, R_5, V, W, X, Y, and Z) may be substituted by other than hydrogen at one or more available positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein Suitable groups that may be present on a "substituted" A, R_1, R_2, R_3, R_4, R_5, V, W, X, Y, and Z group or other substituent include e g halogen such as fluoro, chloro, bromo and iodo, cyano, hydroxyl, nitro, azido, alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like, carboxamido, alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms, alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, aryloxy such as phenoxy, alkylthio groups including those moieties having one or more thioether linkages

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and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, carbocyclic aryl having 6 or more carbons, particularly phenyl (e g an Ar group being a substituted or unsubstituted biphenyl moiety), aralkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group, aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group, or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e g coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl

When "araalkyl" is specified in the present invention the point of attachment is the alkyl group

By the term "C_1-C_x alkyl" in the present invention is meant straight or branched chain alkyl groups having 1 to x carbon

atoms, generally up to 6 or 7 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl Preferred C_1-C_6 alkyl groups are methyl, ethyl, propyl, butyl, pentyl and cyclopentyl

The term "C_1-C_x alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy

The term "alkenyl" is intended to include hydrocarbon chains of either a straight or branched conf_guration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl

The term "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl

The term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl

In the term "(C_{3-x} cycloalkyl)C_{1-y} alkyl the point of attachment is on the alkyl group This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl,

cyclohexylmethyl

The term "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1) Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl

By the term "halogen" is meant fluorine, chlorine, bromine or iodine

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7-to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3 3 0]bicyclooctane, [4 3 0]bicyclo-nonane, [4 4 0]bicyclodecane, [2 2 2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl

As used herein, the term "heterocycle" or "heterocycloalkyl" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, 0 and S and including any bicyclic

group in which any of the above-defined heterocyclic rings is fused to a benzene ring The nitrogen and sulfur heteroatoms may optionally be oxidized

The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable A nitrogen in the heterocycle may optionally be quaternized It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another It is preferred that the total number of S and O atoms in the heterocycle is not more than 1 As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1

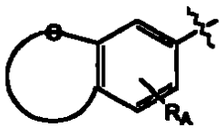
Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benoztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl,

dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl

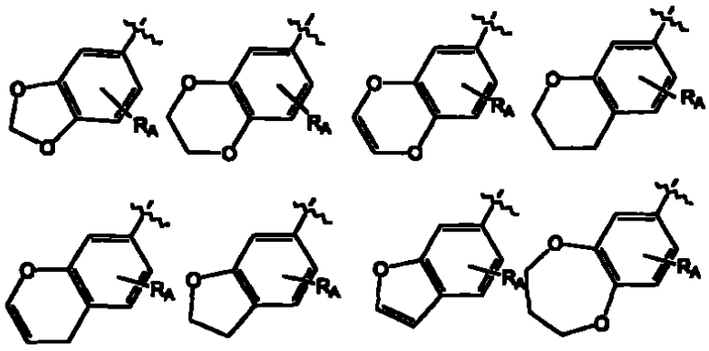
Preferred heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, piperonyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl Also included are fused ring and spiro compounds containing, for example, the above heterocycles

Examples of bicyclic oxygen containing groups of the formula



(R_A may also be indicated R_A') include the following



Pharmaceutical Preparations

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly

preferred The term parenteral as used herein includes injections and the like, such as subcutaneous, intradermal, intravascular (e g , intravenous), intramuscular, intrasternal, spinal, intrathecal, and like injection or infusion techniques, with subcutaneous, intramuscular and intravascular injections or infusions being preferred In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets These excipients may be

for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, corn starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide

with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives Suitable

dispersing or wetting agents and suspending agents are exemplified by those already mentioned above Additional excipients, for example sweetening, flavoring and coloring agents, may also be present

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above The sterile injectable preparation may also be sterile

injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides In addition, fatty acids such as oleic acid find use in the preparation of injectables

The compounds of general Formula I may also be administered in the form of suppositories e g , for rectal administration of the drug These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug Such materials are cocoa butter and polyethylene glycols

Compounds of general Formula I may be administered parenterally, preferably in a sterile non-toxic, pyrogen-free medium The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle

Dosage levels of the order of from about 0 1 mg to about 140 mg per kilogram of body weight per day are useful in the

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treatment or preventions of conditions involving pathogenic C5a activity, particularly those disorders list in the "background of the invention" section (about 0 5 mg to about 7 g per patient per day) The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient

Frequency of dosage may also vary depending on the compound used and the particular disease treated However, for treatment of most disorders, a dosage regimen of 4 times daily, three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i e , other drugs being administered to the patient), the severity of the particular disease undergoing therapy, and other factors, including the judgment of the prescribing medical practitioner

Preferred compounds of the invention will have favorable pharmacological properties Such properties include, but are not limited to bioavailability (e g , oral bioavailibilty, preferably

high enough to permit oral administration), low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lifes Distribution in the body to sites of complement activity is also desirable, e g , compounds to treat compounds used to treat CNS disorders will preferably penetrate the blood brain barrier, while low brain levels of compounds used to treat peripheral disorders are often preferred

Assays may be used to predict these desirable pharmacological properties Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers Toxicity to cultured hepatocyctes may be used to predict compound toxicity Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously

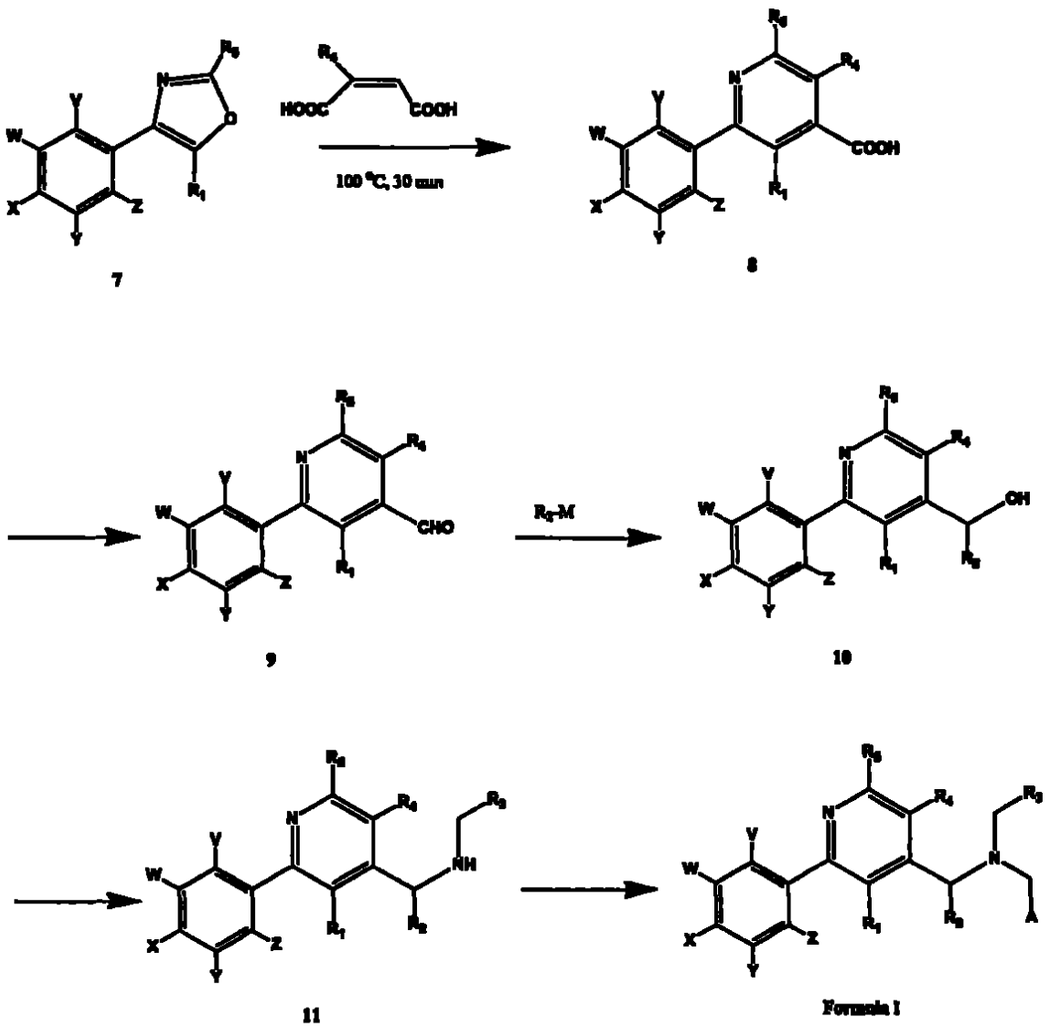
Serum protein binding may be predicted from albumin binding assays Such assays are described in a review by Oravcová, et al (Journal of Chromatography B (1996) volume 677, pages 1-27)

Compound half-life is inversely proportional to the frequency of dosage required for the effective administration of a compound *In vitro* half-lifes of compounds may be predicted, e g , from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127)

Preparation of Compounds

An illustration of the preparation of compounds of the present invention is given in Scheme 1 Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention Within Scheme 1 the variables A, R_1, R_2, R_3, R_4, R_5, V, W, X, Y and Z are defined as previously described

Scheme 1 Preparation of compounds of Formula I



7 8 9 10 11 Formula I

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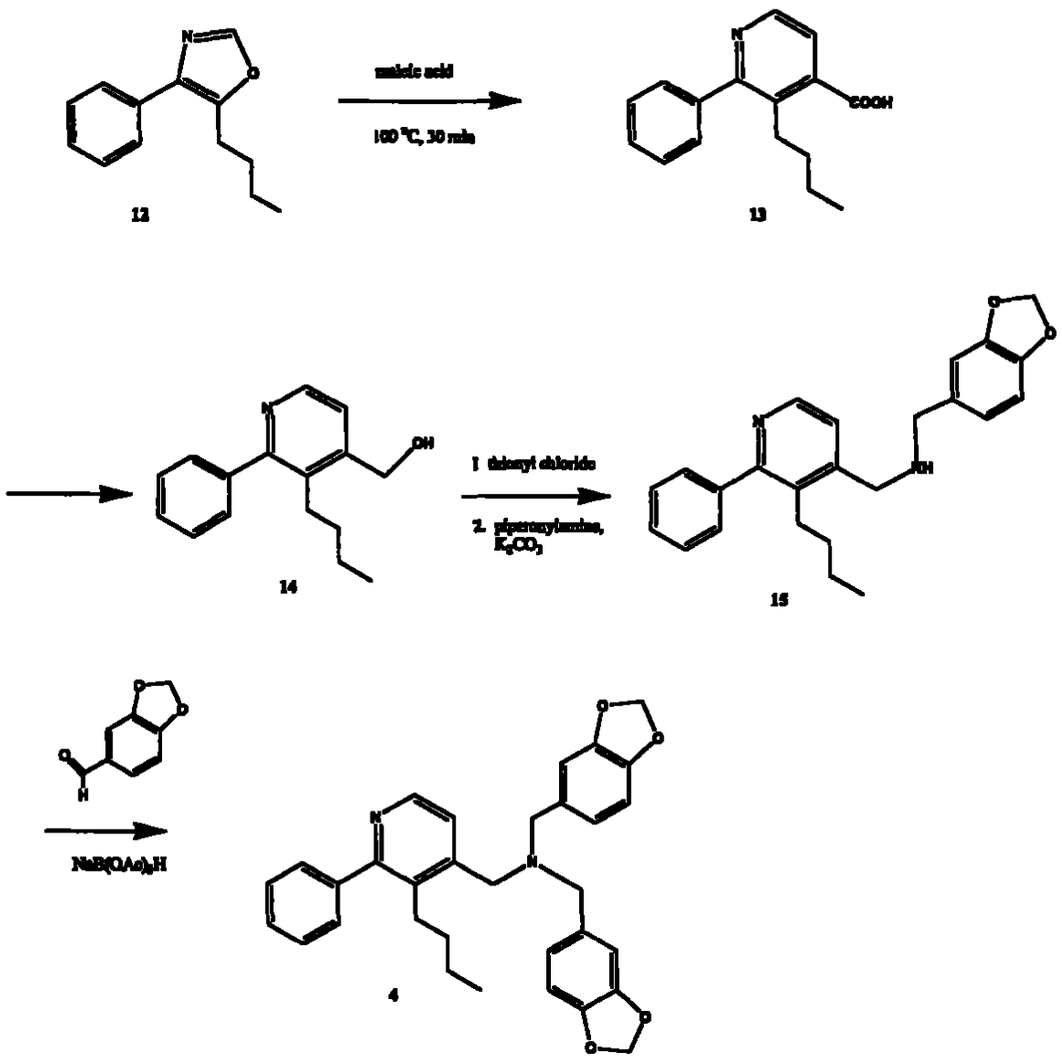
As shown in Scheme 1, an appropriately substituted 4-phenyloxazole 7 is condensed with an appropriately substituted maleic acid to provide a 2-phenylisonicotinic acid 8 The carboxylic acid functionality of 8 can reduced directly to the primary alcohol (10, R_2 = H) or converted by methods known to the art to an intermediate aldehyde 9 and subsequently treated with the appropriate the appropriate organometallic (for cases where R_2 is alkyl) to give a secondary alcohol 10 Compounds of general formula 11 can be prepared from 10 by one of several methods described in the chemical literature, for instance, by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a primary amine Compounds of formula 11 can then be transformed into compounds of general Formula I by direct treatment with the appropriate alkylating agent or, alternatively, by reductive alkylation Alternatively, the tertiary amine functionality of Formula I may be realized directly from compounds of formula 10 by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a secondary amine

Scheme 2 is a graphical representation of the preparation of a specific compound of this invention (Compound 4) according to

the general route described graphically in Scheme 1 The preparation of Compound 4 and the subsequent demonstration of its ability to inhibit C5a mediated chemotaxis represents a reduction to practice of the described invention

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Scheme 2. Preparation of compound 4



The invention is further illustrated by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them

EXAMPLE I Preparation of 2-phenyl-4-(N,N-di{2H-Benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}amino)methyl-3-butylpyridine (Compound 4, Table 1)

4-Phenyl-5-butyloxazole (12) A mixture of α-bromohexanophenone (25 5 g, 0 1 mole), ammonium formate (22 g, 0 35 mole) and formic acid (110 mL) was refluxed with stirring for 3 h The reaction mixture was poured onto ice and made basic with 10 N NaOH and extracted with ether The organic layer was washed with water, dried over sodium sulfate and concentrated The crude product was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane To provide the desired compound as an oil (8 3 g, 41 %), ^{1}H NMR (δ, $CDCl_3$, 400 MHz) 7 55 (m, 2H), 7 40 (s, 1H), 7 34 (dd, J = 7,7 Hz, 2H), 7 22 (dd, J = 7, 7 Hz, 1H), 2 74 (m, 2H), 1 6 (m, 2H), 1 30 (m, 2H), 0 84 (t, J = 7 Hz, 3H) ppm

2-Phenyl-3-butylisonicotinic acid (13) A mixture of 4-phenyl-5-butyloxazole (12, 5 g, 25 mmol) and maleic acid (3 5 g, 30 mmol) was heated at 100 °C for 30 min After cooling, the semisolid mass was triturated with ether and the solid collected by filtration ^{1}H NMR (δ, $CDCl_3$, 400 MHz) 11 68 (brs, 1H),

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8 72 (d, J = 6 0 Hz, 1H), 7 73 (d, J = 5 6 Hz, 1H), 7 48-7 51 (m, 2H), 7 42-7 44 (m, 2H), 6 25 (s, 1H), 2 86 (d, J = 7 6 Hz, 2H), 1 36 (m, 2H), 1 11 (dt, J = 7 6, 7 2 Hz, 2H), 0 68 (t, J = 7 6 Hz, 3H) MS (M+1) 256, (M - 1) 254

2-Phenyl-4-hydroxymethyl-3-butylpyridine (14) To a solution of 2-phenyl-3-butylisonicotinic acid (13, 510 mg, 2 mmol) in tetrahydrofuran (20 mL) was added 4 mL of a 1M solution of lithium aluminum hydride in tetrahydrofuran The reaction was stirred overnight and then quenched with 5 mL of 15% aqueous NaOH The resulting mixture was extracted with ether, dried (Na_2SO_4) and concentrated to provide the desired hydroxymethylpyridine as an oil (470 mg) LC-MS (M+1) 242, ^1H NMR (□, $CDCL_3$) 8 35 (1H, d, J = 5 2 Hz), 7 30-7 39 (6H, m), 4 59 (2H, s), 2 43 (2H, t, J = 8 0 Hz), 1 23 (2H, m), 1 13 (2H, m), 0 70 (3H, t, J = 7 2 Hz)

2-Phenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl})aminomethyl-3-butylpyridine (15) To a solution of 2-phenyl-4-hydroxymethyl-3-butylpyridine (400 mg, 1 66 mmol) in pentene stabilized chloroform (8 mL) was added thionyl chloride (200 mg, 1 67 mmol) and the mixture heated to 50 °C for 2 h The resulting mixture was cooled, washed with saturated sodium bicarbonate solution , dried (Na_2SO_4) and concentrated The resulting crude chloride was taken up in dimethylformamide (10 mL) and added dropwise to a refluxing solution of piperonylamine (1 0 g, 4 equiv) in dimethylformamide (30 mL) containing 3 g of

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powdered potassium carbonate After the addition was complete, the resulting mixture was refluxed for an additional 3 h, cooled and partitioned between water (200 mL) and ether (100 mL) The ethereal layer was washed 2 times with water, dried (Na_2SO_4) and concentrated The resulting material was purified by chromatography on silica eluting with 10% $CH_3OH/CHCl_3$ to give the desired secondary amine 15 LC-MS (M+1) 375 3, ^1H-NMR (δ, $CDCl_3$) 0 73 (3H, t, J = 7 2 Hz), 1 15 (2H, m J = 7 2 Hz), 1 30 (2H, m), 2 58 (2H, t, J = 8 0 Hz), 3 79 (2H, s), 3 83 (2H, s), 5 93 (2H, s), 6 75-6 82 (2H, m), 6 89 (1H, d, J = 1 2 Hz), 7 36-7 42 (6H, m), 8 45 (1H, d, J = 4 8 Hz) ppm

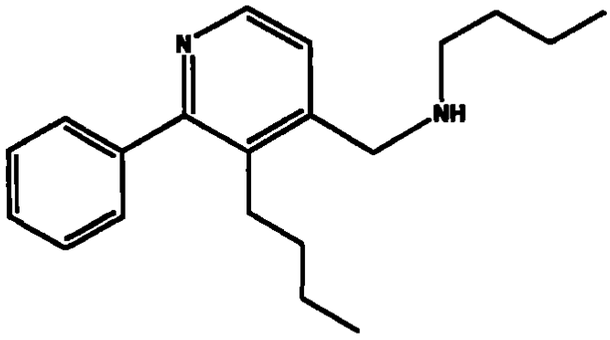
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2-Phenyl-4-(*N*,*N*-di{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl})aminomethyl-3-butylpyridine (4) To a solution of 14 (38 mg) in dichloroethane (5 mL) was added piperonal (30 mg) The resulting mixture was stirred for 3 h after which time sodium triacetoxyborohydride (150 mg) was added in one portion and the resulting mixture was stirred overnight The reaction mixture was quenched with 10% ammonium hydroxide solution (5 ml) The organic layer was washed with water and extracted with 1N HCl solution The acidic extract was made basic with 1N NaOH solution and extracted with chloroform The organic extract was dried (Na_2SO_4) and concentrated The resulting oil was purified on preparative thin layer chromatography eluting with 10% $CH_3OH/CHCl_3$ to give the desired tertiary amine 4 as an oil (18

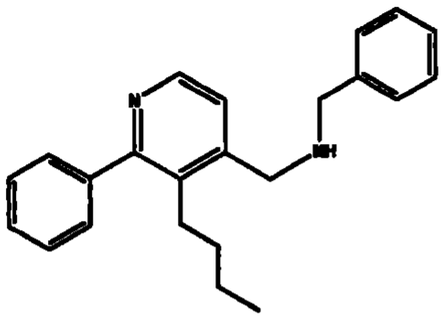
mg) LC-MS (M+1) 509 4, ^{1}H-NMR (δ, $CDCl_3$) 0 71 (3H, t, J = 7 2 Hz), 1 10 (2H, m, J = 7 2 Hz), 2 60 (2H, t, J = 8 0 Hz), 3 48 (4H, s), 3 58 (2H, s), 5 94 (4H, s), 6 75 (1H, d, J = 8 0 Hz),6 80 (1H, dd, J = 0 8, 8 0 Hz), 6 91 (1H, d, J = 0 8 Hz), 7 36-7 43 (5H, m), 7 56 (1H, d, J = 5 2 Hz), 8 47 (1H, d, J = 5 2 Hz) ppm

Example 2

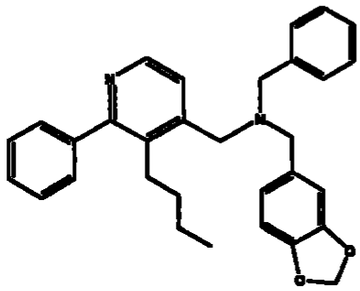
The following compounds were prepared using methods similar to those described in Example 1 Those skilled in the art will recognized where reagents or reaction conditions may be modified to provide the described final products



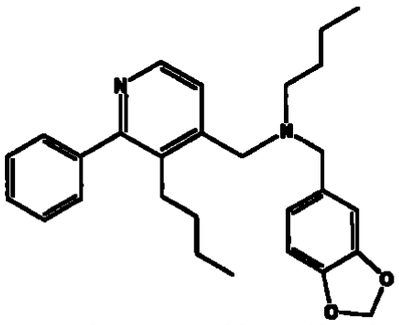
2-Phenyl-4-(*N*-{n-butyl})aminomehyl-3-butylpyridine LC-MS (M+1) 297 3, ^{1}H-NMR (δ, $CDCl_3$) 8 43 (1H, d, J = 5 2 Hz), 7 34 - 7 42 (5H, m), 7 32 (1H, d, J = 4 8 Hz), 3 85 (2H, s), 2 68 (2H, t, J = 7 2 Hz), 2 61 (2H, m), 1 53 (2H, m), 1 30 - 1 44 (4H, m), 1 19 (2H, m, J = 7 6 Hz), 0 92 (3H, t, J = 7 2 Hz,), 0 74 (3H, t, J = 7 2 Hz)



2-Phenyl-4-(*N*-benzyl)aminomethyl-3-butylpyridine LC-MS (M+1) 331 3, ^{1}H-NMR (δ, $CDCl_3$) 8 40 (1H, d, J = 5 Hz), 7 35 - 7 45 (10H, m), 7 30 (1H, d, J = 5 Hz), 3 90 (2H, s), 3 75 (2H, s), 2 58 (2H, M), 1 30 (2H, m), 1 14 (2H, m, J = 7 2 Hz), 0 74 (3H, t, J = 7 2 Hz)

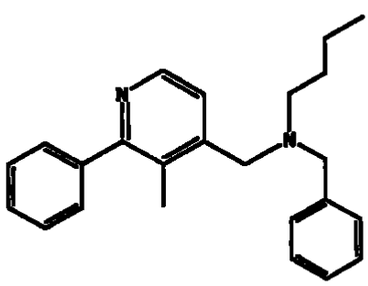


2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-benzyl)aminomethyl-3-butylpyridine (Compound 2, Table 1) LC-MS (M+1) 465 3, ^{1}H-NMR (δ, $CDCl_3$) 0 70 (3H, t, J = 7 2 Hz), 1 09 (2H, m, J = 7 2 Hz), 1 22 (2H, m), 2 59 (2H, t, J = 8 0 Hz), 3 49 (2H, s), 3 58 (2H, s), 3 60 (2H, s), 5 94 (2H, s), 6 75 (1H, d, J = 8 0 Hz), 6 81 (1H, dd, J = 1 6, 8 0 Hz), 6 88 (1H, d, J = 1 6 Hz), 7 22-7 44 (10H, m), 7 60 (1H, d, J = 5 2 Hz), 8 47 (1H, d, J = 5 2 Hz) ppm

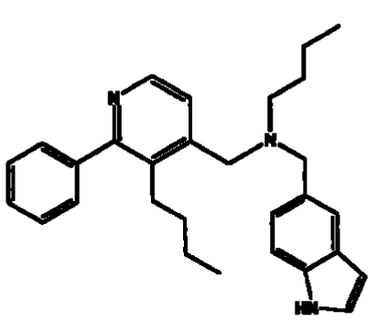


2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-butyl)aminomethyl-3-butylpyridine (Compound 1, Table 1)

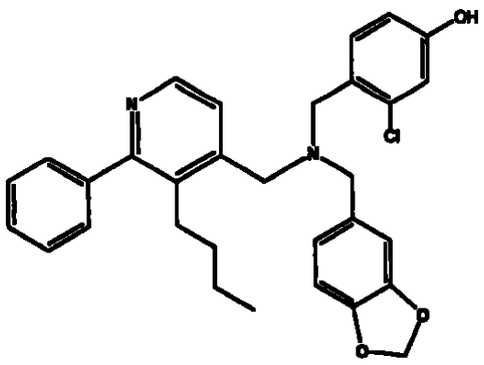
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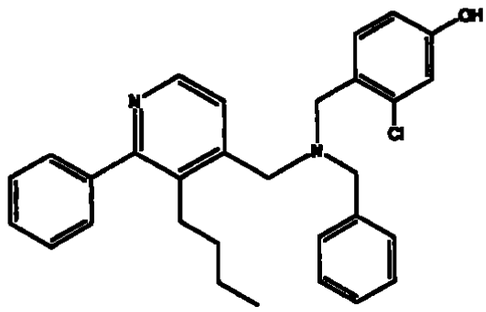
2-Phenyl-4-(*N*-benzyl-*N*-{n-butyl})aminomethyl-3-methylpyridine (Compound 3, Table 1)



2-Phenyl-4-(*N*-indol-5-ylmethyl-*N*-{n-butyl})aminomethyl-3-butylpyridine (Compound 5, Table 1)

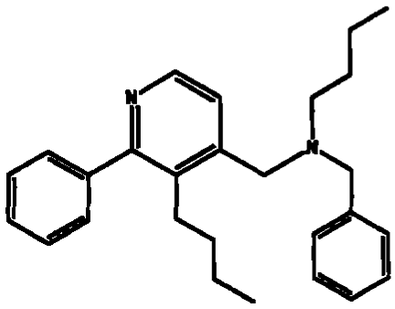


2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-{2-chloro-4-hydroxybenzyl})aminomethyl-3-butylpyridine LC-MS (M+1) 515 3, ^{1}H-NMR (δ, $CDCl_3$) 0 69 (3H, t, J = 7 2 Hz), 1 08 (2H, m, J = 7 2 Hz), 1 20 (2H, m), 2 57 (2H, t, J = 8 0 Hz), 3 50 (2H, s), 3 58 (2H, s), 3 60 (2H, s), 5 92 (2H, s), 6 52 (1H, dd, J = 2 8, 8 4 Hz), 6 61 (1H, d, J = 2 8 Hz), 6 73 (1H, d, J = 8 4 Hz), 6 79 (1H, dd, J = 1 2, 8 0 Hz), 6 89 (1H, d, J = 1 2 Hz), 7 23 (1H, d, J = 8 0 Hz), 7 30-7 43 (5H, m), 7 58 (1H, d, J = 5 2 Hz), 8 37 (1H, d, J = 5 2 Hz) ppm

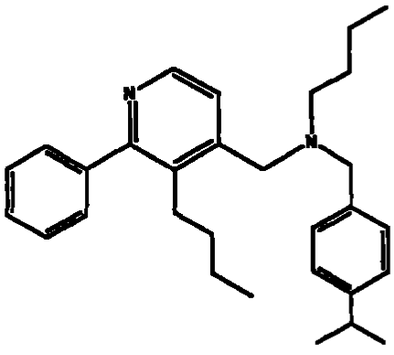


2-Phenyl-4-(*N*-{2-chloro-4-hydroxybenzyl}-*N*-benzyl)aminomethyl-3-butylpyridine (Compound 6, Table 1) LC-MS (M+1) 471 3, ^{1}H-NMR (δ, $CDCl_3$) 0 69 (3H, t, J = 7 2 Hz), 1 08 (2H, m, J = 7 2 Hz),

1 20 (2H, m), 2 57 (2H, t, J = 8 0 Hz), 3 60 (2H, s), 3 61 (2H, s), 3 63 (2H, s), 6 53 (1H, dd, J = 2 8, 8 4 Hz), 6 62 (1H, d, J = 2 8 Hz), 7 23-7 41 (11H, m), 7 63 (1H, d, J = 5 2 Hz), 8 38 (1H, d, J = 5 2 Hz) ppm



2-Phenyl-4-(*N*-benzyl-*N*-{n-butyl})aminomethyl-3-butylpyridine LC-MS (M+1) 437 4, ^{1}H-NMR (δ, $CDCl_3$) 0 72 (3H, t, J = 7 2 Hz), 0 86 (3H, t, J = 7 2 Hz), 1 13 (2H, m, J = 7 2 Hz), 1 21-1 36 (4H, m), 1 53 (2H, m), 2 45 (2H, t, J = 7 2 Hz), 2 58 (2H, t, J = 8 0 Hz), 3 59 (4H, s), 6 49 (1H, dd, J = 2 8, 8 4 Hz), 6 59 (1H, d, J = 2 8 Hz), 7 19 (1H, d, J = 8 4 Hz), 7 30-7 40 (5H, m), 7 56 (1H, d, J = 5 2 Hz), 8 36 (1H, d, J = 5 2 Hz) ppm



2-Phenyl-4-(N-{4-[2-propyl]benzyl}-N-{n-butyl})aminomethyl-3-butylpyridine LC-MS (M+1) 429 6, ^{1}H-NMR (δ, $CDCl_3$) 0 73 (3H, t, J = 7 2 Hz), 0 87 (3H, t, J = 7 2 Hz), 1 12 (2H, m, J = 7 2 Hz), 1 25 (6H, d, J = 7 2 Hz), 1 21-1 38 (4H, m), 1 54 (2H, m, J = 7 2 Hz), 2 46 (2H, t, J = 7 2 Hz), 2 61 (2H, t, J = 8 0 Hz), 2 90 (1H, m, J = 7 2 Hz), 3 58 (2H, s), 3 59 (2H, s), 7 19 (2H, d, J = 8 0 Hz), 7 30 (2H, d J = 8 0 Hz), 7 35-7 44 (5H, m), 7 55 (1H, d, J = 5 2 Hz), 8 45 (1H, d, J = 5 2 Hz) ppm

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Example 3

Assay for C5a Receptor Mediated Chemotaxis

This assay is a standard assay of C5a receptor mediated chemotaxis

Human promonocytic U937 cells are treated with dibutyryl cAMP for 48 hours prior to performing the assay The cells are pelleted and resuspended in culture media containing 0 1% fetal bovine serum (FBS) and 10 ug/ml calcein AM (a fluorescent dye) This suspension is then incubated at 37 °C for 30 minutes such that the cells take up the fluorescent dye The suspension is then centrifuged briefly to pellet the cells, which are then resuspended in culture media containing 0 1% FBS at a concentration of approximately 3 x 10^6 cells/mL Aliquots of this cell suspension are transferred to clean test tubes, which contain vehicle (1% DMSO) or varying concentrations of a compound of interest, and incubated at room temperature for at least 30

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minutes The chemotaxis assay is performed in ChemoTx 101-8, 96 well plates The bottom wells of the plate are filled with varying concentrations of human C5a (0-10 nM) The top wells of the plate are filled with cell suspensions (compound or vehicle-treated) The plate is then placed in a tissue culture incubator for 60 minutes The top surface of the plate is washed with PBS to remove excess cell suspension The number of cells that have migrated into the bottom well is then determined using a fluorescence reader Chemotaxis index (the ratio of migrated cells to total number of cells loaded) is then calculated for each compound concentration to determine an EC_{50} value

As a control to insure that cells retain chemotactic ability in the presence of the compound of interest, the bottom wells of the plate may be filled with varying concentrations chemoattractants that do not mediate chemotaxis via the C5a receptor, e g zymosan-activated serum (ZAS), N-formylmethionyl-leucyl-phenylalanine (FMLP) or leukotriene B4(LTB4)

Compounds of the accompanying Examples exhibit EC_{50} values of less than 1 5 μM in the above assay for C5a mediated chemotaxis Data is shown for several representative compounds of this invention in Table 2

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TABLE 2	
Compound Number	EC_{50}
2	442 nM
4	488 nM
6	485 nM

Example 4
Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I) Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds Such suppliers include Amersham Corporation, Arlington Heights, IL, Cambridge Isotope Laboratories, Inc Andover, MA, SRI International, Menlo Park, CA, Wizard Laboratories, West Sacramento, CA, ChemSyn Laboratories, Lexena, KS, American Radiolabeled Chemicals, Inc , St Louis, MO, and Moravek Biochemicals Inc , Brea, CA

Tritium labeled probe compourds are also conveniently prepared catalytically via platinum-catalyzed exchange in

tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate

Example 4a

Preparation of a Radiolabeled compounds of the invention

Maleic acid, [1,4-^{14}C], ARC-568, supplied by American Radiolabeled Chemicals, Inc , St Louis MO, may be used in one synthetic method for preparing radiolabeled compounds of the invention In this method, an appropriately substituted 4-phenyloxazole (7) is condensed with ^{14}C labeled maleic acid to provide the labeled 2-phenylisonicotinic acid (8) as shown in Scheme I above

Example 5

Use of compounds of the invention as probes for C5a receptors in cultured cells and tissue samples

Receptor autoradiography (receptor mapping) of C5a receptors in cultured cells or tissue samples is carried out in vitro as described by Kuhar in sections 8 1 1 to 8 1 9 of Current

Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example

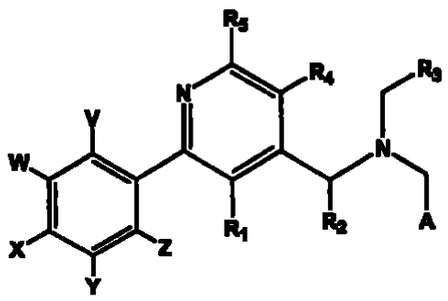
The disclosures in this application of all articles and references, including patents, are incorporated herein by reference

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference

The invention and the manner and process of making and using it are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims To particularly point out and distinctly claim the subject matter regarded as the invention, the following claims conclude the specification

What is claimed is

1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted aralkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

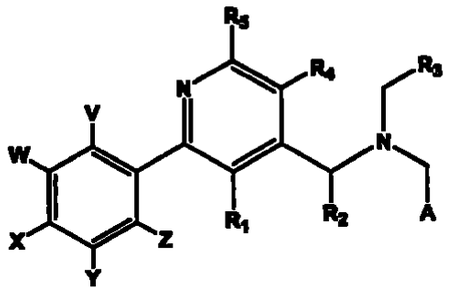
R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

A represents optionally substituted carbocyclic aryl, optionally substituted aralkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

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2 A compound according to Claim 1, of the formula



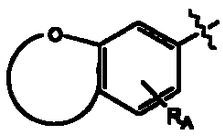
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, or

R_3 is a phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl or indolyl group, each of which is optionally susbstituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

R_4 is hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl or alkoxy, or

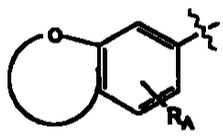
R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono

or dialkyl sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cyclolalkyl)alkyl or haloalkyl, each of which may be substituted or unsubstituted,

A is phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, or indolyl group, each of which is optionally substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or dialkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

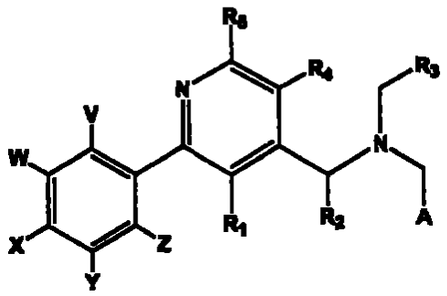
A is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or dialkylamino, alkyl, alkoxy, akenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, trifluoromethyl, or trifluoromethoxy

3 A compound according to Claim 1, of the formula



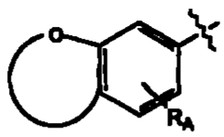
R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

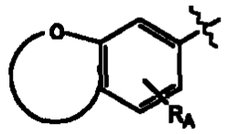
R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-

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C_8 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

A is a bicyclic oxygen containing group of the formula



wherein R_A, represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

4 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

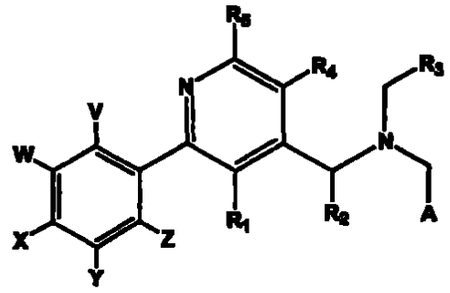
R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

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V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

4 A compound according to Claim 1, of the formula



R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

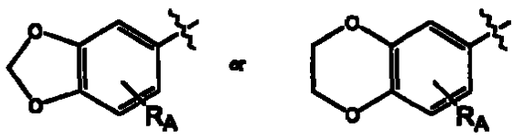
R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-

C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

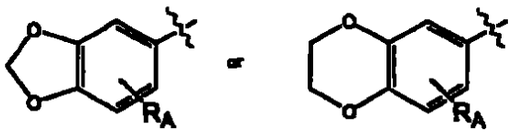
R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which

may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

A is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

5 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

6 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

7 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl,

C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_8)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

8 A compound according to claim 1, which is selected from

2-Phenyl-4-(*N*,*N*-di{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl})aminomethyl-3- butylpyridine,

2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-benzyl)aminomethyl-3- butylpyridine,

2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-butyl)aminomethyl-3- butylpyridine,

2-Phenyl-4-(*N*-benzyl-*N*-{n-butyl})aminomethyl-3-methylpyridine,

2-Phenyl-4-(*N*-indol-5-ylmethyl-*N*-{n-butyl})aminomethyl-3-butylpyridine,

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2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-{2-chloro-4- hydroxybenzyl})aminomethyl-3-butylpyridine,

2-Phenyl-4-(*N*-{2-chloro-4-hydroxybenzyl}-*N*-benzyl)aminomethyl-3-butylpyridine, and

2-Phenyl-4-(N-{4-[2-propyl]benzyl}-N-{n-butyl})aminomethyl-3-butylpyridine

9 A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient

10 A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 9 in a container and comprising instructions for using the composition to treat a patient in need of anti-inflammatory treatment

11 The packaged pharmaceutical composition of claim 9, wherein said patient is suffering from rheumatoid arthritis, Crohn's disease, irritable bowel syndrome, ARDS, extracorporeal post-dialysis syndrome, systemic lupus erythematosus, psoriasis or bronchial asthma

12 The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a

medicament for the treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory diseases

13 A method of treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory disorders which comprises administering to patient in need of such treatment a C5a receptor-modulatory effective amount of a compound according to Claim 1

14 A method of inhibiting leukocyte chemotaxis, which comprises
contacting a compound of Claim 1 with white blood cells, wherein the compound is present at a concentration sufficient to inhibit chemotaxis of white blood cells *in vitro*

15 A method for the treatment of physiological disorders associated with localized excess concentrations of C5a, which method comprises administration to a patient in need of such treatment a compound according Claim 1, wherein the compound is administered in an amount sufficient to yield, at a site of localized excess concentrations of C5a, a concentration of the compound sufficient to inhibit chemotaxis of white blood cells *in vitro*

16 A method for localizing C5a receptors in tissue section

samples comprising

contacting with a sample of tissue a detectably-labelled compound of claim 1 under conditions that permit binding of the compound to the sample of tissue,

washing the tissue sample to remove unbound compound, and

detecting the bound compound

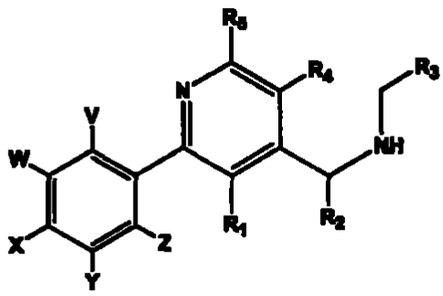
17 A method of inhibiting the binding of C5a to C5a receptors, which method comprises contacting a solution comprising the compound of Claim 1 with C5a receptors, wherein the compound is present in the solution at a concentration sufficient to alter the chemotactic responses to C5a of white blood cells *in vitro*

18 A method for altering the activity of cell surface C5a receptors, said method comprising contacting cells expressing such receptors with a solution comprising the compound of Claim 1, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white blood cells in vitro

19 A compound according to claim 1 wherein in an assay of C5a mediated chemotaxis the compound exhibits an IC_{50} of 1 micromolar or less

20 A compound according to claim 1 wherein in an assay of C5a mediated chemotaxis the compound exhibits an IC_{50} of 100 nanomolar or less

21 A compound of the formula



wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

22 A compound according to Claim 21, wherein

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano,

carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

23 A compound according to Claim 21, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

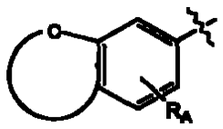
24 A compound according to Claim 21, wherein

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

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R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

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25 A compound according to Claim 21, wherein

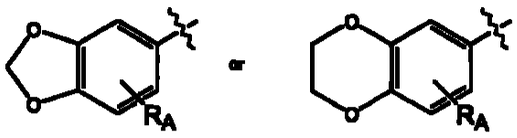
R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-

C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

ABSTRACT

Disclosed are 2-Phenyl-4-aminomethylpyridine compounds These compounds are selective modulators of human complement C5a receptors that are, therefore, useful in the treatment of a variety of immune system and inflammatory disorders Methods of treatment of such disorders and well as packaged pharmaceutical compositions are also provided

Compounds of the invention are also useful as probes for the localization of C5a receptors and as standards in assays for C5a mediated chemotaxis Methods of using the compounds in receptor localization studies are given

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(Attorney's Docket No. N2000.006)

Applicant or Patentee. Andrew Thurkauf, et. al

Serial or Patent No. _____ Filed _____Herewith_____

Title: 2-Phenyl-4-Ammomethylpyridines

US PATENT & TRADEMARK OFFICE 27 2002

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 C.F.R. § 1.9(f) AND § 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am an official of the small business concern empowered to act on behalf of the concern identified below

NAME OF SMALL BUSINESS CONCERN	NEUROGEN CORPORATION
ADDRESS OF SMALL BUSINESS CONCERN	35 NORTHEAST INDUSTRIAL ROAD BRANFORD CT 06405

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 C.F.R § 121 and referenced in 37 C.F.R. § 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year and (2) concerns are affiliates of each other when either directly or indirectly one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled 2-Phenyl-4-Ammomethylpyridines by inventor(s) Andrew Thurkauf, et. al.

described in

☒ the specification filed herewith.
☐ Application Serial No _____ filed _____
☐ Patent No. _____ issued _____

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NEUROGEN CORPORATION
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

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If the rights held by the above identified small business concern are not exclusive, each individual concern or organization having rights in the invention must file verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor who would not qualify as an independent inventor under 37 CFR § 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR § 1.9(d), or a nonprofit organization under 37 CFR § 1.9(e)

Each person, concern or organization having any rights to the invention is listed below:

☒ No such person, concern or organization exists.
☐ Each such person, concern or organization is listed below

FULL NAME _____

ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____

ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

Separate verified statements are required from each named person, concern or organization having rights in the invention averring to their status as small entities. (37 CFR § 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. § 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed

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NAME OF PERSON SIGNING Harry H. Penner, Jr

TITLE IN ORGANIZATION President and Chief Executive Officer

ADDRESS OF PERSON SIGNING 35 Northeast Industrial Road
Branford, CT 06405

Signature. _____

Date: 6/15/00

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DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

26 de diciembre de 2000

LA PRESENTE ES PARA CERTIFICAR QUE ADJUNTA A LA MISMA HAY UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA EN LO QUE SIGUE, QUE CUMPLEN LOS REQUISITOS PARA OTORGARLE UNA FECHA DE PRESENTACIÓN BAJO 35 USC 111

NÚMERO DE SOLICITUD 60/212,449
FECHA DE PRESENTACIÓN 16 de junio de 2000

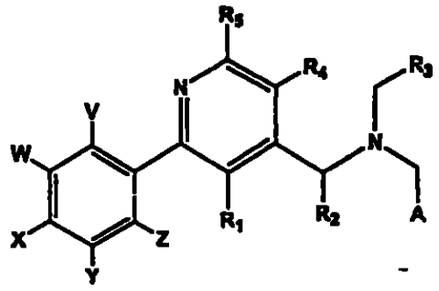
Por la Autoridad del
COMISARIO DE PATENTES Y MARCAS

E BORNETT

Oficial certificador

Lo que se reivindica es

1 Un compuesto de la fórmula



o una sal farmacéuticamente aceptable del mismo, donde

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, o alquinilo,

R_3 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o arilo carbocíclico opcionalmente sustituido, aralquilo opcionalmente sustituido, o un grupo heteroaromático o heteroalicíclico opcionalmente sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

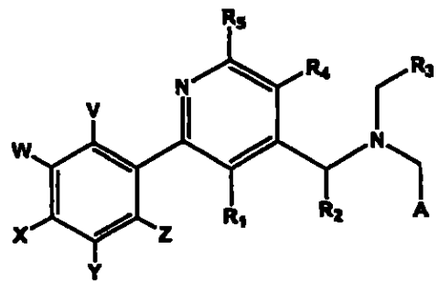
R_4 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o fenilo opcionalmente sustituido,

R_5 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

A representa arilo carbocíclico opcionalmente sustituido, aralquilo opcionalmente sustituido, o un grupo heteroaromático o

heteroalicíclico opcionalmente sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos, y V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquilamino opcionalmente sustituido, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, alquenil opcionalmente sustituido, alquinilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, (cicloalquilo) alquilo opcionalmente sustituido, o haloalquilo opcionalmente sustituido, alquiltio opcionalmente sustituido, alquilsulfinilo opcionalmente sustituido, o alquilsulfonilo opcionalmente sustituido

2 Un compuesto de acuerdo con la reivindicación 1, de la fórmula



R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo,

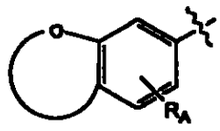
R_2 es hidrógeno, alquilo, alquenilo, o alquinilo,

R_3 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, o

R_3 es un grupo fenilo, piridilo, pirimidinilo, dihidrobenzofuranilo, cromanilo, benzodioxanilo, o indolilo, cada de los cuales puede estar opcionalmente sustituido con hasta 4 grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo,

alquenilo, alquinilo, alcoxi, ciano, amino, mono- o alquilamino, haloalquilo, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

R_4 es hidrógeno, halógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo o alcoxi, o

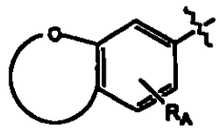
R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo, alquenilo, alquinilo, alcoxi, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquilamino, aminocarbonilo, sulfonamido, mono o dialquilsulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo y trifluorometoxi,

R_5 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

A es un grupo fenilo, piridilo, pirimidinilo, dihidrobenzofuranilo, cromanilo, benzodioxanilo, o indolilo, cada de los cuales puede estar opcionalmente sustituido con hasta 4 grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo,

alquenilo, alquinilo, alcoxi, ciano, amin , mono- o dialquilamino, haloalquilo, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

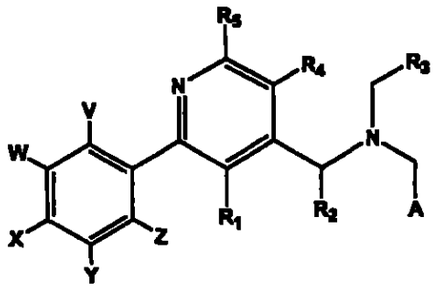
A es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquilamino, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, trifluorometilo o trifluorometoxi

3 Un compuesto de acuerdo con la reivindicación 1, de la fórmula



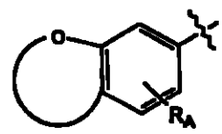
R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquiloC_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8,

R_3 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8, o

R_3 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

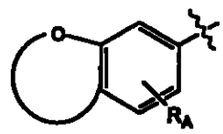
R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8

A es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

A es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

4 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

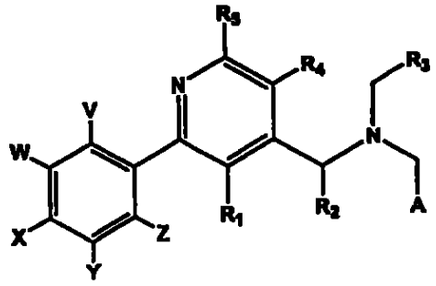
R_2 es hidrógeno, metilo o etilo,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

4 Un compuesto de acuerdo con la reivindicación 1 de la fórmula



R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquiloC_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

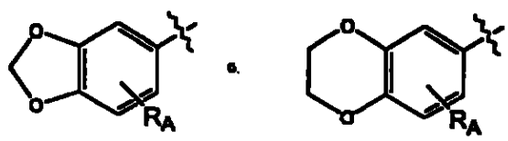
R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_3 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8, o

R_3 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-

C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

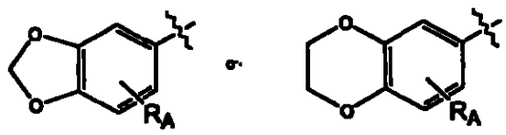
R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8

A es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo,

trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

A es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

5 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

6 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es alquilo C_1-C_8,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

7 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es fenilo el cual puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, 3,4-metilendioxi, y 3,4-(1,2-etilen) dioxi,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

8 Un compuesto de acuerdo con la reivindicación 1, el cual se selecciona de

2-fenil-4-(N,N-di{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil}) aminometil-3-butilpiridina,

2-fenil-4-(N-{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil})-N-bencil) aminometil-3-butilpiridina,

2-fenil-4-(N-{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil})-N-butil) aminometil-3-butilpiridina,

2-fenil-4-(N-bencil-N-{n-butil}) aminometil-3-butilpiridina,

2-fenil-4-(N-{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil})-N-{2-cloro-4-hidroxibencil}) aminometil-3-butilpiridina,

2-fenil-4-(N-{2-cloro-4-hidroxibencil}-N-bencil) aminometil-3-butilpiridina, y

2-fenil-4-(N-{4-[2-propil] bencil}-N-{n-butil}) aminometil-3-butilpiridina

9 Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, junto con al menos un adyuvante o excipiente farmacéuticamente aceptable

10 Una composición farmacéutica empacada que comprende la composición farmacéutica de la reivindicación 9 en un envase y que comprende instrucciones para el uso de la composición para tratar un paciente que necesita un tratamiento anti inflamatorio

11 La composición farmacéutica empacada de la reivindicación 9 en donde dicho paciente sufre de artritis reumatoide, enfermedad de Chron, síndrome de intestino irritable, ARDS, síndrome post-diálisis extracorpóreo, lupus sistémic eritematoso, soriasis o asma bronquial

12 El uso de un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en la manufactura de un medicamento para el tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes

13 Un método de tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes, el cual comprende administrar a un paciente que necesita dicho tratamiento una cantidad efectiva C5a receptor-moduladora de un compuesto de acuerdo con la reivindicación 1

14 Un método para inhibir la quimiotaxia, el cual comprende

Poner en contacto un compuesto de la reivindicación 1 con glóbulos blancos, en donde el compuesto está presente en una cantidad suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

15 Un método para el tratamiento de desórdenes fisiológicos asociados con el exceso de concentraciones de C5a localizadas, en donde dicho método comprende la administración a un paciente que necesita dicho tratamiento de un compuesto de acuerdo con la reivindicación 1, en donde el compuesto se administra en cantidad suficiente para producir, en un sitio del exceso de concentraciones de C5a localizadas, una concentración del compuesto suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

16 Un método para localizar receptores C5a en muestras de secciones de tejido que comprende

Poner en contacto una muestra de tejido con un compuesto de la reivindicación 1, detectable etiquetado, bajo condiciones que permiten el ligamiento del compuesto a la muestra de tejido,

Lavar la muestra de tejido para remover el compuesto no ligado, y

Detectar el compuesto ligado

17 Un método para inhibir el ligamiento de C5a a receptores C5a, en donde dicho método comprende poner en contacto una solución que comprende el compuesto de la reivindicación 1 con receptores C5a, en donde el compuesto está presente en la solución a una concentración suficiente para alterar las respuestas quimiotácticas a C5a de los glóbulos blancos in vitro

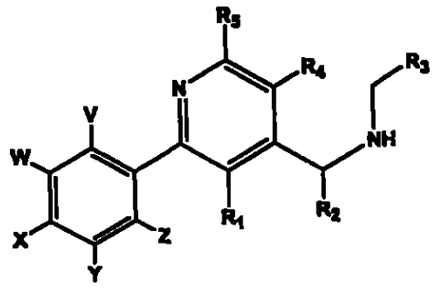
18 Un método para alterar la actividad de receptores C5a de superficie de célula, en donde dicho método comprende poner en

contacto células que expresan dichos receptores con una solución que comprende el compuesto de la reivindicación 1, en donde el compuesto está presente en la solución a una concentración suficiente para alterar específicamente las respuestas quimiotácticas de C5a de glóbulos blancos in vitro

19 Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de quimiotaxia mediada por C5a, el compuesto exhibe un IC_{50} de 1 micromolar o menos

20 Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de quimiotaxia mediada por C5a, el compuesto exhibe un IC_{50} de 100 nanomolar o menos

21 Un compuesto de la fórmula



En donde

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, o alquinilo,

R_3 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o arilo carbocíclico opcionalmente sustituido, aralquilo opcionalmente sustituido, o un grupo heteroaromático o heteroalicíclico opcionalmente sustituido que

tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_4 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o fenilo opcionalmente sustituido,

R_5 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquilamino opcionalmente sustituido, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, alquenilo opcionalmente sustituido, alquinilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, (cicloalquilo) alquilo opcionalmente sustituido, o haloalquilo opcionalmente sustituido, alquiltio opcionalmente sustituido, alquilsulfinilo opcionalmente sustituido, o alquilsulfonilo opcionalmente sustituido

22 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8,

R_3 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

23 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es alquilo C_1-C_8,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

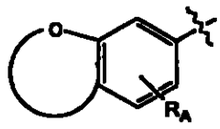
24 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_3 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8,

alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8 y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

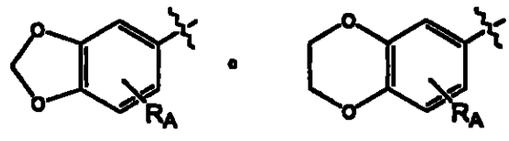
25 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es fenilo el cual puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



En donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

COLO 10611-801-006-0

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PTO 246085

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December 26, 2000

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

APPLICATION NUMBER *60/224,036*
FILING DATE *August 09, 2000*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

PART (1) OF (2) PART(S)

E. Bornett
E. BORNETT
Certifying Officer

09/60/00 jc644 U S PTO

Customer Number 000959

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney
In re the application of Andrew Thurkauf, et. al. Docket No. N2000.010

For

Assistant Commissioner For Patents
Box Provisional patent Application
Washington, DC 20231

jc644 U S PTO
60/224036
08/09/00

COVER SHEET FOR FILING PROVISIONAL PATENT APPLICATION

Dear Sir

The accompanying application, entitled Heterocyclic Compounds as Modulators of the C5a Receptor, is a provisional patent application under 37 C.F.R. § 1 51 (a)(2) and § 1.53 (b)(2)

US Express Mailing No EL074500410US 080900 "Express Mail" 08/09/00

1 ☒ The names and addresses of the inventors of this application are as follows

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2	et al			
3				
4				
5				
6				

Attorney Docket N2000.[redacted]

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2 ☐ This invention was made by an agency of the United States Government or under contract with an agency of the United States Government. The name of the U.S Government agency and the Government contract number are.

Agency _____

Contract No. _____

3 ☒ The following documents are enclosed.

☒ 376 pages of Specification and Claims

☐ 1 page of abstract

4 ☒ A verified statement to establish small entity status under 37 CFR 1 9 and 1.27 is enclosed.

5 ☐ An Assignment of the invention to _____ is enclosed. A check in the amount of $40.00 for recording this assignment and a recordation form cover sheet (Form PTO 1595) are also enclosed.

6 ☒ The fee for filing this provisional application, as set forth in 37 CFR 1 16(k), is $75.00

a. ☒ A check for this filing is enclosed.

b ☐ Charge the filing fee to Deposit Account No. 501116

c. ☐ The filing fee is not being paid at this time.

7 ☒ Please charge any fee deficiencies associated with this filing to Deposit Account No. 501116. *A duplicate copy of this sheet is enclosed.*

Please address all future communications to:

Patent Department
Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405

and direct telephone calls to. Leslie-Anne Horvath or Seth A. Fidel.

Respectfully submitted,

Leslie-Anne Horvath

8/9/00
Date

Leslie-Anne Horvath
Registration No 44,778

Neurogen Corporation
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

US Express Mailing No. EL074500410US 09001100 '09501.2205

APPLICATION FOR UNITED STATES LETTERS PATENT
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

N2000.010

Title Heterocyclic Compounds as Modulators of the C5a Receptor

Inventors

Andrew Thurkauf
16 Fox Den Road
Danbury, CT 06811

et al

09220305 080900

HETEROCYCLIC MODULATORS OF COMPLEMENT C5a SIGNAL TRANSDUCTION

BACKGROUND OF THE INVENTION

1 Field of the Invention

This invention relates to certain heterocyclic derivatives which when appropriately substituted, are modulators of human complement C5a receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating a variety of inflammatory and immune system disorders.

2 Description of Related Art

Inflammation is the normal physiological response to cellular injury – microbial infection, physical or chemical trauma, or invasion of cancerous cells. While necessary to remove infectious particles and damaged tissue, inflammation can also cause pain and further tissue damage. Pathogenic inflammation is associated with various diseases, and is a hallmark of autoimmune disease.

Inflammation is largely mediated by proteins of the complement cascade. This system of more than 20 interacting soluble and membrane-bound proteins undergoes a series of proteolytic reactions that set in motion a number of important immune functions including the formation of the membrane attack complex, which mediates the immune lysis of foreign cells. Additionally, proteins of the complement system effect changes in vascular permeability and blood flow, target cells for opsonization, and recruit leukocytic cells to sites of injury and/or infection.

C5a, a 74 amino acid polypeptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement enzyme C5 convertase. The anaphylatoxic effects of the C5a peptide are mediated through the C5a receptor, a 52 kD membrane bound G-coupled protein receptor C5a is a potent chemoattractant for

polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to the site of cellular injury Additionally C5a stimulates the release of inflammatory mediators (e.g , histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes, C5a also promotes the production of activated oxygen radicals and the contraction of smooth muscle

Considerable experimental evidence implicates increased levels of C5a in a number of autoimmune diseases and inflammatory disorders including rheumatoid arthritis, systemic lupus erythematosus, psoriasis, tissue graft rejection, ischemic heart disease, Crohn's disease, irritable bowel syndrome, sepsis, septic shock, atherosclerosis, Alzheimer's disease, multiple sclerosis, lung injury, bronchial asthma, neutropenia, sunburn pain, dandruff in humans and companion animals, extracorporeal post-dialysis syndrome and acute respiratory distress syndrome (ARDS) Antagonists that block the binding of C5a to its receptor or which modulate the signal transduction subsequent to C5a-receptor interactions can inhibit the pathogenic chemotaxis associated with such conditions Indeed, certain modified C5a peptides have been identified as C5a antagonists and have been shown to block a number of C5a mediated actions including neutrophil chemotaxis, neutropenia and superoxide formation.

C5a is a highly cationic protein, therefore the search for modulators of its activity has included examining molecules that would interact with the presumably anionic binding site of the receptor

Peptides, peptidomimetics and non-peptidic compounds have all been disclosed as modulators of C5a activity The peptide-based compounds in particular are, at best, short acting due to their destruction by proteolytic enzymes.

SUMMARY OF THE INVENTION

The present invention provides substituted 1-Alkyl-2-aryl-5-aminoalkylimidazoles that display activity as modulators of C5a activity

This invention provides novel compounds of Formula I. These compounds interact with complement C5a receptors, preferably mammalian C5a receptors, including human C5a receptors. Cloned receptors are particularly preferred.

The invention also provides pharmaceutical compositions comprising compounds of Formula I

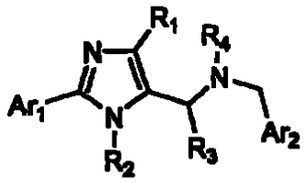
The compounds and compositions of the invention are useful as inhibitors of C5a-mediated chemotaxis (e.g., they may be used as standards in assays of such chemotaxis) The compounds are particularly useful in the treatment of C5a-mediated inflammation, e.g., inflammation associated with various inflammatory and immune system disorders

The invention further comprises methods of treating patients, preferably mammals, in need of such anti-inflammatory treatment with an effective amount of a compound of the invention. A preferred amount is one that produces a concentration sufficient to inhibit white blood cell chemotaxis in vitro More preferably the patient is a domestic mammal. Most preferably the subject is a human patient.

The invention additionally comprises methods of inhibiting C5a-mediated chemotaxis, preferably leukocyte chemotaxis. These methods comprise contacting white blood cells with a chemotaxis-inhibiting amount of a compound of the invention. Preferably the amount results in a concentration sufficient to inhibit chemotaxis of white blood cells in an in vitro chemotaxis assay, so that the levels of chemotaxis observed in a control assay (e.g., one to which a compound of the invention has not been added) are significantly higher (significantly here

measured as $p \leq 0.05$ using a conventional parametric statistical analysis method) than the levels observed in an assay to which one or more compounds of the invention have been added. Compounds of the invention are also useful as controls in assays for C5a-mediated chemotaxis

Accordingly, a broad aspect of the invention is directed to compounds of Formula I



I

wherein:

R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl,

R_3 is hydrogen or C_1-C_7 alkyl,

R_4 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl, or

R_4 is arylalkyl wherein the aryl group is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy, or

Ar_1 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; or

Ar_1 is 2-thienyl or pyridyl, each of which is optionally substituted with halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, or trifluoromethyl,

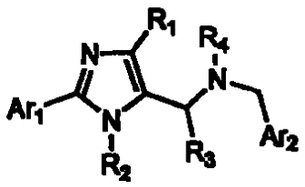
Ar_2 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4- methylenedioxy; or

Ar_2 is 1 or 2-naphthyl, 1, 2, or 3-indolyl, 2,3-dihydroindolyl, 1,2,3,4-tetrahydroquinolyl, 1- or 2-benzamidazolyl, 1,4-benzodioxan-6-yl, 2-, 3-, or 4-pyridyl, quinolyl, 2- or 3-thienyl, 2- or 3-benzo[b]thiophenyl, 2,3-dihydrobenzofuranyl or 2-, 3-, or 4-chromanyl, each of which may be substituted by up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, acetoxy, trifluoromethyl and trifluoromethoxy

The invention further provides intermediates useful in preparing compounds of Formula I

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention can be described by general formula I.



I

wherein

R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl,

R_3 is hydrogen or C_1-C_7 alkyl,

R_4 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl, or

R_4 is arylalkyl wherein the aryl group is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; or

Ar_1 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; or

Ar_1 is 2-thienyl or pyridyl, each of which is optionally substituted with halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino mono- or di(C_1-C_6)alkylamino, or trifluoromethyl,

Ar_2 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4- methylenedioxy; or

Ar_2 is 1 or 2-naphthyl, 1, 2, or 3-indolyl, 2,3-dihydroindolyl, 1,2,3,4-tetrahydroquinolyl, 1- or 2-benzimidazolyl, 1,4-benzodioxan-6-yl, 2-, 3-, or 4-pyridyl, quinolyl, 2- or 3-thienyl, 2- or 3-benzo[b]thiophenyl, 2,3-dihydrobenzofuranyl or 2-, 3-, or 4-chromanyl, each of which may be substituted by up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1 C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, acetoxy, trifluoromethyl and trifluoromethoxy

Preferred compounds of Formula I include those where R_3 is hydrogen or methyl and R_4 is benzyl or phenylethyl. Such compounds are referred to herein as compounds of Formula II. Preferred compounds of II include those where

R_1 is hydrogen or methyl,

Ar_1 is phenyl optionally substituted with up to three groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_6 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is phenyl which may be substituted with up to three groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, or 3,4-methylenedioxy

Still other preferred compounds of II include those where

R_1 is hydrogen or methyl,

Ar_1 is phenyl, and

Ar_2 is phenyl optionally substituted with up to three groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, nitro, hydroxy, trifluoromethyl, or trifluoromethoxy

Yet other preferred compounds of Formula II are those where

R_1 is hydrogen or methyl,

Ar_1 is phenyl, and

Ar_2 is phenyl which may be substituted with up to three substituents independently selected from consisting of halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, nitro, hydroxy, trifluoromethyl, and trifluoromethoxy and is substituted by at least one member of the group consisting of mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and 3,4-methylenedioxy

Still other preferred compounds of Formula II include those where

R_1 is hydrogen or methyl,

Ar_1 is phenyl which is substituted with up to three substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, dialkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is phenyl optionally substituted with up to three substituents independently selected from the group consisting of:

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4-methylenedioxy

Other preferred compounds of Formula II include those where

R_1 is hydrogen or methyl,

Ar_1 is phenyl which may be substituted with up to three substituents independently chosen from the group consisting of

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is 1 or 2-naphthyl, indolyl, 2,3-dihydroindolyl, 1,2,3,4-tetrahydroquinolyl, benzimidazole, 1,4-benzodioxan-6-yl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-quinolyl, 2- or 3-thienyl, 2- or 3-benzo[b]thiophenyl, 2- or 3-(2,3-dihydrobenzofuranyl) or 2-, 3-, or 4-chromanyl, each of is optionally substituted by up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, acetoxy, trifluoromethyl and trifluoromethoxy

Such compounds are referred to herein as compounds of Formula II-a.

Preferred compounds of Formula II-a include those where Ar_1 is phenyl

Other preferred compounds of Formula II-a are those where Ar_1 is phenyl substituted with up to three groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy

Other preferred compounds of Formula I are those where R_3 is hydrogen or methyl and R_4 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl. Such compounds are referred to herein as compounds of Formula III. Preferred compounds of Formula III include those where

Ar_1 is phenyl, and

Ar_2 is phenyl which may be substituted with up to four substituents independently selected from the group consisting of halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_7)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl trifluoromethoxy, and 3,4- methylenedioxy

Still other preferred compounds of Formula I, hereinafter referred to as compounds of Formula IV, are those where

R_3 is hydrogen or methyl, and

R_4 is arylalkyl wherein the aryl portion is substituted by up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy,trifluoromethyl, and trifluoromethoxy

Preferred compounds of Formula IV include those where

Ar_1 is phenyl substituted with up to three substituents independently selected from the group consisting of halogen, C_1-C_7 alkoxy, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is phenyl substituted with up to three substituents independently selected from the group consisting of halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4-methylenedioxy

Still other preferred compounds of Formula IV include those where

Ar_1 is phenyl, and

Ar_2 is phenyl substituted with up to three substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4-methylenedioxy

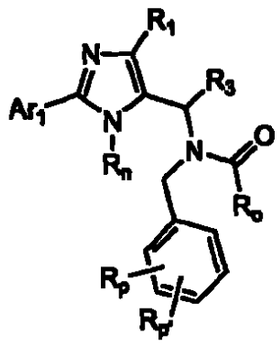
Yet other preferred compounds of Formula IV are those where

Ar_1 is phenyl, and

Ar_2 is 1 or 2-naphthyl, 1-, 2-, or 3-indolyl, 2,3-dihydroindolyl, 1,2,3,4-tetrahydroquinolyl, 1-, 2-, or 3-benzimidazole, 1,4-benzodioxan-6-yl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-quinolyl, 2- or 3-thienyl, 2- or 3-benzo[b]thiophenyl, 2- or 3-(2,3-dihydrobenzofuranyl) or 2-, 3-, or 4-chromanyl, each of which is optionally substituted by up to four substituents independently selected from halogen, C_1-C_7, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, acetoxy, trifluoromethyl and trifluoromethoxy

Yet other preferred compounds of Formula I are those where Ar_1 is 2-thienyl or 2-, 3-, or 4-pyridyl. Such compounds are referred to herein as compounds of Formula V

The invention also encompasses intermediates of Formula VI useful in preparing compounds of the invention.



VI

where Ar_1, R_1, and R_3 are as defined above for Formula I,

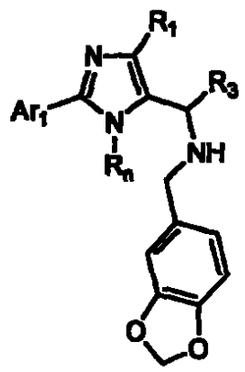
R_n is hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl,

R_o is C_1-C_8 alkyl, or phenyl or benzyl where the phenyl portion of each is optionally substituted with up to three four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

each R_p is hydrogen, halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy

Preferred compounds of Formula VI include those where R_o is an optionally substituted phenyl or benzyl group, and R_n is C_1-C_8 alkyl. More preferred compounds of Formula VI are those where R_n is C_1-C_4 alkyl and R_o is 3,4-methylenedioxyphenyl

The invention also encompasses compounds of Formula VII which are useful as intermediates in the preparation of compounds of Formula I.



VII

where Ar_1, R_1, and R_3 are as defined above for Formula I, and

R_n is hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

Preferred compounds of Formula VII include those where R_n is C_1-C_8 alkyl. More preferred compounds of Formula VII are those where R_n is C_3-C_5 alkyl

Compounds of this invention inhibit C5a mediated chemotaxis. Preferred compounds exhibit EC_{50} values of less than 1μM in an assay of C5a mediated chemotaxis, more preferred compounds exhibit EC_{50} values of less than 500 nM, and most preferred compounds exhibit EC_{50} values of less than 250 nM.

Compounds of this invention are selective modulators of the C5a receptor Preferably, compounds of this invention do not bind to dopamine receptors. Most preferably compounds of this invention do not exhibit binding constants less than 1μM at dopamine receptors in a standard radioligand binding assay for dopamine binding activity A suitable assay for determining

dopamine binding activity is described in U S Patent No 5,159,083, the disclosure of which is incorporated herein by reference in its entirety See, in particular, column 8

In certain situations, the compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

The invention also encompasses a method for treating a method for treating or preventing inflammatory and certain autoimmune disorders, such as for example rheumatoid arthritis and Crohn's disease, which comprises administering to a patient in need of such treatment a compound of the invention.

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds of Table 1 and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0 – 4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be

employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compound encompasses by Formula I.

By "C_1-C_x alkyl" or "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1 to x carbon atoms, generally up to 6 or 7 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl Preferred C_1-C_6 alkyl groups are methyl, ethyl, propyl, butyl, cyclopropyl

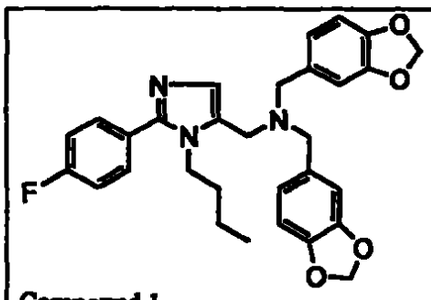
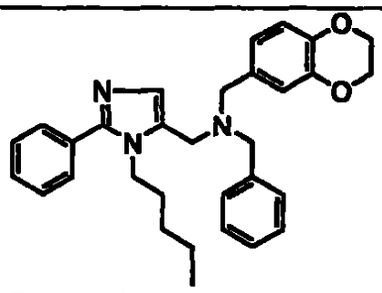
By the term alkyloxy is meant the group –O-R wherein R is alkyl as defined above.

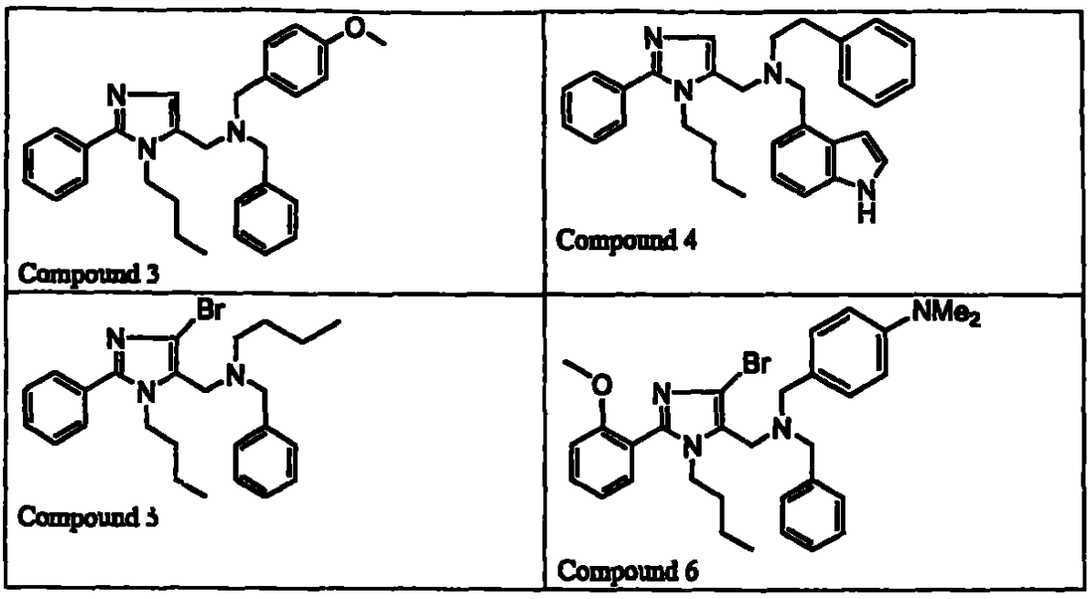
By the term halogen is meant fluorine, chlorine, bromine or iodine.

The pharmaceutical utility of compounds of this invention are indicated by the following assay for inhibition of C5a mediated chemotaxis.

Representative compounds of the invention are shown in Table 1

Table 1

 Compound 1	 Compound 2



The invention also pertains to the use of compounds of general Formula I in the treatment of various inflammatory and immune system disorders. The interaction of compounds of the invention with C5a receptors is shown by the inhibition of C5a-mediated chemotaxis e.g., as described in Example VI below While not wishing to be bound by any particular theory of operation, it is believed that this interaction results in the pharmacological activity of these compounds.

In a separate aspect, this invention provides compounds that are useful in inhibiting chemotaxis

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound

of general Formula I and a pharmaceutically acceptable carrier One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/ or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipents are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydropropyl methylcellulose, sodium algmate, polyvinylpyrrolidone, gum tragcanth and gum acacia, dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene sterate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensatin products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condenstaion products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydlides, for example polyethylene sorbitan monoleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or cocount oil, or in a mineral oil such as liquid paraffin. The oily suspension may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may by be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents

and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleginous suspension, This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefor melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

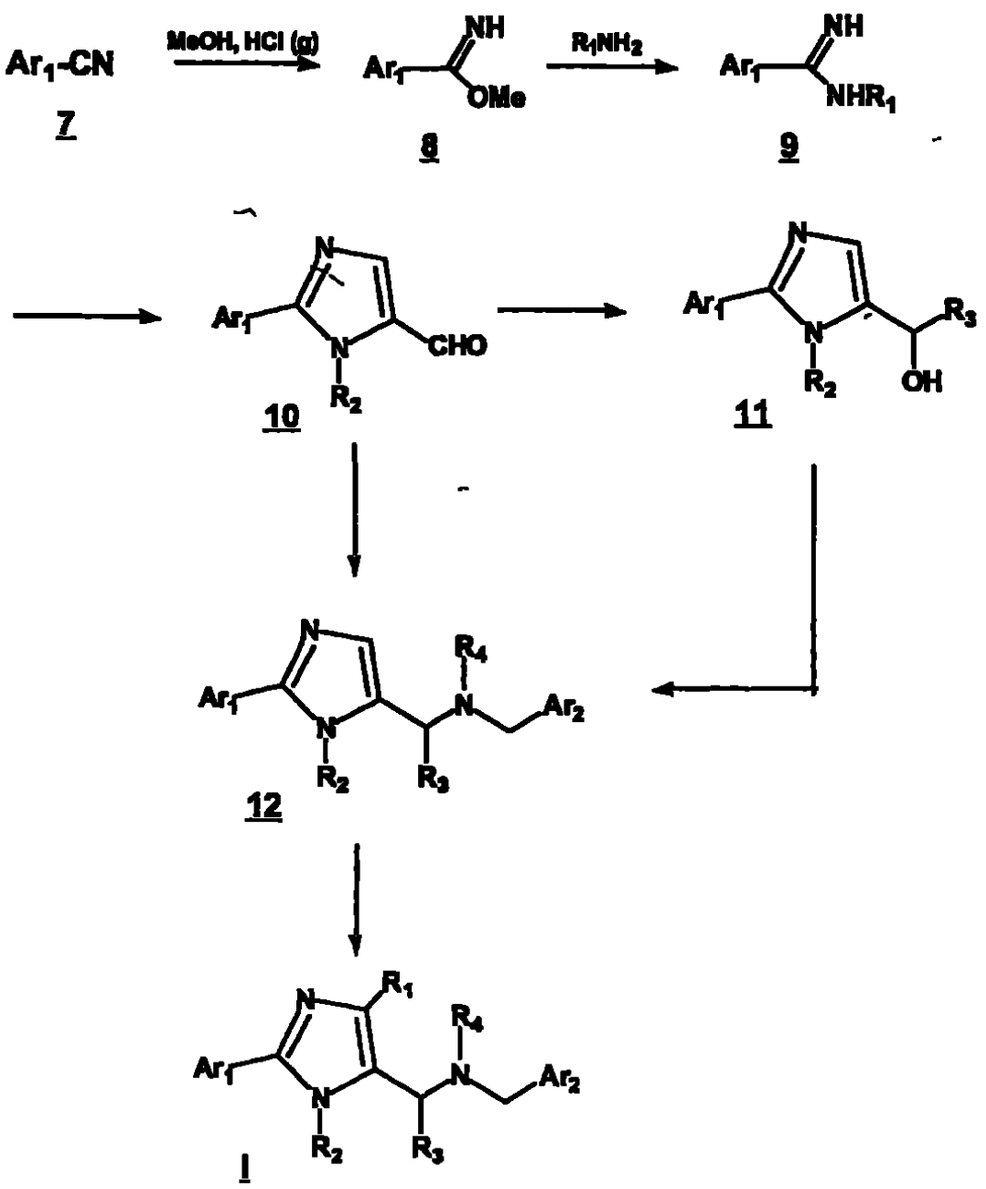
Dosage levels of the order of from about 0 1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0 5 mg to about 7 g per patient per day) Initial dosage levels are conveniently determined by providing dosages sufficient to produce in vivo serum concentrations sufficient to inhibit chemotaxis in vitro The amount of active ingredient that mat be combined with the carrier materials to produce a single dosage form will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease.

Representative methods for preparing the compounds of the invention are shown in Schemes 1 and 2 Scheme 1 illustrates the preparation of compounds where R_3 is hydrogen or halogen. Scheme 2 represents of the preparation of compounds where R_3 is alkyl. Those having

skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. Within Schemes 1 and 2 the variables Ar_1, Ar_2, R_1, R_2, R_3 and R_4 are defined as above for Formula I.

Scheme 1. Synthesis of 1-Alkyl-2-aryl-5-aminomethylimidazoles



As shown in Scheme 1, an appropriately substituted arylnitrile 7 is converted to the imidate 8 via treatment with hydrogen chloride gas in methanol followed by subsequent treatment with base to release the free base Amidine 9 is prepared from 8 by treatment with a primary amine. 2-Arylimidazole-4-carboxaldehyde 10 is prepared from 9 by one of several methods described in the chemical literature, for instance, by treatment with 2-bromo-3-isopropoxyacrolein in the presence of base. See, for example, *J Org. Chem.*, 62 8449 (Shulcrat et al., 1997)

Aldehyde 10 can then be transformed into hydroxymethylimidazole 11 either by reduction (for cases where R_4 is hydrogen) or by treatment with the appropriate organometallic (for cases where R_4 is C1-C6 alkyl). The hydroxy group of 11 is converted to either a halogen or sulfonate ester leaving group Treatment of this intermediate with an appropriate secondary amine in the presence of base provides 2-aryl-4-aminomethylimidazole 12 Alternatively , the aminoalkyl functionality of 12 may be elaborated by sequential amination-acylation-reduction steps In situations where R_3 is a halogen, *I* may be prepared from 12 by treatment with the molecular halogen, a halosuccinimide or the like.

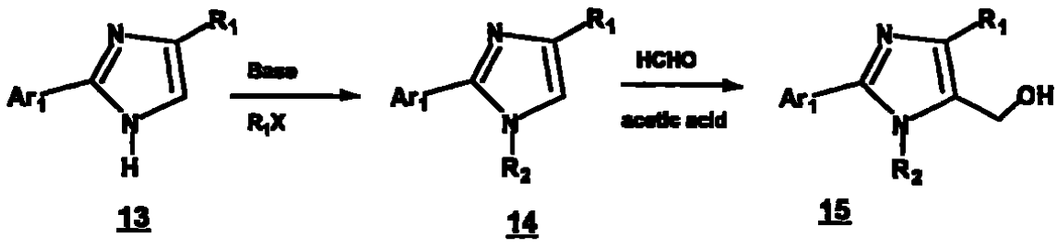
As shown in Scheme 2, an appropriately substituted 2-aryl-4-alkylimidazole 13 can be N-alkylated by treatment with base such as sodium hydride and an alkyl halide or alkylsulfonate ester to provide the trisubstituted imidazole 14 Hydroxymethylation of 14 under the conditions of the Mannich reaction provides hydroxymethylimidazole 15 In examples where R_3 is alkyl, hydroxymethyl derivative 17 is prepared from 15 by oxidation to aldehyde 16 and subsequent treatment with an appropriate organometallic reagent such as an alkyl lithium or Grignard reagent Conversion of 15 or 17 to the desired 2-aryl-5-aminomethylimidazoles I is carried out by conversion of the hydroxymethyl to a halogen or sulfonate ester leaving group followed by

treatment with a secondary amine. Alternatively, the aminoalkyl functionality of I may be elaborated by sequential amination-acylation-reduction steps.

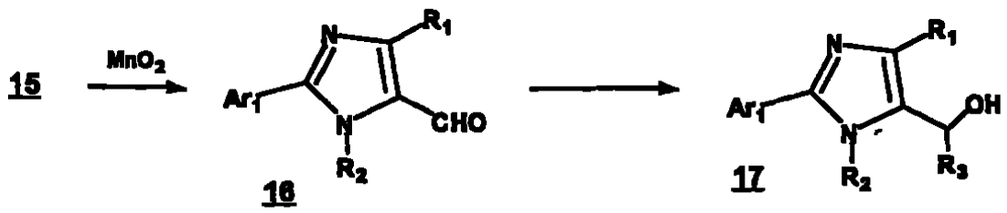
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Scheme 2 Synthesis of 2-Arylimidazoles

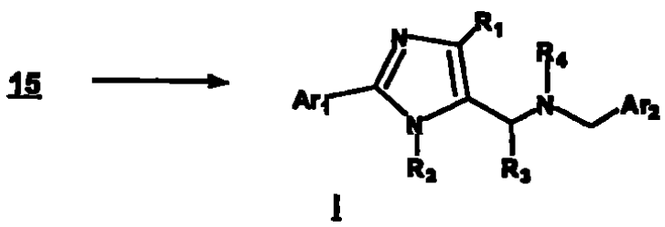
Where R_1 is alkyl



Where R_3 is alkyl



Where R_3 is hydrogen



The 2-aryl-4-alkylimidazoles 13 may be prepared by methods described in the chemical literature, for instance, via condensation of an arylamidine with a halomethyl or hydroxymethyl ketone.

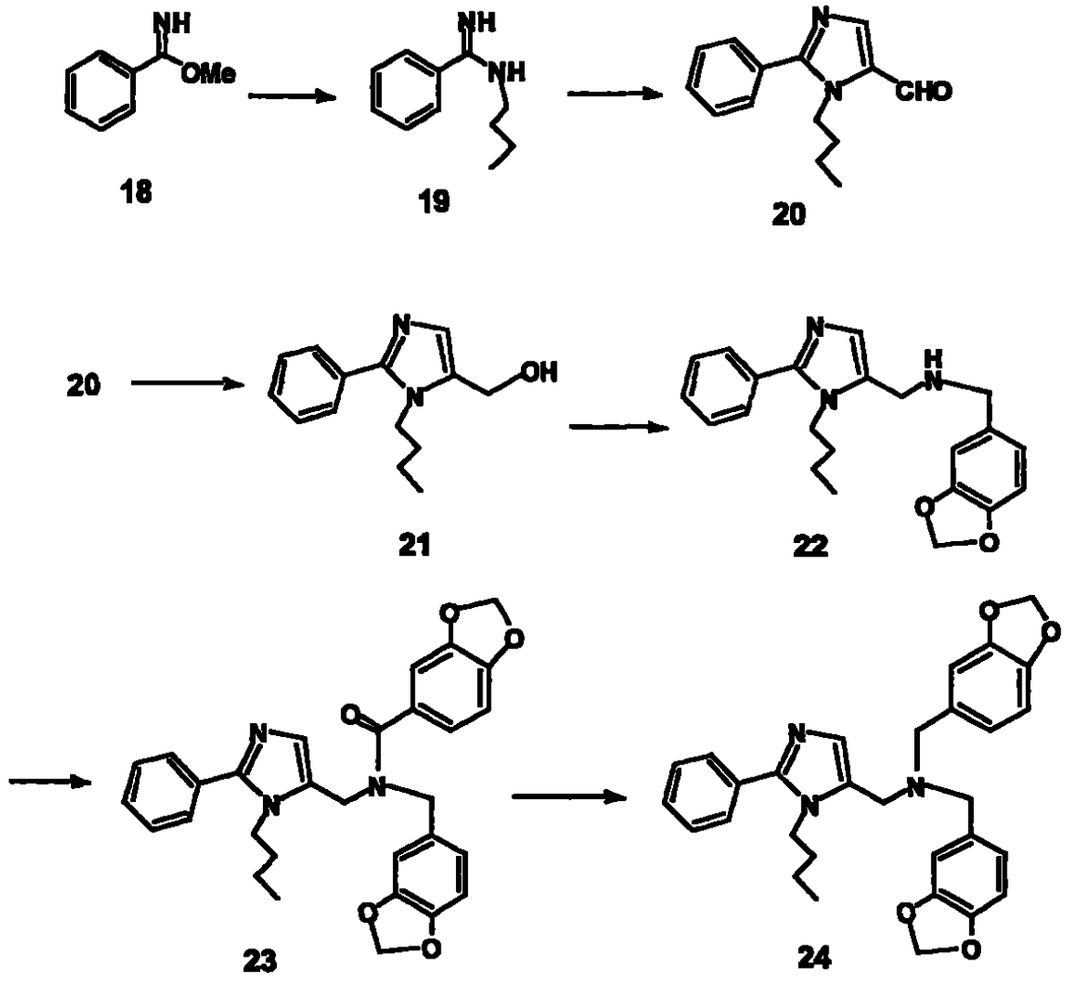
The invention is further illustrated by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them. Schemes 3 to 6 pertain to the synthetic procedures described below

EXAMPLE I. Preparation of 1-(1-butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenyl methyl])aminomethylimidazole (Compound 24, Scheme 3).

N-(n-butyl)-benzamidine (19). To a solution of methyl benzimidate hydrochloride (12 g, 0 07 mole) in dimethylformamide (DMF, 20 mL) was added 7 ml of triethylamine at 0 °C After 2 h the reaction was filtered to remove triethylamine hydrochloride. To the filtrate was added 3 68 g of 1-butylamine and the mixture heated to 60 °C for 6 h. After cooling the mixture was partitioned between ethyl acetate and water The organic layer was washed with brine, dried over sodium sulfate and concentrated to provide 13.28 g of the amidine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 55 (m, 2H), 7.4 (m, 3H), 3 37 (bm, 2H), 1 62 (m, 2H), 1.42 (m, 2H), 0 95 (t, J = 7 Hz, 3H)

1-(1-Butyl)-2-phenylimidazole-5-carboxaldehyde (20) To a solution of 14 (13.28 g) and 2-bromo-3-isopropoxyacrolein (22 g) in chloroform (150 ml) was added a potassium carbonate (15 5 g) and water (19 ml) The mixture was stirred at room temperature overnight. The aqueous layer was discarded and the organic layer was washed with water (3X 100 mL), dried (Na_2SO_4) and concentrated. The residue was purified via flash chromatography (5% MeOH/$CHCl_3$) to provide the desired imidazole carboxaldehyde as a pale yellow oil (21 55 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9 75 (s, 1H), 7.90 (s, 1H), 7 55 (m, 2H), 7 45 (m, 3H), 4 38 (t, J = 8Hz, 2H), 1 75 (m, 2H), 1.22 (m, 2H), 0.91 (t, J = 7 Hz, 3H)

Scheme 3. Representative preparation of 1-Alkyl-2-aryl-4-aminomethylimidazoles 1-(1-Butyl)-2-phenyl-5-(N,N-di [3,4-methylenedioxyphenylmethyl])aminomethylimidazole (Compound 24)



1-(1-Butyl)-2-phenyl-5-hydroxymethylimidazole (21) Aldehyde 20 was dissolved in methanol (150 mL). Sodium borohydride (3 g) was added in portions. After the addition was complete, the reaction was diluted with water and concentrated The residue was dissolved in

ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated. The product was purified by flash chromatography on silica gel (5% MeOH/$CHCl_3$) to give 4 17 g of 21 as a cream colored solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, t, d=7.4), 1 18 (2H, m, d=7.4), 1 60 (2H, m, d=7 6), 4 03 (2H, dd, d=7.6), 4.56 (2H, s), 6 84 (1H, s), 7.39-7.50 (3H, m),7.50-7.53 (2H, m).

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl])ammomethylimidazole (22) Hydroxymethylimidazole 21 (0 82 g) was dissolved in chloroform (10 ml) and treated with thionyl chloride (1 ml). The solution was heated to 50 °C for 30 min, cooled and evaporated. The residue was washed with benzene and evaporated to give the intermediate chloromethyl hydrochloride as a white powder which was taken up in acetonitrile (30 mL). This was added dropwise to a solution of piperonylamine (5 ml) in acetonitrile (10 mL). The reaction was allowed to stand overnight and then evaporated. The residue was taken up in ethyl acetate and washed with water The organic layer was dried (Na_2SO_4) and concentrated. Purification on silica gel (10% MeOH/$CHCl_3$) provided the product as a pale yellow oil (0 91 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0 79 (3H, t, d=7 4), 1 18 (2H, m, d=7.4), 1.56 (2H, m, d=7.4), 3 75 (4H, s), 4.04 (2H, dd, d=6), 5 92 (2H, s), 6.76 (2H, m), 6.84 (1H,s), 6.97 (1H, s), 7.38-7.44 (3H, m), 7 53-7.56 (2H, m)

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-(3,4-methylenedioxyphenylcarboxy])ammomethylimidazole (23) Compound 22 (160 mg, 0 44 mmol) was dissolved in chloroform (5 ml, pentene stabilized) and treated sequentially with piperonyloyl chloride (100 mg) and triethylamine (1 ml). The mixture was stirred at room temperature overnight. The solution was concentrated and the residue taken up in ethyl acetate. The organic was washed with water, dried (Na_2SO_4) and concentrated. Purification by preparative thin layer chromatography (5% MeOH/$CHCl_3$) provided compound 23 as a pale

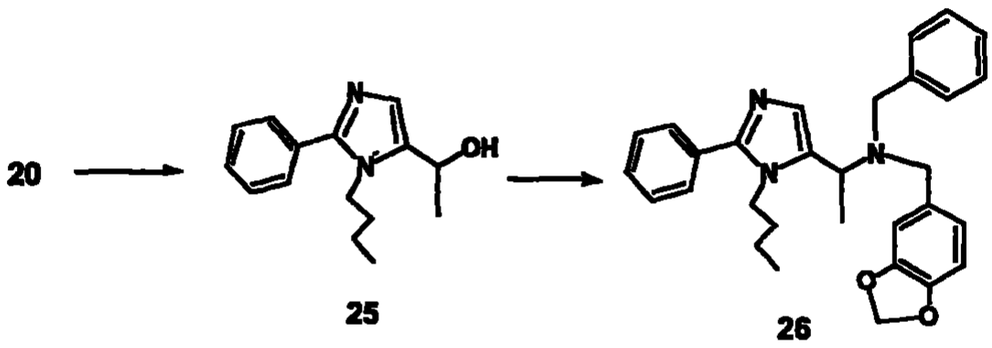
yellow oil (240 mg) ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0 75 (3H, br), 1 16 (2H, br), 1.49 (2H, br), 4 01 (2H, br), 4 54 (2H, br), 4.68 (2H, br), 5 97 (2H, s), 5.99 (2H, s), 6 66 (2H, d, d=7 2), 6 80 (2H, t, d=8), 6 98-7 02 (2H, m), 7.40-7 47 (3H, m), 7 56 (2H, d, d=6 8)

1-(1-Butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenylmethyl])-aminomethylimidazole (24) Amide 23 (215 mg) in tetrahydrofuran (THF, 3 ml) was added dropwise to a solution of alane (1 M in THF, 2 ml) and the resulting solution was stirred for 2.5 h at room temperature. A solution of sodium hydroxide (15% NaOH, 1 ml) was added and the mixture was extracted with chloroform. The organic extracts were dried (Na_2SO_4) and concentrated. Purification by preparative thin layer chromatography (10% MeOH/$CHCl_3$) provided compound 24 as a colorless oil (115 mg). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 70 (3H, t, d=7 6), 0.98 (2H, m, d=7 6), 1 30 (2H, m), 3 44 (4H, s), 3 52 (2H, s), 3.98 (2H, dd, d=8), 5 92 (4H, s), 6 74 (4H, s), 6 69 (2H, s), 7 02 (1H, s), 7 36-7.42 (3H, m), 7 54 (2H, dd, d=1 4, 6 6) The hydrochloride salt (m.p 187-190 °C) was prepared in isopropanol.

Example II. Preparation of 1-(1-butyl)-2-phenyl-5-(1-[N-{3,4-methylenedioxyphenylmethyl}-N-phenylmethyl]amino)ethylimidazole (Compound 26, Scheme 4).

1-Butyl-2-phenyl-5-(1-hydroxyethyl)imidazole (25). A solution of aldehyde 20 (230 mg) in diethyl ether (30 mL) was placed in a separatory funnel and treated with a solution of

Scheme 4. Preparation of 1-(1-Butyl)-2-phenyl-5-(1-[N-[(3,4-methylenedioxyphenylmethyl)-N-phenylmethyl]amino)ethyl imidazole (compound 26)



25 26

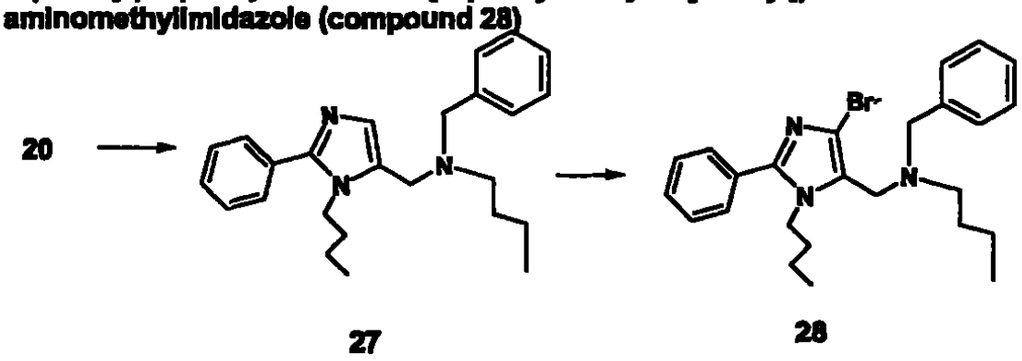
methyl lithium (1.4 M in THF, 1.5 ml) After 10 min, the solution was washed with ammonium chloride solution (1 M, 20 ml), dried (Na_2SO_4) and concentrated. The resulting dark oil was purified by preparative TLC (10% MeOH/$CHCl_3$) to provide compound 25 as a colorless oil (180 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 56 (d, J = 2 Hz, 2H), 7 4 (m, 3H), 7 01 (s, 1H), 4.86 (q, J = 7 Hz, 1H), 4 18 (m, 1H), 4.0 (m, 1H), 1 63 (d, J = 6.6 Hz, 3H), 1 63 (m, 2H), 1 23 (m, 2H), 0 81 (t, J = 7 Hz, 3H)

1-Butyl-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]-N-phenylmethyl)aminoethylimidazole (26) A solution of compound 25 (80 mg) in chloroform (10 ml) was treated with thionyl chloride (1 ml) and heated to 50 °C for 30 min. The solution was then concentrated, diluted with chloroform and reconcentrated to provide the intermediate chloromethyl hydrochloride as an oil. This material was taken up in chloroform (5 ml) and treated sequentially with N-benzylpiperonylamine (80 mg) and triethylamine After stirring overnight, the reaction was washed with saturated potassium carbonate solution, dried (Na_2SO_4) and concentrated. Purification by preparative thin layer chromatography (10% MeOH/$CHCl_3$) provided compound 26 as a colorless oil (62 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 46-7 43 (m,

1H), 7.2-7.3 (m, 9H), 6.74-6.86 (m, 4H), 5 94 (s, 2H), 4.82 (q, J = 6.8 Hz, 1H), 4.33 (m, 2H), 3 78 (s, 2H), 3 53 (s, 2H), 1 83 (d, J = 6 8 Hz, 3H), 1 62-1 68 (m, 2H), 1.21 (q, J = 7 8 Hz, 2H), 0 82 (t, J = 7 8 Hz, 3H).

Example III. Preparation of 1-Butyl-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl]amino-methylimidazole. (Compound 28, Scheme 5).

Scheme 5. Preparation of 1-(1-Butyl)-2-phenyl-4-bromo-5-[N-phenylmethyl-N-[1-butyl]) aminomethylimidazole (compound 28)



1-Butyl-2-phenyl-5-(N-benzyl-N-butyl)ammomethylimidazole (27). A solution of compound 20 (115 mg) and N-butylbenzylamine (85 mg) in toluene (10 ml) was allowed to stand overnight. Treatment of the reaction with sodium borohydride (100 mg) and ethanol (2 mL) followed by aqueous workup and purification on silica gel (10% MeOH/$CHCl_3$) provided compound 27 as a colorless oil (35 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.2-7 5 (m, 10H), 6.98 (s, 1H), 4.0 (t, J = 8 Hz, 2H), 3.55 (s, 2H), 3 52 (s, 2H), 2.42 (t, J = 8 Hz, 2H), 1.2-1 55 (m, 6 H), 1 05 (m, 2H), 0.84 (t, J = 7 Hz, 3H), 0 72 (t, J = 7 Hz, 3H)

1-Butyl-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl]aminomethylimidazole (28). To a solution of 27 (30 mg) in acetonitrile (4 mL) was added N-bromosuccinimide (16 mg) The

resulting mixture was heated to 60 °C and the progress of the reaction followed by TLC The cooled reaction mixture was diluted with ethyl acetate and washed twice with water Purification by preparative thin layer chromatography (10% MeOH/$CHCl_3$) provided compound 28 as a colorless oil (22 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 7 2-7.5 (m, 10 H), 3.98 (t, J = 8 Hz, 2H), 3 55 (s, 2H), 3 53 (s, 2H), 2 46 (t, J = 7 Hz, 2H), 1 52 (m, 2H), 1 3 (m, 4H), 0.98 (q, J = 7 Hz, 2H), 0 84 (t, J = 7 Hz, 3H), 0 70 (t, J = 7 Hz, 3H)

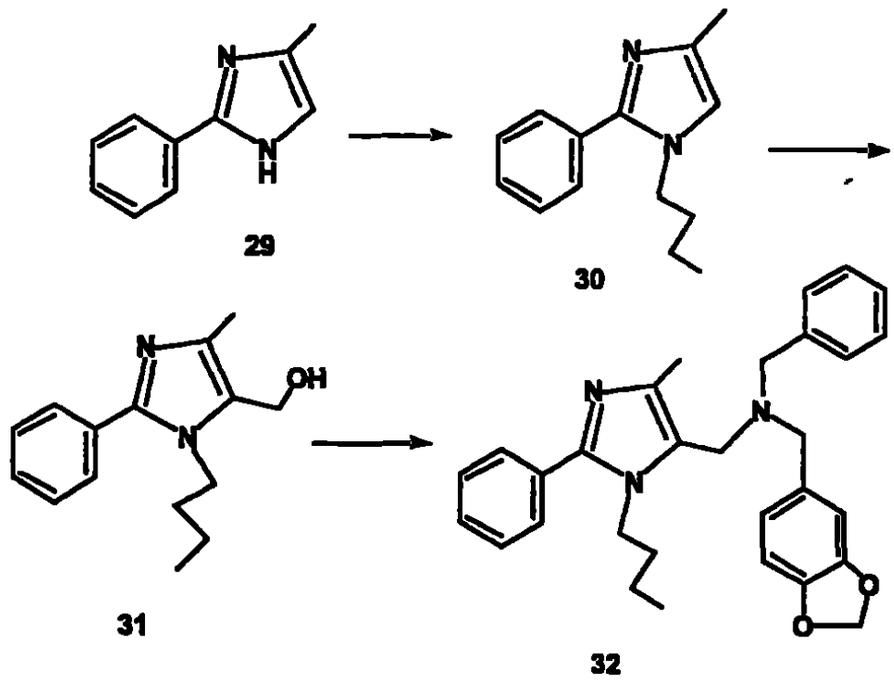
Example IV Preparation of 1-(1-Butyl)-2-phenyl-4-methyl-5-(N-[3,4-methylenedioxyphenyl methyl]-N-phenylmethyl)ammomethylimidazole. (Compound 32, Scheme 6)

1-Butyl-2-phenyl-4-methylimidazole (30) To a solution of 4-methyl-2-phenylimidazole (29, 15 8 g) in dimethylformamide (100 ml) was added sodium hydride (4 4 g, 60% in mineral oil) in small portions. After the addition was complete, the mixture was stirred for an additional 20 min and treated with 1-iodobutane (18 8 g). The reaction was fitted with a reflux condensor and heated at 100 °C for 12 h. The cooled reaction mixture was partitioned between water (300 ml) and diethyl ether (300 ml). The organic layer was washed with water (3X 200 ml), dried (Na_2SO_4) and concentrated to provide the 20.5 g of N-butylimidazoles. Analysis by ^1H-NMR and GC-MS revealed mixture of 1-butyl-2-phenyl-4-methylimidazole (30) and 1-butyl-2-phenyl-5-methylimidazole in a ratio of 11.5/1 The mixture was carried on to the next step without purification.

1-Butyl-2-phenyl-4-methyl-5-hydroxymethylimidazole (31). A solution of 30 (1 g) in acetic acid (10 mL) and 40% aqueous formaldehyde (2 mL) was refluxed for 14 h The reaction was then concentrated and dried by repeated reconcentration with toluene. The residue was purified by column chromatography (10% MeOH/$CHCl_3$). The fractions were assayed by GC

and those fractions uncontaminated by the isomeric hydroxymethylimidazole combined. Concentration of the combined fractions provided the 31 (320 mg) as a pale yellow oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 4-7 6 (m, 6H), 4 61 (s, 2H, CH_2OH), 4 02 (t, J = 7 Hz, 2H, NCH_2), 2 22 (s, 3H, Me), 1.63 (m, 2H, 1.25 (m, 2H), 0 81 (t, J = 7 Hz, 3H)

Scheme 6. Preparation of 1-(1-Butyl)-2-phenyl-4-methyl-5-(N-[3,4-methylenedioxyphenyl]-N-phenylmethyl)aminomethylimidazole (Compound 32)

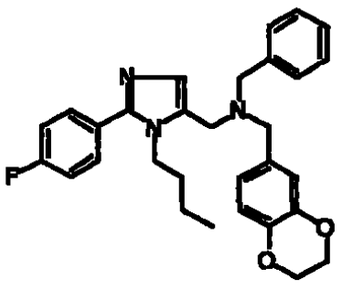


1-Butyl-2-phenyl-4-methyl-5-(N-benzyl-N-butyl)ammomethylimidazole (32)

Compound 32 (23 mg) was prepared from 31 (50 mg) in a method similar to that used to obtain compound 26 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7 5-7 55 (m,2H), 7 38-7.42 (m, 3H), 7 23-7 30 (m, 5H), 3 95 (t, J = 7 5 Hz, 2H), 3 55 (s, 2H), 3 53 (s, 2H), 2.40 (t, J = 7 Hz, 2H), 2.22 (s, 3H), 1 25-

1.40 (m, 6H), 1 05 (m, 2H), 0.82 (t, J = 7 Hz, 3H). 0 70 (t, J = 7 Hz, 3H), MS (LCMS) *m/e* 390 (M^++1)

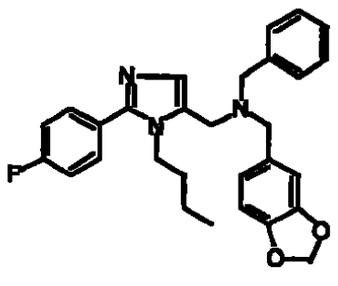
Example V The following compounds were prepared essentially according to the procedures described in Example I-IV



1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[1,4-benzodioxan-6-yl]methyl-N-phenylmethyl) aminomethylimidazole (compound 33)

LC-MS (M^++1) 486.

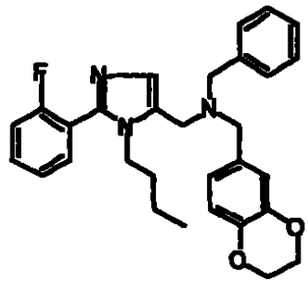
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, t, *J* = 7 6 Hz), 1 71 (2H, m), 1 85 (2H, m), 3 53 (2H, s), 3 75 (2H, s), 3 85 (2H, m), 3 95 (2H, s), 4.28 (4H, s), 6.72-6 84 (5H, m), 7 18-7 25 (8H, m) ppm.



1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole (Compound 34)

LC-MS (M^++1) 472

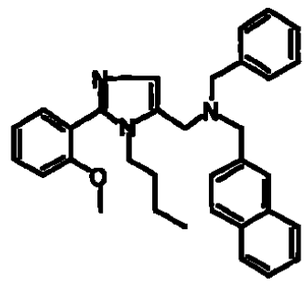
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 88 (3H, t, J = 7 4 Hz), 1 19 (2H, m), 1 53 (2H, m), 3 50 (2H, s), 3.56 (2H, s), 3 73 (2H, s), 3 92 (2H, t, J = 7.2 Hz), 5 96 (2H, s), 6 75-6 84 (4H, m), 7.25-7.44 (9H, m) ppm.



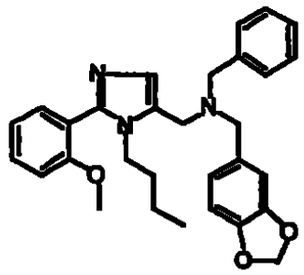
1-(1-Butyl)-2-(2-fluorophenyl)-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)amino-methylimidazole (Compound 35)

LC-MS (M^++1) 486

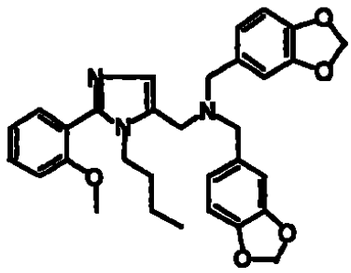
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 77 (3H, t, J = 7.2 Hz), 1 09 (2H, m), 1.48 (2H, m), 3.50 (2H, s), 3 65 (2H, s), 3 75 (2H, s), 3.97 (2H, m), 4.38 (4H, s), 6.74-6.87 (4H, m), 7.36-7.48 (9H, m) ppm.



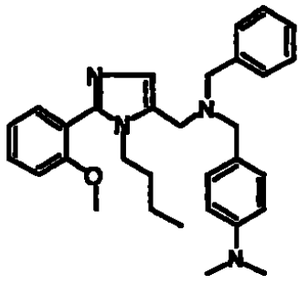
1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[naphtha-2-ylmethyl]-N-phenylmethyl)ammo-methylimidazole (Compound 36)



1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole (Compound 37)



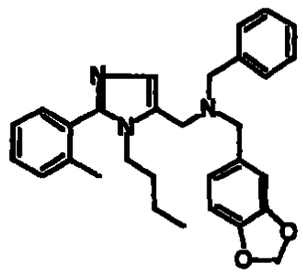
1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole (Compound 38)



1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole (Compound 39)

LC-MS (M^++1) 483

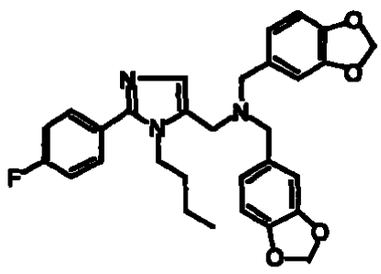
^{1}H-NMR (400 MHz, $CDCl_3$) 8 0 77 (3H, t, J = 7 6 Hz), 1 12 (2H, m), 1.39 (2H, m), 3 57 (2H, s), 3 61 (2H, s), 3 73 (4H, m), 3 89 (3H, s), 3 97 (6H, s), 6.84-7 01 (5H, m), 7 28-7 43 (9H, m) ppm.



1-(1-Butyl)-2-(2-methylphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole (compound 40)

LC-MS (M^++1) 468

^{1}H-NMR (400 MHz, $CDCl_3$) 8 0 71 (3H, t, J = 7 6 Hz), 1 08 (2H, m), 1.49 (2H, m), 2 21 (3H, s), 3 56 (2H, s), 3 60 (2H, s), 3 71 (2H, s), 3 84 (2H, m), 6.00 (2H, s), 6 81-6 92 (4H, m), 7.22-7.48 (9H, m) ppm.

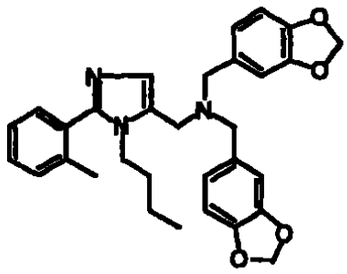


1-(1-Butyl)-2-(4-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino-methylimidazole (Compound 41)

LC-MS (M^++1) 516

902

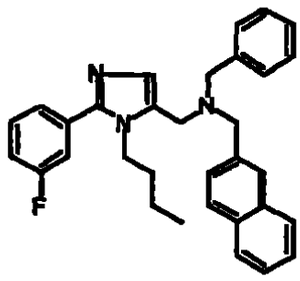
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 81 (3H, t, J = 7 6 Hz), 1 11 (2H, m), 1.38 (2H, m), 3.43 (4H, s), 3 60 (2H, s), 3 79 (2H, m), 5 97 (4H, s), 6 91-7 01 (3H, m), 7 11-7.35 (8H, m) ppm.



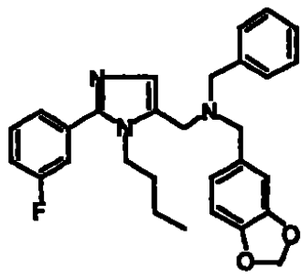
1-(1-Butyl)-2-(2-methylphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])ammo-methylimidazole (Compound 42)

LC-MS (M^++1), 512

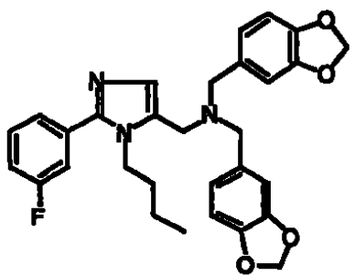
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 83 (3H, t, J = 7 8 Hz), 1 21 (2H, m), 1 42 (2H, m), 2 19 (3H, s), 3.38 (4H, s), 3.53 (2H, s), 3 72 (2H, m), 5 95 (4H, s), 6.72-6 89 (4H, m), 7 28-7.42 (7H, m) ppm



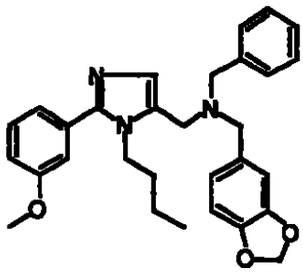
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[naphth-2-ylmethyl]-N-phenylmethyl)amino methylimidazole (Compound 43)



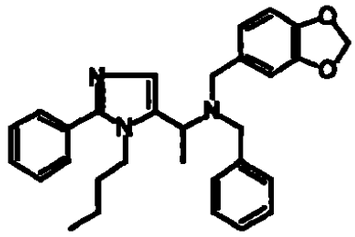
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole (Compound 44)



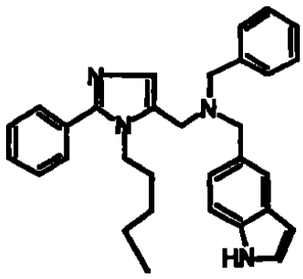
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino-methylimidazole (Compound 45)



1-(1-Butyl)-2-(3-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole (Compound 46)



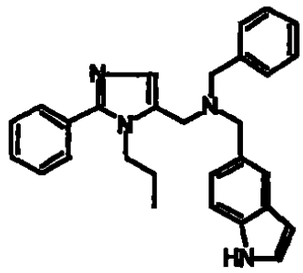
1-(1-Butyl)-2-phenyl-5-{1-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)amino} ethylimidazole (Compound 47)



1-(1-Pentyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl) aminomethylimidazole (Compound 48)

LC-MS (M^++1) 463 4,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.66 (3H, t, J = 7 6 Hz), 0 75 (2H, m), 1.21 (2H, m, J = 7 6 Hz), 3 57 (2H, s), 3 60 (2H, s), 3 64 (2H, s), 3.93 (2H, t, J = 8 0 Hz), 6 50 (1H, m), 7 05 (1H, s), 7 14 (1H, dd, J = 1.6, 8.4 Hz), 7 18 (1H, t, J = 2 8 Hz), 7.24 (1H, m), 7 29-7.43 (8H, m), 7 49-7 51 (2H, m), 7 57 (1H, s), 8 47 (1H, br) ppm

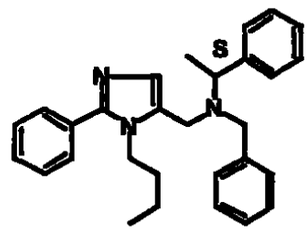


1-(1-Propyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl) aminomethylimidazole

(Compound 49)

LC-MS (M^++1) 435.3,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.46 (3H, t, J = 7 6 Hz), 1.26 (2H, m), 3.57 (2H, s), 3 60 (2H, s), 3 65 (2H, s), 3.93 (2H, t, J = 8.0 Hz), 6.52 (1H, t, J = 2.4 Hz), 7 05 (1H, s), 7 16 (1H, dd, J = 1.6, 8 4 Hz), 7 19 (1H, t, J = 2 8 Hz), 7 23-7.26 (2H, m), 7 30-7 43 (7H, m), 7 55 (2H, dd, J = 1 6, 8 0 Hz), 7 57 (1H, s), 8 30 (1H, br) ppm

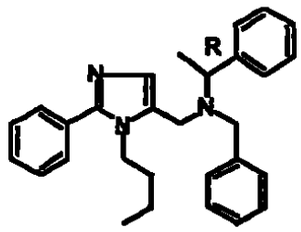


1-(1-Butyl)-2-phenyl-5-(N-[1-(*S*)-phenylethyl]-N-phenylmethyl)aminomethylimidazole

(Compound 50)

LC-MS (M^++1) 424.4,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 63 (3H, t, J = 7.2 Hz), 0 85 (2H, m, J = 7.2 Hz), 1 17 (2H, m), 1.47 (3H d, J = 6 8 Hz), 3 48-3 66 (4H, m), 3 95 (2H, m), 4.04 (1H, q, J = 6 8 Hz), 7 03 (1H, s), 7.21-7 30 (5H, m), 7 33-7 43 (3H, m), 7.48-7 51 (2H, m) ppm.

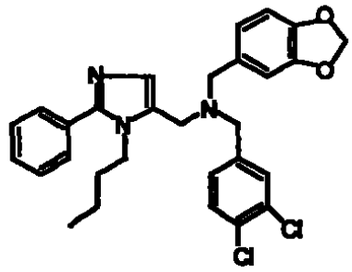


1-(1-Butyl)-2-phenyl-5-(N-[1-(*R*)-phenylethyl]-N-phenylmethyl)ammomethylimidazole (Compound 51)

LC-MS (M^++1) 424.4,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.63 (3H, t, J = 7.2 Hz), 0 85 (2H, m, J = 7 2 Hz), 1 17 (2H, m), 1 47 (3H, d, J = 6.8 Hz), 3.48-3 66 (4H, m), 3.95 (2H, m), 4 04 (1H, q, J = 6 8 Hz), 7 03 (1H, s), 7.21-7 30 (5H, m), 7 33-7.43 (3H, m), 7.48-7.51 (2H, m) ppm.

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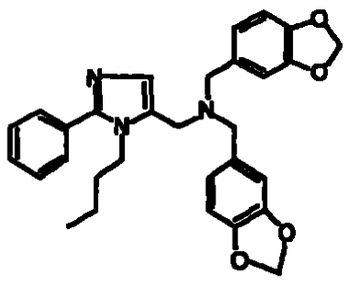


1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenyl]methyl) ammomethylimidazole (Compound 52)

LC-MS (M^++1) 522.2,

1H-NMR (400 MHz, $CDCl_3$) δ 0 71 (3H, t, J = 7.2 Hz), 0 98 (2H, m, J = 7 6 Hz), 1.31 (2H, m), 3.46 (2H, s), 3 50 (2H, s), 3.53 (2H, s), 3 94 (2H, t, J = 7.6 Hz), 5 93 (2H, s), 6 75 (2H, s), 6 80-6 86 (4H, m), 7 04 (1H, s), 7.36-7 45 (3H, m), 7 52 (2H, dd, J = 1 6, 8 0 Hz) ppm.

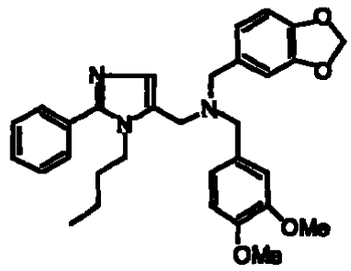
907



1-(1-Butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole (Compound 53)

LC-MS $(M^+ + 1)^+$ 498.3

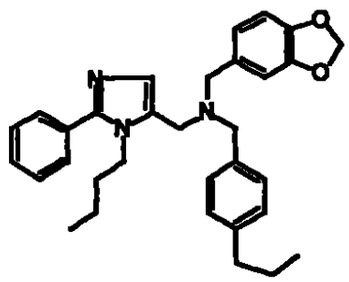
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.70 (3H, t, J = 7.6 Hz), 0.98 (2H, m, J = 7.6), 1.30 (2H, m), 3.44 (4H, s), 3.52 (2H, s), 3.98 (2H, dd, J = 8.0 Hz), 5.92 (4H, s), 6.74 (4H, s), 6.69 (2H, s), 7.02 (1H, s), 7.36-7.42 (3H, m), 7.54 (2H, dd, J = 1.4, 6.6 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-methoxyphenylmethyl])-aminomethylimidazole (Compound 54)

LC-MS $(M^+ + 1)$ 514.7,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.69 (3H, t, J = 7.6 Hz), 0.96 (2H, m, J = 7.6 Hz), 1.30 (2H, m), 3.48 (2H, s), 3.50 (2H, s), 3.55 (2H, s), 3.86 (3H, s), 3.87 (3H, s), 3.96 (2H, t, J = 8.0 Hz), 5.93 (2H, s), 6.75 (2H, s), 6.80-6.86 (4H, m), 7.04 (1H, s), 7.36-7.45 (3H, m), 7.52 (2H, dd, J = 1.6, 8.0 Hz) ppm.

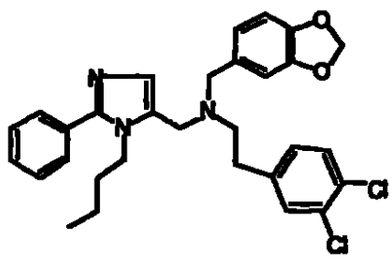


1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyl}phenylmethyl]

aminomethylimidazole (Compound 55)

LC-MS (M^++1) 496.4,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 68 (3H, t, J = 7 6 Hz), 0 93 (3H, t, J = 7 6 Hz), 0 94 (2H, m, J = 7.6 Hz), 1.27 (2H, m), 1 62 (2H, m, J = 7 6 Hz), 2.56 (2H, t, J = 7 6 Hz), 3.47 (2H, s), 3.51 (2H, s), 3 53 (2H, s), 3 97 (2H, t, J = 7 6 Hz), 5 93 (2H, s), 6 75 (2H, s), 6 82 (1H, s), 7 02 (1H, s), 7 12 (2H, d, J = 8 0 Hz), 7.21 (2H, d, J = 8 0 Hz), 7 36-7 44 (3H, m), 7.53 (2H, dd, J = 1 6, 8 0 Hz) ppm.



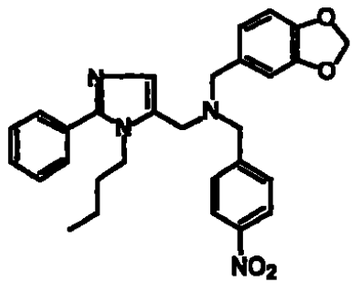
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenylethyl])

aminomethylimidazole. (Compound 56)

LC-MS (M^++1) 536.6

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.70 (3H, t, J = 7 6 Hz), 0 99 (2H, m, J = 7 6 Hz), 1 29 (2H, m), 2 71 (4H, s) 3 52 (2H, s), 3 55 (2H, s), 3 76 (2H, t, J = 8 0 Hz), 5 93 (2H, s), 6 71-6 76 (3H, m),

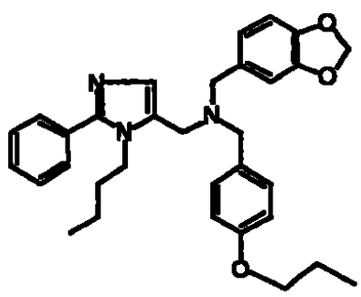
6 85 (1H, dd, J = 2 0, 8 0 Hz), 6.98 (1H, s), 7 17 (1H, d, J = 2 0 Hz), 7.24 (1H, d, J = 8.0 Hz), 7 37-7 45 (3H, m), 7 50 (2H, dd, J = 1 6, 8 0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[4-nitrophenylmethyl]) aminomethylimidazole (Compound 57)

LC-MS (M^++1) 499 3,

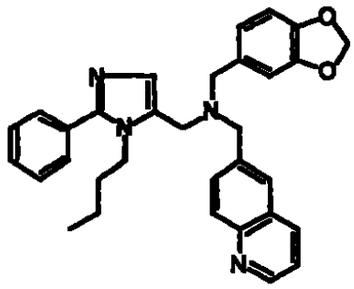
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 70 (3H, t, J = 7 2 Hz), 0 98 (2H, m, J = 7 6 Hz), 1 31 (2H, m), 3 48 (2H, s), 3 57 (2H, s), 3 67 (2H, s), 3 94 (2H, t, J = 7 6 Hz), 5 95 (2H, s), 6 76 (2H, s), 6 79 (1H, s), 7 04 (1H, s), 7 40-7.49 (6H, m), 8 17 (2H, d, J = 8 4 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyloxy} phenylmethyl])aminomethylimidazole (Compound 58)

LC-MS (M^++1) 512.4,

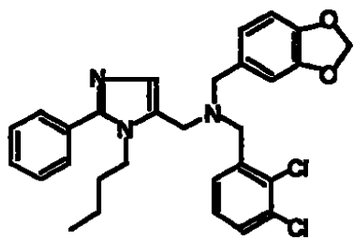
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.68 (3H, t, J = 7.2 Hz), 0 95 (2H, m, J = 7 6 Hz), 1 02 (3H, t, J = 7 6 Hz), 1.27 (2H, m), 1 79 (2H, m, J = 6.8 Hz), 3.45 (2H, s), 3.47 (2H, s), 3 52 (2H, s), 3 89 (2H, t, J = 6.8 Hz), 3 95 (2H, t, J = 7 6 Hz), 5.92 (2H, s), 6.74 (2H,s), 6.80 (1H, s), 6 84 (2H, d, J = 8 4 Hz), 7 02 (1H, s), 7 19 (2H, d, J = 8.4 Hz), 7.36-7 44 (3H, m), 7.52 (2H, dd, J = 1 6, 8 0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[quinol-6-ylmethyl])-aminomethylimidazole (Compound 59)

LC-MS (M^++1). 505.3,

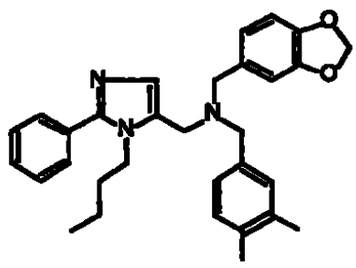
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 57 (3H, t, J = 7 6 Hz), 0 87 (2H, m, J = 7.6 Hz), 1 23 (2H, m), 3 52 (2H, s), 3 60 (2H, s), 3 73 (2H, s), 3 94 (2H, t, J = 8 0 Hz), 5 94 (2H, s), 6 77 (2H, s), 6 83 (1H, s), 7 07 (1H, s), 7.36-7 43 (4H, m), 7.48 (2H, dd, J = 1 6, 8 0 Hz), 8 07 (1H, d, J = 9.2 Hz), 8 12 (1H, dd, J = 1.2, 8 4 Hz), 8 89 (1H, dd, J = 1 6, 4.2 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2,3-dichlorophenylmethyl]-aminomethylimidazole (Compound 60)

LC-MS (M^++1) 522.2,

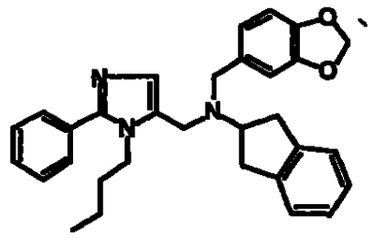
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.66 (3H, t, J = 7.2 Hz), 0.92 (2H, m, J = 7.6 Hz), 1.22 (2H, m), 3.52 (2H, s), 3.56 (2H, s), 3.72 (2H, s), 3.92 (2H, d, J = 8.0 Hz), 5.92 (2H, s), 6.74 (2H, s), 6.79 (1H, s), 7.04 (1H, s), 7.16 (1H, d, J = 8.0 Hz), 7.30-7.44 (5H, m), 7.49 (2H, dd, J = 1.6, 8.0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dimethylphenylmethyl]-aminomethylimidazole (Compound 61)

LC-MS (M^++1) 482.4,

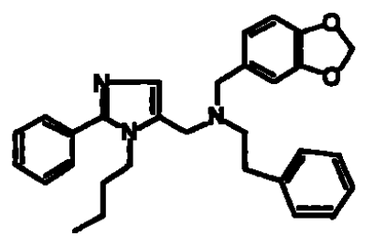
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.70 (3H, t, J = 7.6 Hz), 0.95 (2H, m, J = 7.6 Hz), 1.29 (2H, m), 2.24 (3H, s), 2.26 (3H, s), 3.47 (2H, s), 3.49 (2H, s), 3.53 (2H, s), 3.97 (2H, t, J = 8.0 Hz), 5.93 (2H, s), 6.76 (2H, s), 6.83 (1H, s), 7.03 (1H, s), 7.06 (3H, m), 7.37-7.45 (3H, m), 7.54 (2H, dd, J = 1.6, 8.0 Hz) ppm.



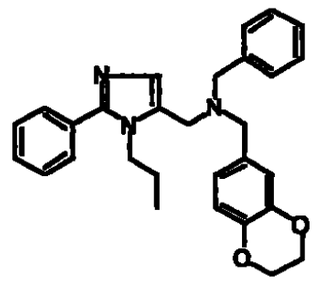
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[indan-2-yl])-aminomethylimidazole (Compound 62)

LC-MS (M^++1) 480 4,

^{1}H-NMR (400 MHz, $CDCl_3$)· δ 0 76 (3H, t, J = 7 6 Hz), 1 09 (2H, m, J = 7 6 Hz), 1 44 (2H, m, J = 7.6 Hz), 3 05 (4H, d, J = 7.6 Hz), 3.49 (2H, s), 3 62 (2H, s), 3 85 (1H, m, J = 7 6 Hz), 3 99 (2H, m, J = 7.6 Hz), 5 90 (2H, s), 6 71 (2H, s), 6.80 (1H, s), 7 01 (1H, s), 7 14 (2H, m), 7.20 (2H, m), 7.37-7.44 (3H, m), 7.52 (2H, dd, J = 1.6, 8 0 Hz) ppm



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-phenylethyl])amino-methylimidazole (Compound 63)

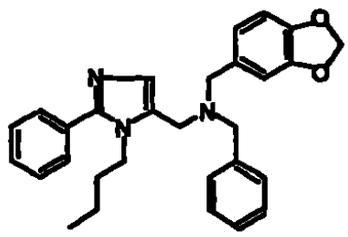


913

1-(1-Propyl)-2-phenyl-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)aminomethyl-imidazole (Compound 64)

LC-MS (M^++1) 454.3,

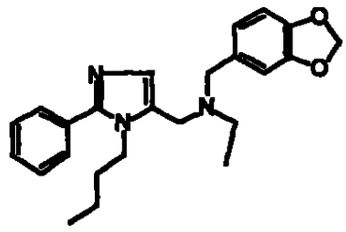
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.56 (3H, t, J = 7 6 Hz), 1.31 (2H, m, J = 7 6 Hz), 3.45 (2H, s), 3.52 (2H, s), 3.54 (2H, s), 3 95 (2H, t, J = 8.0 Hz), 4.24 (4H, d, J = 2.4 Hz), 6 76-6.87 (3H, m), 7 02 (1H, s), 7.31-7.36 (5H, m), 7.37-7.44 (3H, m), 7.52 (2H, dd, J = 1 6, 8 0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole (Compound 65)

LC-MS (M^++1): 454.3,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 68 (3H, t, J = 7.4 Hz), 0.94 (2H, m, J = 7.6 Hz), 1.27 (2H, m), 3.46 (2H, s), 3 53 (2H, s), 3.54 (2H, s), 3.97 (2H, t, J = 7 6 Hz), 5 91 (2H, s), 6 74 (2H, s), 6 81 (1H, s), 7 03 (1H, s), 7.24 (1H, m), 7.29-7.31 (4H, m), 7.35-7 43 (3H, m), 7 51-7 54 (2H, m) ppm.

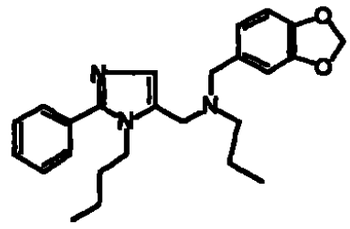


1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-ethyl)aminomethylimidazole (Compound 66)

LC-MS (M^++1) 378.3,

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 79 (3H, t, J = 7 6 Hz), 1 14 (2H, m, J = 7.6 Hz), 1.51 (2H, m, J = 8 0 Hz), 2 18 (3H, s), 3.44 (2H, s), 3.47 (2H, s), 4.05 (2H, t, J = 7 6 Hz), 5 93 (2H, s), 6 75 (2H, s), 6 83 (1H, s), 6 99 (1H, s), 7.37-7 45 (3H, m), 7.57 (2H, dd, J = 1 6, 8.0 Hz) ppm.

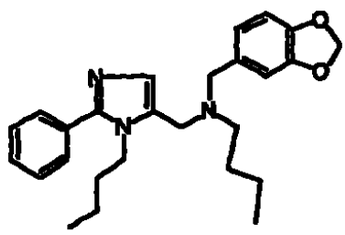
000080 '8201203



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-propyl])aminomethyl-imidazole (Compound 67)

LC-MS (M^++1) 392.4.

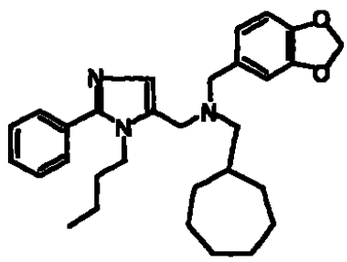
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 77 (3H, t, J = 7.4 Hz), 1 07 (3H, t, J = 7 0 Hz), 1 11 (2H, m, J = 7 6 Hz), 1 48 (2H, m), 2.53 (2H, q, J = 7.2 Hz), 3 48 (2H, s), 3 53 (2H, s), 4 04 (2H, t, J = 8 0 Hz), 5.92 (2H, s), 6 74 (2H, s), 6.81 (1H, s), 6.98 (1H, s), 7 36-7 45 (3H, m), 7 54-7 57 (2H, m) ppm



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-butyl])aminomethyl-imidazole (Compound 68)

LC-MS (M^++1) 420.3

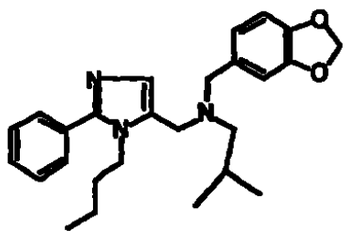
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 75 (3H, t, J = 7 6 Hz), 0 84 (3H, t, J = 7.2 Hz), 1 07 (2H, m, J = 7.6 Hz), 1 28 (2H, m, J = 7.6 Hz), 1 42 (2H, m), 1 47 (2H, m, J = 7 6 Hz), 2.43 (2H, t, J = 7.2 Hz), 3 46 (2H, s), 3 50 (2H, s), 4 02 (2H, t, J = 8 0 Hz), 5 92 (2H, s), 6 74 (2H, s), 6 81 (1H, s), 6.97 (1H, s), 7 37-7 45 (3H, m), 7.54 (2H, dd, J = 1 6, 7 6 Hz) ppm



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cycloheptylmethyl)amino-methylimidazole (Compound 69)

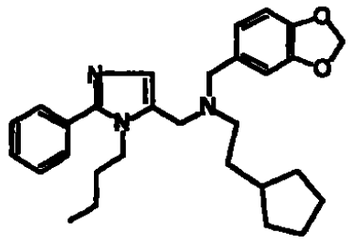
LC-MS (M^++1) 474.4.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 71 (3H, t, J = 7.2 Hz), 1 02 (4H, m, J = 7 6 Hz), 1 25-1 59 (9H, m), 1 65-1 75 (4H, m), 2.20 (2H, d, J = 6 8 Hz), 3 43 (2H, s), 3 46 (2H, s), 4.00 (2H, t, J = 8 0 Hz), 5.93 (2H, s), 6 74 (2H, s), 6.81 (1H, s), 6.97 (1H, s), 7 37-7 46 (3H, m), 7.52 (2H, dd, J = 1 6, 8 0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-isobutyl)ammomethyl-imidazole (Compound 70)

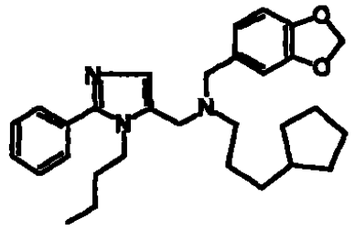
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.71 (3H, t, J = 7.2 Hz), 0 84 (6H, d, J = 6.4 Hz), 1 01 (2H, m, J = 7 2 Hz), 1.34 (2H, m), 1.81 (1H, m, J = 6 8 Hz), 2 18 (2H, d, d, J = 7.2 Hz), 3.44 (2H, s), 3.46 (2H, s), 4.02 (2H, t, J = 8 0), 5 93 (2H, s), 6 75 (2H, s), 6.83 (1H, s), 6.97 (1H, s), 7.37-7.45 (3H, m), 7 52 (2H, dd, J = 1 6, 8 0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-cyclopentylethyl])ammomethylimidazole (Compound 71)

LC-MS (M^++1) 460.4

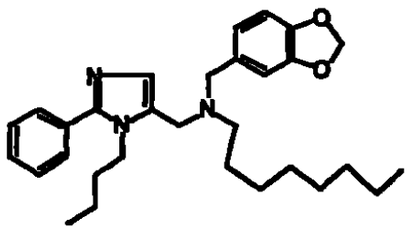
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 73 (3H, t, J = 9 6 Hz), 1 04 (4H, m), 1.39-1 75 (11H, m), 2.45 (2H, t, J = 9 6 Hz), 3 47 (2H, s), 3 51 (2H, s), 4.02 (2H, t, J = 9 6 Hz), 5 91 (2H, s), 6.73 (2H, s), 6 80 (1H, s), 7 02 (1H, s), 7.39-7.45 (3H, m), 7.53 (2H, dd, J = 2.4, 10 4 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3-cyclopentylpropyl])ammomethylimidazole (Compound 72)

LC-MS (M^++1) 474.3,

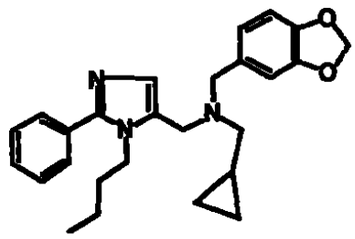
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 76 (3H, t, J = 7 2 Hz), 1 06 (4H, m), 1.24 (2H, m), 1 43-1 59 (8H, m), 1 65-1 75 (3H, m), 2.42 (2H, t, J = 7.4 Hz), 3 46 (2H, s), 3 50 (2H, s), 4.02 (2H, t, J = 8 0 Hz), 5 92 (2H, s), 6 74 (2H, s), 6 81 (1H, s), 6.97 (1H, s), 7 36-7 44 (3H, m), 7.53-7 55 (2H, m) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-n-octyl])ammomethylimidazole (Compound 73)

LC-MS (M^++1) 476.4

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 75 (3H, t, J = 7 6 Hz), 0 85 (3H, t, J = 6.8 Hz), 1 07 (2H, m, J = 7 2 Hz), 1 21 (10H, m), 1 41-1.48 (4H, m), 2.41 (2H, t, J = 7.2 Hz), 3.45 (2H, s), 3 49 (2H, s), 4.01 (2H, t, J = 8 0 Hz), 5 92 (2H, s), 6 73 (2H, s), 6 80 (1H, s), 6.96 (1H, s), 7.36-7.44 (3H, m), 7 53 (2H, dd, J = 1 6, 8 0 Hz) ppm

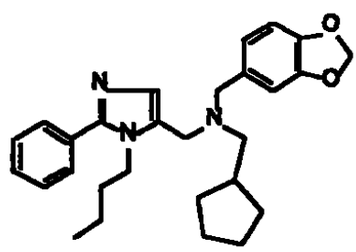


1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopropylmethyl)amino-methylimidazole. (Compound 74)

LC-MS (M^++1) 418.3

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.07 (2H, m), 0.51 (2H, m), 0 77 (3H, t, J = 7.2 Hz), 0 90 (1H, m), 1 12 (2H, m, J = 7 6 Hz), 1.50 (2H, m), 2.32 (2H, d, J = 6 8 Hz), 3 55 (2H, s), 3 63 (2H, s), 4 10 (2H, t, J = 7 6 Hz), 5 92 (2H, s), 6 73 (2H, s), 6 82 (1H, s), 6.98 (1H, s), 7 37-7.46 (3H, m), 7 55 (2H d, J = 1 6, 8 0 Hz) ppm.

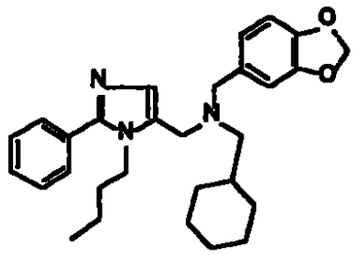
08/08/2003 SEQUENCE



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopentylmethyl)amino-methylimidazole (Compound 75)

LC-MS (M^++1) 446.3

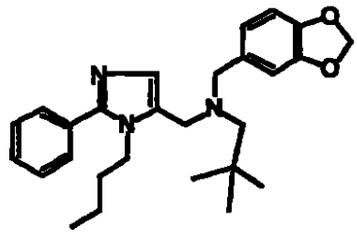
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.72 (3H, t, J = 7 4 Hz), 1 02 (2H, m, J = 7 6 Hz), 1 09 (2H, m), 1.36 (2H, m), 1 48 (4H, m), 1 72 (2H, m), 2 13 (1H, m, J =7 6 Hz), 2.31 (2H, d, J = 7 6 Hz), 3.46 (2H, s), 3 49 (2H, s), 4 03 (2H, t, J = 7 6 Hz), 5 92 (2H, s), 6 74 (2H, s), 6 82 (1H, s), 6 96 (1H, s), 7.36-7 45 (3H, m), 7 50-7 54 (2H, m) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclohexylmethyl)ammo-methylimidazole (Compound 76)

LC-MS (M^++1) 460 6

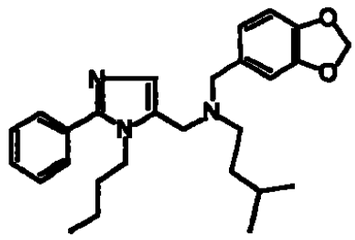
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 72 (3H, t, J = 7 6 Hz), 0.76 (2H, m), 1 02 (2H, m, J = 7 6 Hz), 1 09-1.24 (6H, m), 1.35 (2H, m), 1 51 (1H, m), 1 64 (2H, m), 1 75 (2H, d, J = 12 8 Hz), 2 22 (2H, d, J = 7.2 Hz), 3 43 (2H, s), 3.46 (2H, s), 4.02 (2H, t, J = 7 6 Hz), 5 93 (2H, s), 6 74 (2H, s), 6 81 (1H, s), 6.97 (1H, s), 7.36-7.45 (3H, m), 7.52 (2H, dd, J = 1 6, 8 0 Hz) ppm



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[t-amyl]) ammonomethylimidazole (Compound 77)

LC-MS (M^++1) 434.6

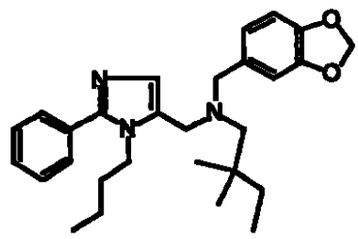
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 64 (3H, t, J = 7 6 Hz), 0 77 (9H, s), 0 88 (2H, m, J = 7 6 Hz), 1 17 (2H, m), 2.32 (2H, s), 3.41 (2H, s), 3 57 (2H, s), 3 90 (2H, t, J = 7 6 Hz), 5.93 (2H, s), 6 76 (1H, d, J = 8 0 Hz), 6 82 (1H, dd, J = 1 6, 8 0 Hz), 6.96 (2H, m), 7 36-7.43 (3H, m), 7 47 (2H, dd, J = 1 6, 8 0 Hz) ppm



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{3-methyl}butyl)]ammo-methylimidazole (Compound 78)

LC-MS (M^++1) 434 6

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 74 (3H, t, J = 7 6 Hz), 0 81 (6H, d, J = 6 8 Hz), 1.39 (4H, m, J = 7 2 Hz), 1 58 (1H, m, J = 6 4 Hz), 2.45 (2H, t, J = 7.2 Hz), 3.46 (2H, s), 3.49 (2H, s), 4.01 (2H, t, J = 7 6 Hz), 5.92 (2H, s), 6 74 (2H, s), 6 80 (1H, s), 6 97 (1H, s), 7 37-7.45 (3H, m), 7.53 (2H, dd, J = 1 6, 7 6 Hz) ppm.

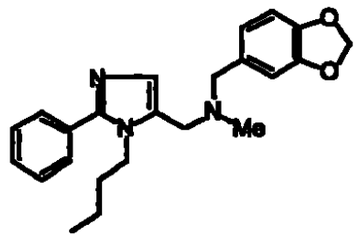


1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{2,2-dimethyl}butyl])

ammonomethylimidazole (Compound 79)

LC-MS (M^++1) 448 3

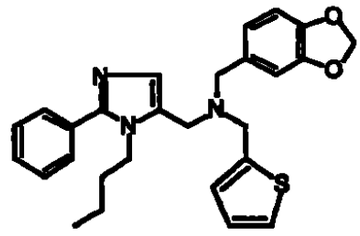
^{1}H-NMR(400 MHz, $CDCl_3$) δ 0.64 (3H, t, J = 7.2 Hz), 0 70 (3H, t, J = 7 6 Hz), 0 72 (6H, s), 0 87 (2H, m), 1 15 (4H, m), 2.34 (2H, s), 3 41 (2H, s), 3 56 (2H, s), 3 90 (2H, t, J = 7 6 Hz), 5.93 (2H, s), 6.76 (1H, d, J = 8.0 Hz), 6.82 (1H, dd, J = 1.2, 8 0 Hz), 6 96 (1H, d, J = 1.2 Hz), 6.97 (1H, s), 7 37-7 44 (3H, m), 7 47 (2H, dd, J = 1 2, 8 0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-methyl)aminomethylimidazole (Compound 80)

LC-MS (M^++1) 364.2

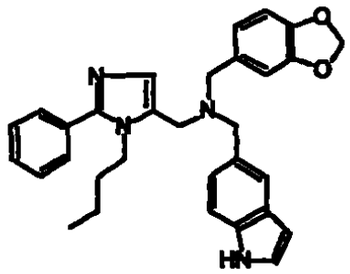
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 78 (3H, t, J = 7.6 Hz), 1 16 (2H, m, J = 7 6 Hz), 1.55 (2H, m, J = 7 6 Hz), 3 73 (4H, s), 4 03 (2H, t, J = 7 6 Hz), 5 89 (2H, s), 6 74 (2H, s), 6 83 (1H, s), 6 96 (1H, s), 7.35-7.42 (3H, m), 7 54 (2H, d, J = 7.6 Hz) ppm.



1-(1-Butyl)-2-phenyl 5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-thiophenylmethyl])amino-methylimidazole. (Compound 81)

LC-MS (M^++1): 460.3

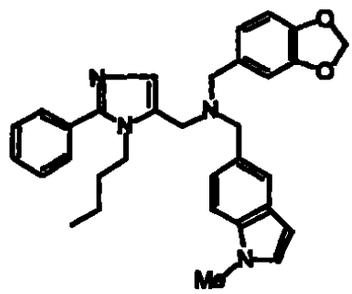
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 72 (3H, t, J = 7.2 Hz), 1 04 (2H, m, J = 7 6 Hz), 1 36 (2H, m), 3 51 (2H, s), 3 58 (2H, s), 3 79 (2H, s), 4.04 (2H, t, J = 8 0 Hz), 5 93 (2H, s), 6 75 (1H, d, J = 8 0 Hz), 6 79 (1H, dd, J = 1 6, 8 0 Hz), 6.88 (1H, d, J = 1 6 Hz), 6.91-6 96 (2H, m), 7 04 (1H, s), 7.24 (1H, dd, J = 1 6, 5 0 Hz), 7.37-7 45 (3H, m), 7 54 (2H, dd, J = 1 6, 8 0 Hz) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[indol-5-ylmethyl])ammo-methylimidazole (Compound 82)

LC-MS (M^++1) 493.2

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 58 (3H, t, J = 7.2 Hz), 0.86 (2H, m, J = 7 6 Hz), 1.22 (2H, m), 3 50 (2H, s), 3.56 (2H, s), 3.63 (2H, s), 3 95 (2H, t, J = 7 6 Hz), 5 93 (2H, s), 6.51 (1H, t, J = 2 0 Hz), 6.73-6 78 (2H, m), 6 84 (1H, s), 7 04 (1H, s), 7 13 (1H, dd, J = 1.2, 4.2 Hz), 7 18 (1H, t, J = 2.4 Hz), 7 30 (1H, d, J = 8.0 Hz), 7 38-7 43 (3H, m), 7 51 (2H, dd, J = 1 6, 8 0 Hz), 7 55 (1H, s), 8 39 (1H, br) ppm

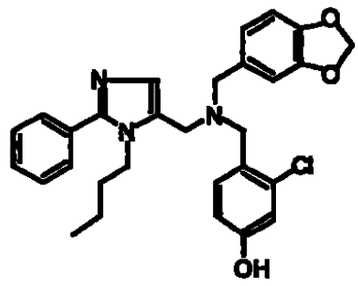


1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[{1-methylindol-5-yl}methyl])ammomethylimidazole. (Compound 83)

LC-MS (M^++1) 507.5

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.58 (3H, t, J = 7.6 Hz), 0.86 (2H, m, J = 7 6 Hz), 1.22 (2H, m), 3 49 (2H, s), 3 55 (2H, s), 3.63 (2H, s), 3 77 (3H, s), 3.95 (2H, t, J = 8 0 Hz), 5 93 (2H, s), 6.44

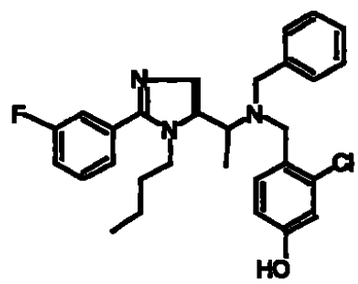
(1H, d, J = 3 2 Hz), 6 73-6.79 (2H, m), 6 84 (1H, s), 7 03 (2H, d, J = 3.2 Hz), 7 16 (1H, dd, J = 1 2, 8 0 Hz), 7.26 (1H, d, J = 8.0 Hz), 7 36-7 43 (3H, m), 7.50 (2H, dd, J = 1.6, 8 0 Hz), 7.53 (1H, s) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[4-hydroxy-2-chlorophenyl]-methyl)ammomethylimidazole. (Compound 84)

LC-MS (M^++1)· 504.4.

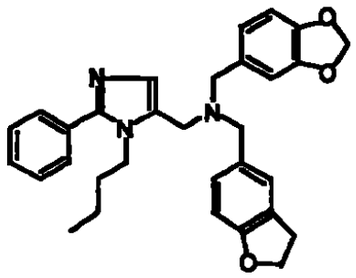
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 62 (3H, t, J = 7 6 Hz), 0 88 (2H, m, J = 7 6 Hz), 1 16 (2H, m), 3 51 (4H, s), 3.56 (2H, s), 3 88 (2H, t, J = 7 6 Hz), 5 90 (2H, s), 6.56 (1H, dd, J = 2.4, 8.4 Hz), 6 73 (2H, s), 6.75 (1H, d, J = 2.4 Hz), 6 80 (1H, s), 6.97 (1H, s), 7 00 (1H, d, J = 8.4 Hz), 7.33-7 40 (5H, m) ppm.



1-(1-Butyl)-2-(3-fluorophenyl)-5-(1-[N-{2-chloro-4-hydroxyphenyl}methyl-N-phenylmethyl]) ammoethylimidazole. (Compound 85)

LC-MS m/e 492 (M^++1)

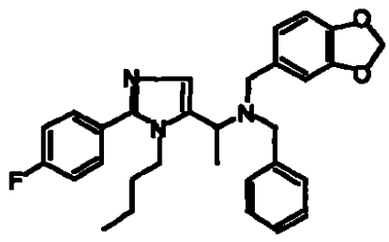
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.53 (t, 7 1 Hz, 3H), 0 63-0 72 (m, 2H), 0 85-1 0 (m, 2H), 1 50 (d, 6.7 Hz, 3H), 3.4-3 5 (m, 2H), 3 6-3 8 (m, 3H), 3 98-4.1 (m, 2H), 6 56 (dd, J = 2.5, 8 3 Hz, 1H), 6 71 (d, J = 2.4 Hz, 1H), 6 94 (d, J = 8 4 Hz, 1H), 7 01-7 12 (m, 3H), 7 16-7.34 (m, 7H) ppm.



1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[2,3-dihydrobenzo[b]furan-5-yl]methyl)aminomethylimidazole. (Compound 86)

LC-MS (M^++1) 496 6

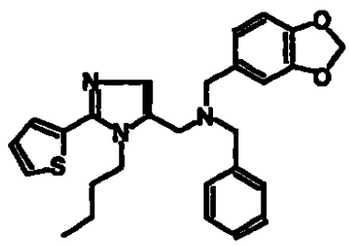
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0 70 (3H, t, J = 7 6 Hz), 0.96 (2H, m, J = 7 6 Hz), 1 29 (2H, m), 3 17 (2H, t, J = 8 8 Hz), 3.46 (4H, s), 3.52 (2H, s), 3 96 (2H, t, J = 8 0 Hz), 4.54 (2H, t, J = 8 8 Hz), 5 92 (2H, s), 6 73 (1H, d, J = 8 0 Hz), 6 74 (2H, s), 6.80 (1H, s), 7 02-7 04 (2H, m), 7 10 (1H, s), 7.36-7.44 (3H, m), 7.53 (2H, dd, J = 1 6, 8 0 Hz) ppm.



1-Butyl-2-(4-fluorophenyl)-5-(1-[N-{3,4-methylenedioxyphenyl}methyl-N-phenylmethyl]-amino)ethylimidazole (Compound 87)

LC-MS (M^++1) 486 4.

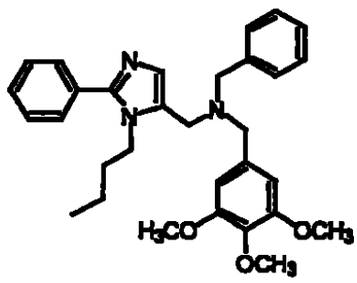
^{1}H-NMR (400 MHz, $CDCl_3$)· δ 0.57 (3H, t, J = 7.2 Hz), 0.75 (2H, m), 0 80-1 10 (2H, m), 1.47 (3H, d, J = 6 8 Hz), 3.32 (2H, dd, J = 13.2, 19 6 Hz), 3 67-3.81 (3H, m), 3 98-4 12 (2H, m), 5 91 (2H, dd, J = 1 6, 4.0 Hz), 6.67-6.73 (3H, m), 7 01 (1H, s), 7 08-7 13 (2H, m), 7.20-7.25 (3H, m), 7.27-7.30 (2H, m), 7.44-7.48 (2H, m) ppm.



1-(1-Butyl)-2-(2-thenyl)-5-(N-[3,4-methylenedioxyphenyl]methyl-N-phenylmethyl] ammomethylimidazole (Compound 88)

LC-MS (M^++1) 460.3

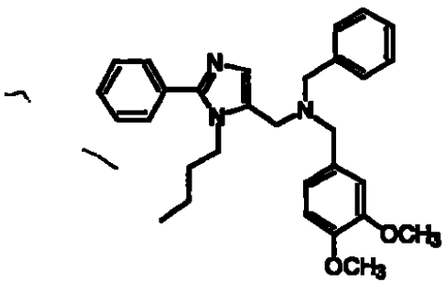
^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.81 (3H, t, J = 7.2 Hz), 1 09 (2H, m, J = 7.2 Hz), 1 44 (2H, m), 3.45 (2H, s), 3 51 (2H, s), 3.53 (2H, s), 4.07 (2H, t, J = 8.0 Hz), 5.93 (2H, s), 6.74 (2H, d, J = 1.2 Hz), 6 80 (1H, d, J = 1.2 Hz), 6.99 (1H, s), 7 07 (1H, dd, J = 4.0, 5 0 Hz), 7.23-7 7 34 (7H, m) ppm



1-(1-Butyl)-2-phenyl-5-(N-[3,4,5-trimethoxyphenylmethyl]-N-phenylmethyl)ammo-methylimidazole (Compound 89)

MS (LCMS) *m/e* 500 (M^++1).

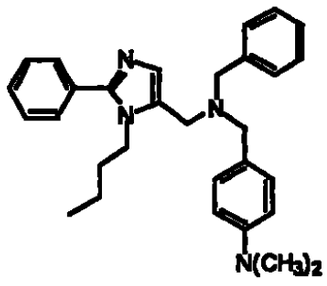
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 67 (t, J=7.69 Hz, 3H), 0 88-0.96 (m, 2H), 1.23-1.29 (m, 2H), 3 53 (s, 2H), 3.59 (s, 4H), 3 82 (s, 6H), 3 84 (s, 3H), 3 95 (t, J=7.42 Hz, 2H), 6.54 (s, 2H), 7 09 (s, 1H), 7.27-7.52 (m, 10H);



1-(1-Butyl)-2-phenyl-5-(N-phenylmethyl-N-[3,4-dimethoxyphenylmethyl])aminomethyl-imidazole. (Compound 90)

MS (LCMS) *m/e* 470 (M^++1).

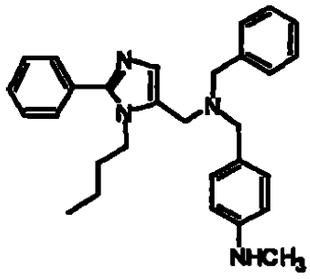
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 66 (t, J=7.33 Hz, 3H), 0.89-0 95 (m, 2H), 1.23-1.29 (m, 2H), 3 52 (s, 2H), 3 57 (s, 4H), 3 85 (s, 3H), 3 86 (s, 3H), 3.94 (t, J=7 88 Hz, 2H), 6 79-6.86 (m, 3H), 7 04 (s, 1H), 7.24-7 32 (m, 5H), 7.37-7 43 (m, 3H), 7.49-7.52 (m, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole (Compound 91)

MS (LCMS) *m/e* 453 (M^++1), Analysis calc'd for $C_{30}H_{36}N_4 \cdot 3HBr \cdot 0.5i\text{-}Pr_2O$ C, 53.10, H, 6.21, N, 7.51, found. C, 52.80; H, 6.19, N, 7.43

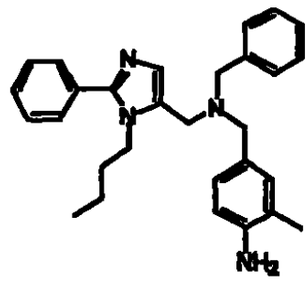
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (t, J=7.33 Hz, 3H), 0.90-0.96 (m, 2H), 1.22-1.29 (m, 2H), 2.92 (s, 6H), 3.46 (s, 2H), 3.53 (s, 2H), 3.55 (s, 2H), 3.96 (t, J=8.06 Hz, 2H), 6.69 (d, J=8.61 Hz, 2H), 7.02 (s, 1H), 7.16 (d, J=8.61 Hz, 2H), 7.24-7.33 (m, 5H), 7.38-7.43 (m, 3H), 7.50-7.53 (m, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[4-methylaminophenylmethyl]-N-phenylmethyl)ammomethyl-imidazole (Compound 92)

MS (LCMS) *m/e* 439 (M^++1)

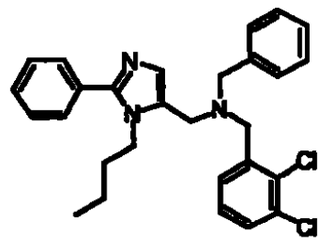
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, J=7.33 Hz, 3H), 0.91-0.97 (m, 2H), 1.23-1.29 (m, 2H), 2.82 (s, 3H), 3.45 (s, 2H), 3.53 (s, 2H), 3.54 (s, 2H), 3.95 (t, J=7.88 Hz, 2H), 6.56 (d, J=8.42 Hz, 2H), 7.02 (s, 1H), 7.11 (d, J=8.42 Hz, 2H), 7.22-7.30 (m, 5H), 7.38-7.43 (m, 3H), 7.50-7.53 (m, 2H)



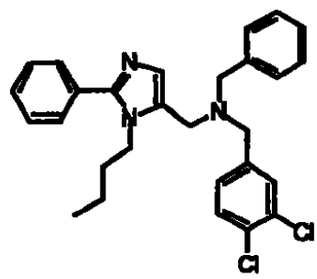
1-(1-Butyl)-2-phenyl-5-(N-[3-methyl-4-aminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole) (Compound 93)

MS (LCMS) *m/e* 439 (M^++1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0 68 (t, J=7 42 Hz, 3H), 0 88-0 97 (m, 2H), 1.24-1 33 (m, 2H), 2 16 (s, 3H), 3.43 (s, 2H), 3 52 (s, 2H), 3.54 (s, 2H), 3 95 (t, J=7 97 Hz, 2H), 6.63 (d, J=8 52 Hz, 1H), 6.97-6.99 (m, 2H), 7 02 (s, 1H), 7.24-7.32 (m, 5H), 7.37-7.45 (m, 3H), 7.51-7.54 (m, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole (Compound 94)

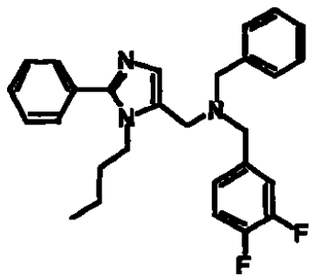


1-(1-Butyl)-2-phenyl-5-(N-[3,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole

(Compound 95)

MS (LCMS) *m/e* 479 (M^++1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (t, J=7 14 Hz, 3H), 0 84-0.89 (m, 2H), 1 13-1 19 (m, 2H), 3 58 (s, 2H), 3 61 (s, 2H), 3 74 (s, 2H), 3 90 (t, J=7 88 Hz, 2H), 7 07 (s, 1H), 7 16 (t, J=7.69 Hz, 1H), 7 26-7.49 (m, 12H).

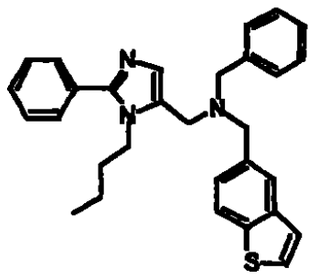


1-(1-Butyl)-2-phenyl-5-(N-[3,4-difluorophenylmethyl]-N-phenylmethyl)aminomethylimidazole

(Compound 96)

MS (LCMS) *m/e* 446 (M^++1).

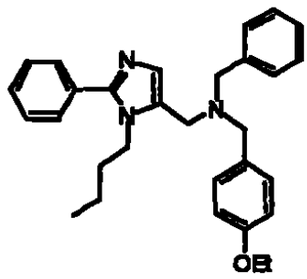
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (t, J=7 14 Hz, 3H), 0 90-0.98 (m, 2H), 1.25-1.27 (m, 2H), 3 53 (s, 2H), 3.55 (s, 4H), 3 91-3.97 (m, 2H), 7 04-7 14 (m, 4H), 7.28-7 53 (m, 10H)



1-(1-Butyl)-2-phenyl-5-(N-(benzo[b]thiophen-5-ylmethyl)-N-phenylmethyl)aminomethyl-imidazole (Compound 97)

MS (LCMS) *m/e* 466 (M^++1).

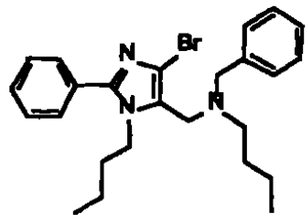
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (t, J=7 33 Hz, 3H), 0 80-0.86 (m, 2H), 1 16-1 27 (m, 2H), 3.58 (s, 2H), 3 60 (s, 2H), 3 67 (s, 2H), 3.92 (t, J=7 88 Hz, 2H), 7 05 (s, 1H), 7.26-7 50 (m, 13H), 7 74 (s, 1H), 7 82 (d, J=8 24 Hz, 1H)



1-(1-Butyl)-2-phenyl-5-(N-[4-ethoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole (Compound 98)

MS (LCMS) *m/e* 454 (M^++1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0 66 (t, J=7 51 Hz, 3H), 0.88-0 94 (m, 2H), 1.21-1.26 (m, 2H), 1 40 (t, J=7 14 Hz, 3H), 3.49 (s, 2H), 3 53 (s, 2H), 3.54 (s, 2H), 3 94 (t, J=7 88 Hz, 2H), 4 00 (q, J=6.96 Hz, 2H), 6.84 (.dd, J=2.93, 6.59 Hz, 2H), 7 05 (s, 1H), 7 19 (d, J=8 61 Hz, 2H), 7.24-7.34 (m, 5H), 7.39-7 44 (m, 3H), 7 49-7 52 (m, 2H)

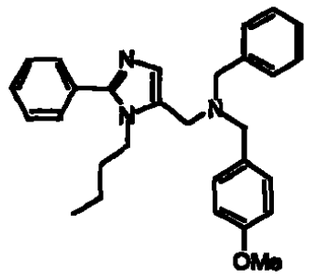


1-(1-Butyl)-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole

(Compound 99)

MS (LCMS) *m/e* 456 (M^++1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0 70 (t, J=7 33 Hz, 3H), 0.84 (t, J=7 33 Hz, 3H), 0 95-1 01 (m, 2H), 1.24-1 35 (m, 4H), 1 49-1 55 (m, 2H), 2.46 (t, J=7.33 Hz, 2H), 3 53 (s, 2H), 3 55 (s, 2H), 3 99 (t, J=7 88 Hz, 2H), 7.24-7.30 (m, 5H), 7.38-7.50 (m, 5H)

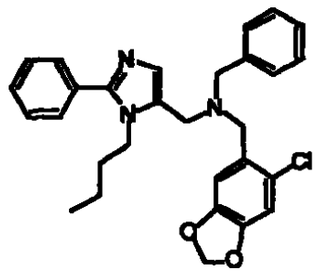


1-(1-Butyl)-2-phenyl-5-(N-[4-methoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole

(Compound 100)

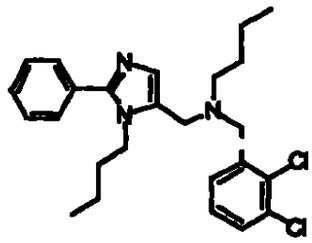
MS (LCMS) *m/e* 440 (M^++1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0 66 (t, J=7.51 Hz, 3H), 0.89-0.95 (m, 2H), 1.21-1.29 (m, 2H), 3 50 (s, 2H), 3 53 (s, 2H), 3.55 (s, 2H), 3 79 (s, 3H), 3 94 (t, J=7 88 Hz, 2H), 6 85 (.dd, J=2 01, 6 59 Hz, 2H), 7 03 (s, 1H), 7.21-7.35 (m, 7H), 7 39-7.44 (m, 3H), 7.50-7.52 (m, 2H),



1-(1-Butyl)-2-phenyl-5-(N-[6-chloro-3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)-ammonomethylimidazole (Compound 101)

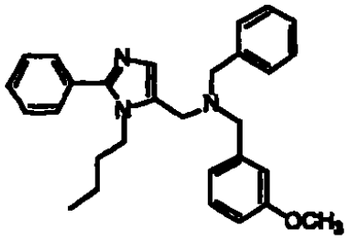
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (t, J=7.33 Hz, 3H), 0.87-0 93 (m, 2H), 1 17-1.26 (m, 2H), 3.57 (s, 2H), 3.58 (s, 2H), 3 60 (s, 2H), 3 93 (t, J=7 87 Hz, 2H), 5 94 (s, 2H), 6.81 (s, 1H), 6.86 (s, 1H), 7 08 (s, 1H), 7.26-7.31 (m, 5H), 7 41-7.50 (m, 5H); MS (LCMS) *m/e* 488 (M^++1).



1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl]ammonomethylimidazole (Compound 102)

MS (LCMS) *m/e* 445 (M^++1).

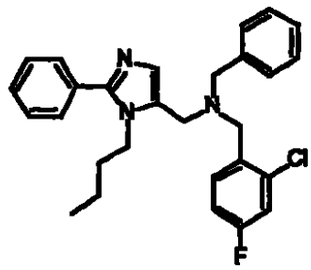
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (t, J=7.51 Hz, 3H), 0 84 (t, J=7 33 Hz, 3H), 1 00-1.29 (m, 2H), 1.33-1.38 (m, 4H), 1.49-1.55 (m, 2H), 2.49 (t, J=7 33 Hz, 2H), 3.58 (s, 2H), 3.70 (s, 2H), 3.99 (t, J=7 87 Hz, 2H), 7 01 (s, 1H), 7 15 (t, J=7 69 Hz, 1H), 7.29-7.44 (m, 5H), 7.49-7 52 (m, 2H).



1-(1-Butyl)-2-phenyl-5-(N-[3-methoxyphenylmethyl]-N-phenylmethyl)ammonomethylimidazole (Compound 103)

MS (LCMS) *m/e* 440 (M^++1)

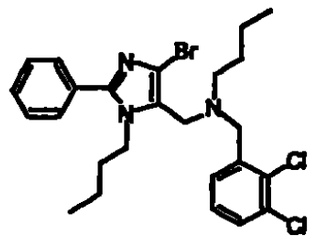
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (t, J=7 69 Hz, 3H), 0.88-0 94 (m, 2H), 1.21-1.27 (m, 2H), 3 54 (s, 2H), 3.55 (s, 2H), 3.56 (s, 2H), 3 79 (s, 3H), 3 96 (t, J=7 69 Hz, 2H), 6 78 (dd, J=2.56, 8 15 Hz, 1H), 6 88-6 92 (m, 2H), 7 06 (s, 1H), 7.21-7.32 (m, 7H), 7.38-7.44 (m, 2H), 7.49-7 52 (m, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-fluorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole (Compound 104)

MS (LCMS) *m/e* 463 (M^++1)

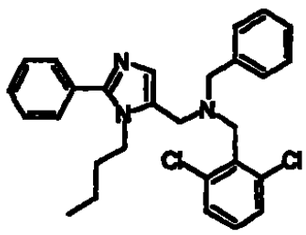
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (t, J=7.33 Hz, 3H), 0 84-0.90 (m, 2H), 1 14-1 19 (m, 2H), 3 57 (s, 2H), 3.58 (s, 2H), 3 67 (s, 2H), 3 89 (t, J=7 88 Hz, 2H), 6 94 (dt, J=2.56, 8 33 Hz, 1H), 7.07 (s, 1H), 7 10 (dd, J=2 56, 8 52 Hz, 1H), 7 21-7.48 (m, 11H)



1-(1-Butyl)-2-phenyl-4-bromo-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl])aminomethyl-imidazole (Compound 105)

MS (LCMS) *m/e* 463 (M^++1)

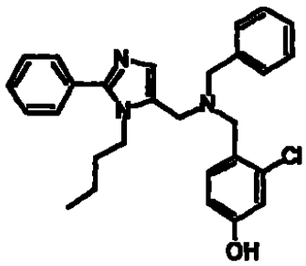
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (t, J=7 14 Hz, 3H), 0.85 (t, J=7 42 Hz, 3H), 0.96-1.03 (m, 2H), 1.21-1.35 (m, 4H), 1.50-1 58 (m, 2H), 2.50 (t, J=7.42 Hz, 2H), 3 59 (s, 2H), 3 71 (s, 2H), 3 99-4.13 (m, 2H), 7 14 (t, J=7 69 Hz, 1H), 7.23-7.26 (m, 1H), 7.35-7.50 (m, 6H).



1-(1-Butyl)-2-phenyl-5-(N-[2,6-dichlorophenylmethyl]-N-phenylmethyl)ammomethylimidazole (Compound 106)

MS (LCMS) *m/e* 478 (M^++1)

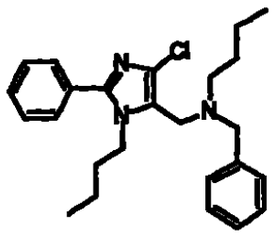
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (t, J=7.33 Hz, 3H), 0 73-0 84 (m, 2H), 1 02-1 06 (m, 2H), 3 59 (s, 4H), 3 87 (s, 2H), 3.92 (t, J=7.87 Hz, 2H), 7 04 (s, 1H), 7 11-7 15 (m, 1H), 7 19-7.23 (m, 7H), 7.26-7.48 (m, 5H).



1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)ammomethyl-imidazole (Compound 107)

MS (LCMS) *m/e* 460 (M^++1)

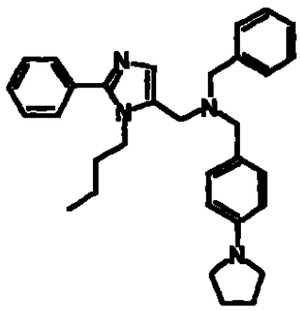
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (t, J=7.33 Hz, 3H), 0 82-0 87 (m, 2H), 1.08-1 14 (m, 2H), 3 54 (s, 2H), 3.63 (s, 2H), 3.65 (s, 2H), 3 86 (t, J=7 69 Hz, 2H), 6.55 (dd, J=2.56, 8.33 Hz, 1H), 6.77 (d, J=2 38 Hz, 1H), 6.98 (s, 1H), 7 05 (d, J=8.24 Hz, 1H), 7.21-7 35 (m, 10H).



1-(1-Butyl)-2-phenyl-4-chloro-5-(N-phenylmethyl-N-[1-butyl]ammomethylimidazole (Compound 108)

MS (LCMS) *m/e* 410 (M^++1)

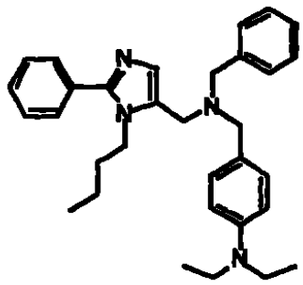
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (t, J=7.33 Hz, 3H), 0.84 (t, J=7 51 Hz, 3H), 0.88-1 00 (m, 2H), 1 18-1 39 (m, 4H), 1.47-1.58 (m, 2H), 2.46 (t, J=7.33 Hz, 2H), 3 53 (s, 2H), 3.55 (s, 2H), 3 97 (t, J=7 88 Hz, 2H), 7.21-7.30 (m, 5H), 7.38-7 44 (m, 3H), 7.48-7.50 (m, 2H).



1-(1-Butyl)-2-phenyl-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl)ammomethyl-imidazole (Compound 109)

MS (LCMS) *m/e* 479 (M^++1)

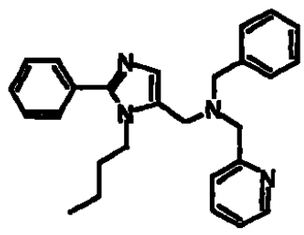
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 65 (t, J=7 14 Hz, 3H), 0 90-0 95 (m, 2H), 1 21-1.29 (m, 2H), 1 97-2 01 (m, 4H), 3.26 (t, J=6.41 Hz, 4H), 3 46 (s, 2H), 3 53 (s, 2H), 3.55 (s, 2H), 3 96 (t, J=7.88 Hz, 2H), 6.51 (d, J=8 61 Hz, 2H), 6 99 (s, 1H), 7 14 (d, J=8.24 Hz, 2H), 7 20-7.31 (m, 5H), 7.35-7 44 (m, 3H), 7.48-7.52 (m, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[4-diethylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole (Compound 110)

MS (LCMS) *m/e* 481 (M^++1).

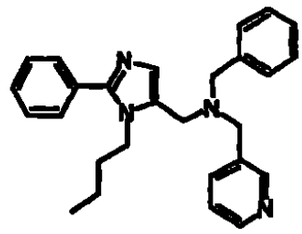
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (t, J=7 14 Hz, 3H), 0 88-0 95 (m, 2H), 1 14 (t, J=6.69 Hz, 6H), 1.21-1.29 (m, 2H), 3.32 (q, J=7 14 Hz, 4H), 3.44 (s, 2H), 3.54 (s, 2H), 3.56 (s, 2H), 3.97 (t, J=7 69 Hz, 2H), 6 62 (d, J=8 79 Hz, 2H), 7 03 (s, 1H), 7 12 (d, J=8 79 Hz, 2H), 7.21-7.31 (m, 5H), 7.35-7.44 (m, 3H), 7.51-7.53 (m, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[pyridin-2-ylmethyl]-N-phenylmethyl)aminomethylimidazole (Compound 111)

MS (LCMS) *m/e* 411 (M^++1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0 67 (t, J=7 51 Hz, 3H), 0.89-0.96 (m, 2H), 1.23-1.30 (m, 2H), 3 64 (s, 4H), 3 77 (s, 2H), 3.95 (t, J=7.69 Hz, 2H), 7 05 (s, 1H), 7 14-7 17 (m, 1H), 7.23-7 44 (m, 9H), 7.50-7.52 (m, 2H), 7 64 (dt, J=1 65, 7 78 Hz, 1H), 8.52-8 54 (m, 1H).

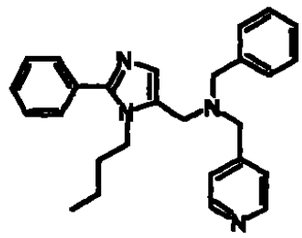


1-(1-Butyl)-2-phenyl-5-(N-[pyridin-3-ylmethyl]-N-phenylmethyl)aminomethylimidazole

(Compound 112)

MS (LCMS) *m/e* 411 (M^++1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (t, J=7 14 Hz, 3H), 0 78-0.93 (m, 2H), 1 18-1.26 (m, 2H), 3.57 (s, 4H), 3.59 (s, 2H), 3 93 (t, J=7 69 Hz, 2H), 7 07 (s, 1H), 7.21-7 50 (m, 10H), 7 58-7 60 (m, 2H), 8.49 (dd, J=1.65, 4.85 Hz, 1H), 8.57 (d, J=1.47 Hz, 1H).

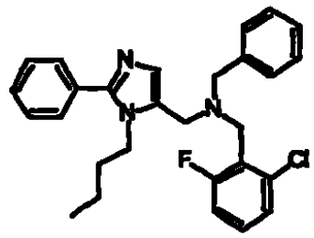


1-(1-Butyl)-2-phenyl-5-(N-[pyridin-4-ylmethyl]-N-phenylmethyl)aminomethylimidazole

(Compound 113)

MS (LCMS) *m/e* 411 (M^++1)

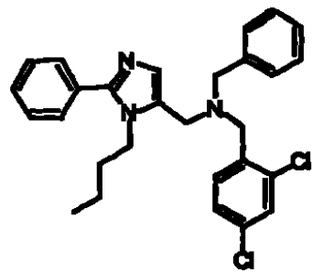
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, J=7 14 Hz, 3H), 0.91-0.96 (m, 2H), 1.25-1.28 (m, 2H), 3 56 (s, 2H), 3 57 (s, 2H), 3 59 (s, 2H), 3.93 (t, J=7 87 Hz, 2H), 7 05 (s, 1H), 7.24-7.50 (m, 12H), 8.54 (dd, J=1 65, 4.40 Hz, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[2-fluoro-6-chlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole). (Compound 114)

MS (LCMS) *m/e* 462 (M^++1)

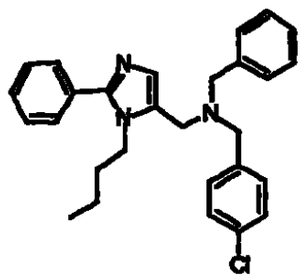
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (t, J=6 78 Hz, 3H), 0 77-0 82 (m, 2H), 1 04-1 12 (m, 2H), 3 57 (s, 2H), 3 58 (s, 2H), 3 73 (s, 2H), 3.94 (t, J=7.51 Hz, 2H), 7 05 (s, 1H), 7 16-7.28 (m, 7H), 7.35-7 48 (m, 5H)



1-(1-Butyl)-2-phenyl-5-(N-[2,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole). (Compound 115)

MS (LCMS) *m/e* 462 (M^++1)

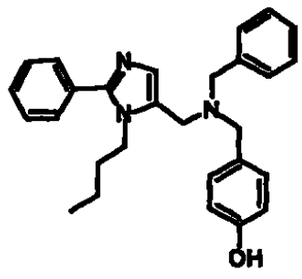
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (t, J=6 78 Hz, 3H), 0 77-0 82 (m, 2H), 1 04-1 12 (m, 2H), 3.57 (s, 2H), 3.58 (s, 2H), 3 73 (s, 2H), 3 94 (t, J=7 51 Hz, 2H), 7 05 (s, 1H), 7 16-7.28 (m, 7H), 7.35-7.48 (m, 5H)



1-(1-Butyl)-2-phenyl-5-(N-[4-chlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole (Compound 116)

MS (LCMS) *m/e* 462 (M^++1).

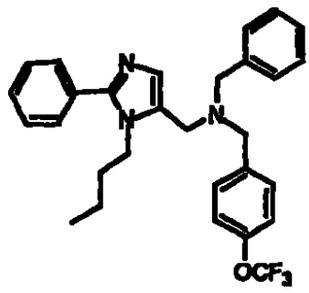
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (t, J=6.78 Hz, 3H), 0.77-0 82 (m, 2H), 1 04-1 12 (m, 2H), 3 57 (s, 2H), 3 58 (s, 2H), 3 73 (s, 2H), 3 94 (t, J=7 51 Hz, 2H), 7 05 (s, 1H), 7 16-7.28 (m, 7H), 7 35-7.48 (m, 5H)



1-(1-Butyl)-2-phenyl-5-(N-[4-hydroxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole (Compound 117)

MS (LCMS) *m/e* 426 (M^++1).

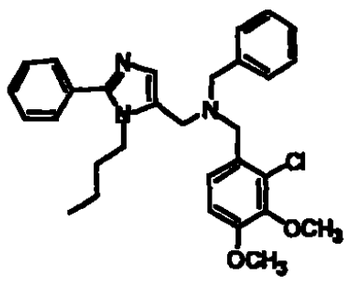
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (t, J=7.51 Hz, 3H), 0 91-0 96 (m, 2H), 1.22-1.28 (m, 2H), 3.49 (s, 2H), 3.52 (s, 2H), 3.56 (s, 2H), 3.92 (t, J=7.88 Hz, 2H), 6.77 (d, J=8.42 Hz, 2H), 7 06 (s, 1H), 7 12 (d, J=8.24 Hz, 2H), 7.30-7.43 (m, 8H), 7.48-7.49 (m, 2H)



1-(1-Butyl)-2-phenyl-5-(N-[4-trifluoromethoxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole) (Compound 118)

MS (LCMS) *m/e* 494 (M^++1)

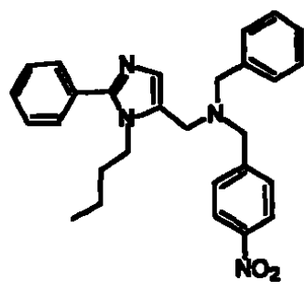
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (t, J=7.33 Hz, 3H), 0.88-0.93 (m, 2H), 1.20-1.28 (m, 2H), 3 55 (s, 2H), 3 56 (s, 4H), 3.94 (t, J=7 88 Hz, 2H), 7 06 (s, 1H), 7.28-7.44 (m, 10H), 7.48-7.52 (m, 2H).



1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-3,4-dimethoxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole) (Compound 119)

MS (LCMS) *m/e* 504 (M^++1).

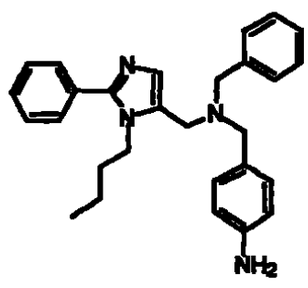
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (t, J=7 51 Hz, 3H), 0.82-0 87 (m, 2H), 1 12-1 17 (m, 2H), 3 56 (s, 2H), 3.59 (s, 2H), 3.65 (s, 2H), 3 84 (s, 6H), 3 91 (t, J=7.69 Hz, 2H), 6 77 (d, J=8 01 Hz, 1H), 7 04 (s, 1H), 7.06 (d, J=8 61 Hz, 1H), 7 21-7.39 (m, 5H), 7.41-7 49 (m, 5H)



1-(1-Butyl)-2-phenyl-5-(N-[4-nitrophenylmethyl]-N-phenylmethyl)aminomethylimidazole (Compound 120)

MS (LCMS) *m/e* 455 (M^++1).

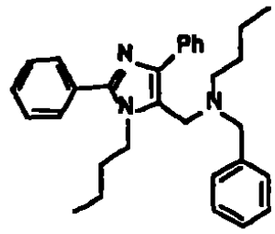
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, J=7.33 Hz, 3H), 0.91-0.96 (m, 2H), 1.23-1.31 (m, 2H), 3.58 (s, 2H), 3 59 (s, 2H), 3.69 (s, 2H), 3.92 (t, J=7 88 Hz, 2H), 7 05 (s, 1H), 7.28-7.49 (m, 12H), 8 17 (d, J=8.79 Hz, 2H).



1-(1-Butyl)-2-phenyl-5-(N-[4-aminophenylmethyl]-N-phenylmethyl)aminomethylimidazole (Compound 121)

MS (LCMS) *m/e* 425 (M^++1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0 68 (t, J=7 14 Hz, 3H), 0 90-0.97 (m, 2H), 1.23-1.31 (m, 2H), 3 45 (s, 2H), 3 53 (s, 2H), 3 54 (s, 2H), 3 95 (t, J=8 06 Hz, 2H), 6.64 (dd, J=2 01, 6.41 Hz, 2H), 7 04 (s, 1H), 7.23-7.31 (m, 5H), 7 39-7.44 (m, 3H), 7 51-7.53 (m, 2H)

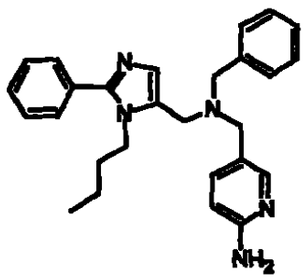


1-(1-Butyl)-2,4-diphenyl-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole.

(Compound 122)

MS (LCMS) *m/e* 452 (M^++1).

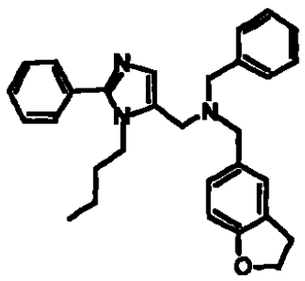
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 73 (t, J=7 14 Hz, 3H), 0 79 (t, J=7.35 Hz, 3H), 1 04-1 06 (m, 2H), 1.20-1.25 (m, 2H), 1.39-1.43 (m, 4H), 2.39-2 43 (m, 2H), 3 51 (s, 2H), 3 79 (s, 2H), 4.13 (t, J=8.24 Hz, 2H), 7.22-7 30 (m, 6H), 7.37-7 45 (m, 5H), 7.58 (d, J=7 87 Hz, 2H), 7.69 (d, J=7.33 Hz, 2H).



1-(1-Butyl)-2-phenyl-5-(N-[2-aminopyridin-5-ylmethyl]-N-phenylmethyl)aminomethyl-imidazole. (Compound 123)

MS (LCMS) *m/e* 426 (M^++1)

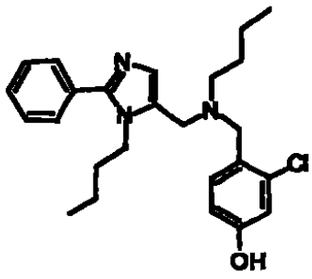
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, J=7.51 Hz, 3H), 0.88-0 95 (m, 2H), 1 22-1.30 (m, 2H), 3.43 (s, 2H), 3 54 (s, 4H), 3 94 (t, J=7 87 Hz, 2H), 4.42 (bs, 2H, NH2), 6.46 (d, J=8.24 Hz, 1H), 7 03 (s, 1H), 7 22-7.49 (m, 9H), 7.50-7.52 (m, 2H), 7.99 (d, J=2.01 Hz, 1H)



1-(1-Butyl)-2-phenyl-5-(N-[2,3-dihydrobenzo[b]furan-5-yimethyl]-N-phenylmethyl)amino-methylimidazole (Compound 124)

MS (LCMS) *m/e* 452 (M^++1).

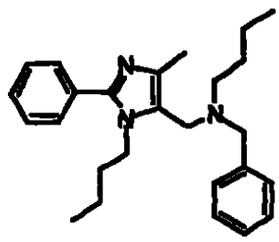
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 66-0.69 (m, 3H), 0 90-0 95 (m, 2H), 1.23-1 28 (m, 2H), 3 18 (t, J=8 79 Hz, 2H), 3.48 (s, 2H), 3 53 (s, 2H), 3 55 (s, 2H), 3 94 (t, J=8 06 Hz, 2H), 4.55 (t, J=8 61 Hz, 2H), 6 72 (d, J=8.06 Hz, 1H), 7 02-7 10 (m, 3H), 7.23-7 52 (m, 10H).



1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-[1-butyl])ammomethyl-imidazole) (Compound 125)

MS (LCMS) *m/e* 426 (M^++1).

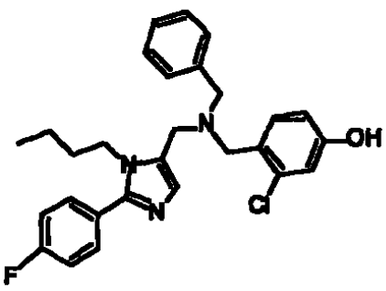
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (t, J=7.33 Hz, 3H), 0.85 (t, J=7.51 Hz, 3H), 1.00-1.05 (m, 2H), 1.24-1.35 (m, 4H), 1.49-1.53 (m, 2H), 2.51 (t, J=6.78 Hz, 2H), 3.55 (s, 2H), 3.57 (s, 2H), 3.97 (t, J=7.51 Hz, 2H), 6.58 (dd, J=2.38, 8.33 Hz, 1H), 6.77 (d, J=2.38 Hz, 1H), 6.96 (s, 1H), 7.06 (d, J=8.42 Hz, 1H), 7.36-7.41 (m, 5H).



1-(1-Butyl)-2-phenyl-4-methyl-5-(N-phenylmethyl-N-[1-butyl])ammomethylumidazole (Compound 126)

MS (LCMS) *m/e* 390 (M^++1).

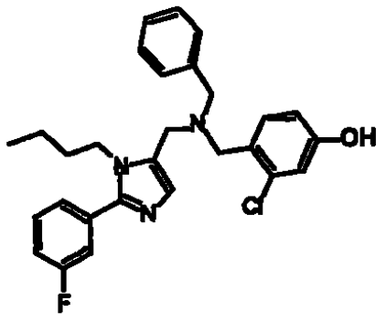
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (t, J=7.33 Hz, 3H), 0.82 (t, J=7.51 Hz, 3H), 1.00-1.05 (m, 2H), 1.25-1.40 (m, 6H), 2.22 (s, 3H), 2.40 (t, J=6.78 Hz, 2H), 3.53 (s, 2H), 3.55 (s, 2H), 3.95 (t, J=7.51 Hz, 2H), 7.23-7.30 (m, 5H), 7.38-7.42 (m, 3H), 7.50-7.55 (m, 2H)



1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)-ammomethylumidazole. (Compound 127)

MS (LCMS) *m/e* 478 (M^++1)

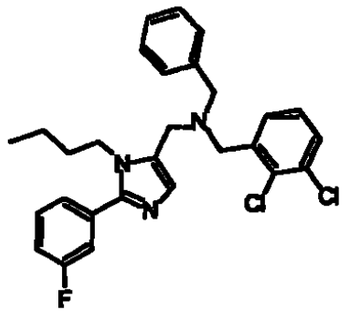
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 58 (t, J=7 14 Hz, 3H), 0 78-0 84 (m, 2H), 1 01-1 09 (m, 2H), 3 53 (s, 2H), 3 64 (s, 2H), 3 67 (s, 2H), 3 81 (t, J=7.33 Hz, 2H), 6 58 (d, J=8 24 Hz, 1H), 6.74 (s, 1H), 6 94-7 01 (m, 3H), 7.24-7.35 (m, 8H)



1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole. (Compound 128)

MS (LCMS) *m/e* 478 (M^++1)

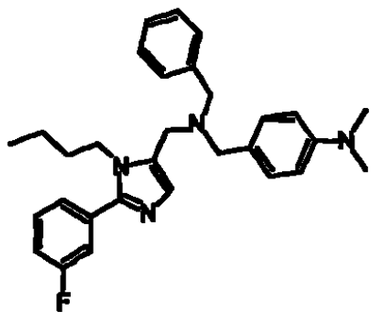
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 61 (t, J=7.42 Hz, 3H), 0.77-0.87 (m, 2H), 1 05-1 16 (m, 2H), 3 53 (s, 2H), 3.59 (s, 2H), 3 60 (s, 2H), 3 87 (t, J=7 69 Hz, 2H), 6.58 (dd, J=2.47, 8.24 Hz, 1H), 6.75 (d, J=2.47 Hz, 1H), 6.99-7.30 (m, 11H)



1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl)amino-methylimidazole. (Compound 129)

MS (LCMS) *m/e* 496 (M^++1)

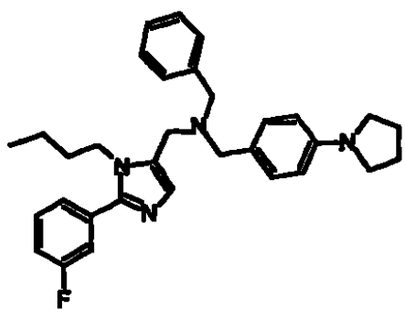
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 65 (t, J=7.33 Hz, 3H), 0 85-0 91 (m, 2H), 1 13-1 19 (m, 2H), 3 58 (s, 2H), 3 61 (s, 2H), 3.74 (s, 2H), 3.91 (t, J=7.87 Hz, 2H), 7 06-7 10 (m, 2H), 7 14-7.42 (m, 11H)



1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-dimethylammophenylmethyl]-N-phenylmethyl)amino-methylimidazole (Compound 130)

MS (LCMS) *m/e* 471 (M^++1).

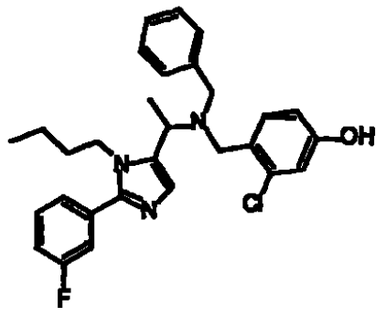
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 68 (t, J=7.33 Hz, 3H), 0.91-0.97 (m, 2H), 1 21-1 29 (m, 2H), 2.93 (s, 6H), 3.47 (s, 2H), 3.53 (s, 2H), 3.55 (s, 2H), 3.96 (t, J=7.88 Hz, 2H), 6 71 (dd, J=2.01, 6.78 Hz, 2H), 7 02 (s, 1H), 7 05-7 10 (m, 1H), 7 16 (d, J=8.61 Hz, 2H), 7.21-7.26 (m, 7H), 7.31-7 41 (m, 1H).



1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl)amino-methylimidazole (Compound 131)

MS (LCMS) *m/e* 511 (M^++1).

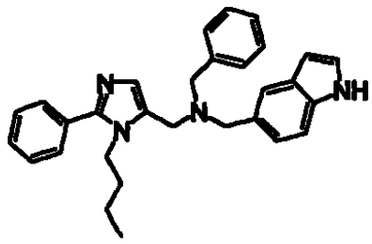
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (t, J=7 33 Hz, 3H), 0 72-0 78 (m, 2H), 0 93-1 08 (m, 2H), 1 48 (d, J=6 78 Hz, 3H), 1.97-2 05 (m, 4H), 3.20-3.35 (m, 6H), 3.67-3 85 (m, 3H), 4.03-4.20 (m, 2H), 6 59 (dd, J=2.56, 11.26 Hz, 2H), 7 06-7 11 (m, 4H), 7 19-7.31 (m, 7H), 7.36-7.41 (m, 1H)



1-(1-Butyl)-2-(3-chlorophenyl)-5-(1-[N-{2-chloro-4-hydroxyphenylmethyl}-N-phenylmethyl] amino)ethylimidazole. (Compound 132)

MS (LCMS) *m/e* 492 (M^++1)

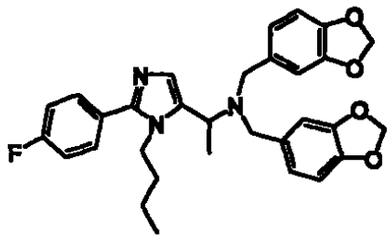
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 53 (t, J=7 14 Hz, 3H), 0 63-0 72 (m, 2H), 0 85-1 00 (m, 2H), 1.50 (d, J=6 78 Hz, 3H), 3.40-3.52 (m, 2H), 3.64-3.81 (m, 3H), 3 98-4.13 (m, 2H), 6.56 (dd, J=2.56, 8.33 Hz, 1H), 6 71 (d, J=2.38 Hz, 1H), 6.94 (d, J=8.42 Hz, 1H), 7 01-7 12 (m, 3H), 7 16-7.34 (m, 7H).



1-(1-Butyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl)ammomethylimidazole (Compound 133)

MS (LC/MS) m/e 449 (M^++1)

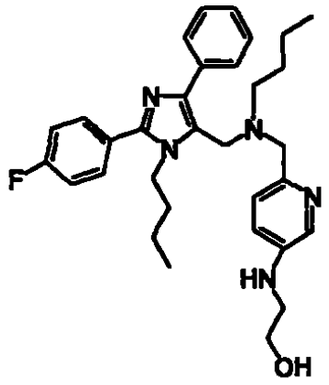
^{1}H NMR (400 MHz, $CDCl_3$) δ 0 59 (t, J=7.32 Hz, 3H), 0 79-0 85 (m, 2H), 1 17-1 25 (m, 2H), 3 54 (s, 2H), 3.58 (s, 2H), 3 68 (s, 2H), 3 96 (dd, J=7.32, 2H), 6.55 (s, 1H), 7 09 (s, 1H), 7 18-7 53 (m, J=15 Hz), 7.58 (s, 1H), 8.35 (s, 1H)



1-(1-Butyl)-2-(4-fluorophenyl)-5-(1-N,N-di[3,4-methylenedioxyphenylmethyl]amino) ethylimidazole (Compound 134)

MS (LC/MS) *m/e* 530 (M^++1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0 62 (t, J=7.4 Hz, 3H), 0.79-0 85 (m, 2H), 1 01-1 26 (m, 2H), 1.46 (d, J=6 8 Hz, 3H), 3 27 (d, J=13.2 Hz, 2H), 3 70 (d, J=13 2 Hz, 2H), 3 78-3 85 (m, 1H), 4.03 (q, J=6 8 Hz, 1H), 4 07-4.15 (m, 1H), 5.92 (m, 4H), 6.67-6 74 (m, 6H), 7 02 (s, 1E), 7 12 (t, J=8 8 Hz, 2H) 7 49 (dd, J=8.8, 5.6 Hz, 2H).



2-{[5-({Butyl[(1-butyl-2,4-diphenylimidazol-5-yl)methyl]amino}methyl)-2-pyridyl]amino}ethan-1-ol (Compound 135)

MS (LC/MS) *m/e* 512 (M^++1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (t, J=7.33 Hz, 3H), 0 80 (t, J=7 14 Hz, 3H), 1 04-1 10 (m, 2H), 1 35-1 46 (m, 4H), 2.38 (t, J=7 14 Hz, 2H) 3 33 (s, 2H), 3.46-3 50 (m, 2H), 3 76-3 78 9m, 4H), 4.09-4.85 (m, 2H), 4.85 (bs, 1H), 6.36 d, J=8 61, 1H), 7.21-7.28 (m, 3H), 7.38-7 46 (m, 4H), 7 57-7 59 (m, 2H), 7 66-7.68 (m, 2H), 7.88 (d, J=1 83 Hz, 1H)

Example VI

Assay for C5a Receptor Mediated Chemotaxis

Human promonocytic U937 cells are treated with dibutyryl cAMP for 48 hours prior to performing the assay The cells are pelleted and resuspended in culture media containing 0 1% fetal bovine serum (FBS) and 10 ug/ml calcein AM (a fluorescent dye) This suspension is then incubated at 37 °C for 30 minutes such that the cells take up the fluorescent dye. The suspension is then centrifuged briefly to pellet the cells, which are then resuspended in culture media containing 0 1% FBS at a concentration of approximately 3 x 10^6 cells/mL. Aliquots of this cell suspension are transferred to clean test tubes, which contain vehicle (1% DMSO) or varying concentrations of a compound of interest, and incubated at room temperature for at least 30 minutes. The chemotaxis assay is performed in ChemoTx 101-8, 96 well plates. The bottom wells of the plate are filled with varying concentrations of human C5a (0-10 nM) The top wells of the plate are filled with cell suspensions (compound and vehicle-treated) The plate is then placed in a tissue culture incubator for 60 minutes. The top surface of the plate is washed with PBS to remove excess cell suspension. The number of cells that have migrated into the bottom well is then determined using a fluorescence reader Chemotaxis index (the ratio of migrated

cells to total number of cells loaded) is then calculated for each compound concentration to determine an EC_{50} value.

Compounds of the accompanying Examples exhibit EC_{50} values of less than 1μM in the above assay for C5a mediated chemotaxis. Data is shown for several representative compounds of this invention in Table 2

TABLE 2

Compound Number	EC_{50}
26	34 nM
53	55 nM
122	370 nM
125	430 nM
132	35 nM
133	370 nM
134	80 nM

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The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

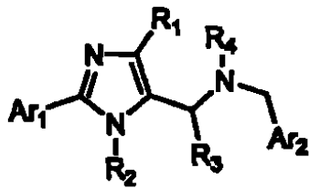
The invention and the manner and process of making and using it are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To

particularly point out and distinctly claim the subject matter regarded as the invention, the following claims conclude the specification.

000080 '92 .12203

What is claimed is

1 A compound of the formula.



or a pharmaceutically acceptable salt thereof, wherein.

R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl,

R_3 is hydrogen or C_1-C_7 alkyl,

R_4 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl, or

R_4 is arylalkyl wherein the aryl group is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; or

Ar_1 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; or

Ar_1 is 2-thienyl or pyridyl, each of which is optionally substituted with halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, or trifluoromethyl,

Ar_2 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4- methylenedioxy; or

Ar_2 is 1 or 2-naphthyl, 1, 2, or 3-indolyl, 2,3-dihydroindolyl, 1,2,3,4-tetrahydroquinolyl, 1- or 2-benzimidazolyl, 1,4-benzodioxan-6-yl, 2-, 3-, or 4-pyridyl, quinolyl, 2- or 3-thienyl, 2- or 3-benzo[b]thiophenyl, 2,3-dihydrobenzofuranyl or 2-, 3-, or 4-chromanyl, each of which may be substituted by up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, acetoxy, trifluoromethyl and trifluoromethoxy

2 A compound according to Claim 1, wherein R_3 is hydrogen or methyl and R_4 is benzyl or phenylethyl.

3 A compound according to Claim 2, wherein.

R_1 is hydrogen or methyl,

Ar_1 is phenyl optionally substituted with up to three groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_6 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is phenyl which may be substituted with up to three groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, or 3,4-methylenedioxy

4 A compound according to claim 3, wherein

Ar_1 is phenyl, and

Ar_2 is phenyl optionally substituted with up to three groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, nitro, hydroxy, trifluoromethyl, or trifluoromethoxy

5 A compound according to claim 3, wherein.

Ar_1 is phenyl, and

Ar_2 is phenyl which may be substituted with up to three substituents independently selected from consisting of halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, nitro, hydroxy, trifluoromethyl, and trifluoromethoxy and is substituted by at least one member of the group consisting of mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and 3,4-methylenedioxy

6 A compound according to claim 3, wherein

R_1 is hydrogen or methyl,

Ar_1 is phenyl substituted with up to three substituents independently chosen from the group consisting of:

halogen, straight or branched chain alkyl having 1 – 7 carbon atoms, straight or branched chain alkyloxy having 1 – 7 carbon atoms, cyano, amino, alkylamino, dialkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is phenyl which may be substituted with up to three substituents independently chosen from the group consisting of:

fluorine, chlorine, bromine, iodine, straight or branched chain alkyl having 1 – 7 carbon atoms, straight or branched chain alkyloxy having 1 – 7 carbon atoms, cyano, amino, alkylamino, dialkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4-methylenedioxy

7 A compound according to claim 2, wherein.

R_1 is hydrogen or methyl,

Ar_1 is phenyl which may be additionally substituted with up to three substituents independently chosen from the group consisting of:

halogen, straight or branched chain alkyl having 1 – 7 carbon atoms, straight or branched chain alkyloxy having 1 – 7 carbon atoms, cyano, amino, alkylamino, dialkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is 1 or 2-naphthyl, indolyl, 2,3-dihydroindolyl, 1,2,3,4-tetrahydroquinolyl, benzimidazole, 1,4-benzodioxan-6-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, quinolyl, thiophene, benzo[b]thiophene, 2,3-dihydrobenzofuran or chromane which may be additionally substituted by up to four substituents independently chosen from the group consisting of:

fluorine, chlorine, bromine, iodine, straight or branched chain alkyl having 1 – 7 carbon atoms, straight or branched chain alkyloxy, having 1 – 7 carbon atoms, cyano, amino, alkylamino, dialkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, acetoxy, trifluoromethyl and trifluoromethoxy

8 A compound according to claim 7, wherein.

Ar_1 is phenyl.

9 A compound according to claim 7, wherein

Ar_1 is phenyl which is substituted with up to three substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy

10 A compound according to claim 1, wherein.

R_3 is hydrogen or methyl, and

R_4 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl

11 A compound according to claim 7, wherein.

Ar_1 is phenyl, and

Ar_2 is phenyl which may be substituted with up to four substituents independently selected from the group consisting of halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_7)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4- methylenedioxy

12 A compound according to claim 1, wherein.

R_3 is hydrogen or methyl, and

R_4 is arylalkyl wherein the aryl portion is substituted by up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy,trifluoromethyl, and trifluoromethoxy

13 A compound according to claim 12, wherein.

Ar_1 is phenyl substituted with up to three substituents independently selected from the group consisting of halogen, C_1-C_7 alkoxy, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

Ar_2 is phenyl substituted with up to three substituents independently selected from the group consisting of halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4-methylenedioxy

14. A compound according to claim 12, wherein.

Ar_1 is phenyl, and

Ar_2 is phenyl substituted with up to three substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, trifluoromethyl, trifluoromethoxy, and 3,4-methylenedioxy

15 A compound according to claim 12, wherein.

Ar_1 is phenyl, and

Ar_2 is 1 or 2-naphthyl, 1-, 2-, or 3-indolyl, 2,3-dihydroindolyl, 1,2,3,4-tetrahydroquinolyl, 1-, 2-, or 3-benzimidazole, 1,4-benzodioxan-6-yl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-quinolyl, 2- or 3-thienyl, 2- or 3-benzo[b]thiophenyl, 2- or 3-(2,3-dihydrobenzofuranyl) or 2-, 3-, or 4-chromanyl, each of which is optionally substituted by up to four substituents independently selected from halogen, C_1-C_7, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, nitro, hydroxy, acetoxy, trifluoromethyl and trifluoromethoxy

16 A compound according to claim 1, wherein Ar_1 is 2-thienyl or pyridyl.

17 A compound according to claim 1, which is

1-(1-Butyl)-2-phenyl-5-(N-3,4-methylenedioxyphenylmethyl]-N-[quinol-6-methyl]) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-3,4-methylenedioxyphenylmethyl]-N-[indan-2-yl]) aminomethylimidazole; or

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[{1-methyl indol-5-yl}methyl])aminomethylimidazole.

18 A compound according to claim 1, which is.

1-(1-Butyl)-2-(2-thienyl)-5-(N-[3,4-methylenedioxyphenyl]methyl-N-phenylmethyl] aminomethylimidazole.

19 A compound according to claim 1, which is

1-(1-Butyl)-2-phenyl-5-(N-[4-methoxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[1-(*S*)-phenylethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[1-(*R*)-phenylethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-phenylethyl]) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4,5-trimethoxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-phenylmethyl-N-[3,4-dimethoxyphenylmethyl])aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3-methyl -4-aminophenylmethyl]-N-phenylmethyl) aminomethylimidazole),

1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-difluorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole,

1-(1-Butyl)-2-phenyl-5-(N-[4-ethoxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-((N-[4-methoxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;

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1-(1-Butyl)-2-phenyl-5-(N-[3-methoxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole,

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-fluorophenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[2,6-dichlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[2-fluoro-6-chlorophenylmethyl]-N-phenylmethyl) aminomethylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-[2,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[4-chlorophenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[4-hydroxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[4-trifluoromethoxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-3,4-dimethoxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[4-nitrophenylmethyl]-N-phenylmethyl)aminomethyl imidazole, or

1-(1-Butyl)-2-phenyl-5-(N-[4-aminophenylmethyl]-N-phenylmethyl)aminomethyl imidazole.

20 A compound according to claim 1, which is

1-(1-Butyl)-2-phenyl-4-methyl-5-(N-[3,4-methylenedioxyphenyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)amino ethylimidazole;

1-(1-Butyl)-2-phenyl-5- (N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)amino methylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[4-methylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-[6-chloro-3,4-methylenedioxyphenylmethyl]-N-phenyl methyl)aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl) aminomethylimidazole, or

1-(1-Butyl)-2-phenyl-5-(N-[4-diethylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole

21 A compound according to Claim 1, which is

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole,

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-(2-methylphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole,

1-(1-Butyl)-2-(3-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-(3-fluorophenyl)-5-(1-[N-(4-hydroxy-2-chlorophenyl)methyl-N-phenylmethyl]amino)ethylimidazole,

1-(1-Butyl)-2-(4-fluorophenyl)-5-(1-[N-(3,4-methylenedioxyphenyl)methyl-N-phenylmethyl] amino)ethylimidazole;

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenyl methyl)aminomethylimidazole;

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenyl methyl)aminomethylimidazole;

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole; or

1-(1-Butyl)-2-(3-fluorophenyl)-5-(1-[N-{2-chloro-4-hydroxyphenylmethyl}-N-phenylmethyl] amino)ethylimidazole

22 A compound according to claim 1, which is

1-(1-Propyl)-2-phenyl-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)amino-methylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[indol-4-ylmethyl]-N-phenylethyl)aminomethylimidazole;

1-(1-Pentyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl)aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl)aminomethylimidazole;

1-(1-Propyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl)aminomethylimidazole;

1-(1-Pentyl)-2-phenyl-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)amino-methylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-(benzo[b]thiophen-5-ylmethyl)-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[pyridin-2-ylmethyl]-N-phenylmethyl)aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[pyridin-3-ylmethyl]-N-phenylmethyl)aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[pyridin-4-ylmethyl]-N-phenylmethyl)aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[2-aminopyridin-5-ylmethyl]-N-phenylmethyl)aminomethyl-imidazole, or

1-(1-Butyl)-2-phenyl-5-(N-[2,3-dihydrobenzo[b]furan-5-ylmethyl]-N-phenylmethyl) ammomethylimidazole.

23 A compound according to claim 1, which is

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[1,4-benzodioxan-6-yl]methyl-N-phenylmethyl)amino methylimidazole;

1-(1-Butyl)-2-(2-fluorophenyl)-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[naphtha-2-ylmethyl]-N-phenylmethyl)ammo-methylimidazole;

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[naphth-2-ylmethyl]-N-phenylmethyl)aminomethyl imidazole, and

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl) ammomethylimidazole.

24. A compound according to claim 1, which is

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-ethyl)aminomethyl-imidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-1-propyl)aminomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-butyl]) aminomethyl-imidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cycloheptylmethyl) ammonomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-isobutyl)ammomethyl-imidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-cyclopentylethyl) ammonomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3-cyclopentylpropyl]) ammonomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-n-octyl])ammo-methylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopropylmethyl) ammonomethylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopentylmethyl) ammonomethylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclohexylmethyl) ammonomethylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-t-amyl)ammonomethyl-imidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{3-methyl}butyl]) ammonomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{2,2-dimethyl}butyl) ammonomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-methyl)aminomethylimidazole,

1-(1-Butyl)-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl]) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-4-bromo-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl])aminomethylimidazole,

1-(1-Butyl)-2-phenyl-4-chloro-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole,

1-(1-Butyl)-2,4-diphenyl-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-[1-butyl])aminomethylimidazole, or

1-(1-Butyl)-2-phenyl-4-methyl-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole.

A compound according to claim 1, which is

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole;

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole;

1-(1-Butyl)-2-(2-methylphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])aminomethylimidazole;

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole,

1-(1-Butyl)-2-(4-fluorophenyl)-5-(1-N,N-di[3,4-methylenedioxyphenylmethyl]amino) ethylimidazole.

26 A compound according to claim 1, which is

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenyl]-methyl)ammomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) ammomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-methoxyphenyl-methyl]) ammomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyl}phenyl-methyl]) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenylethyl]) aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[4-nitrophenylmethyl]) ammomethylimidazole,

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyloxy} phenylmethyl])ammomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2,3-dichlorophenyl methyl])ammomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dimethylphenyl methyl])ammomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-thiophenylmethyl] aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[indol-5-ylmethyl] aminomethylimidazole;

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-hydroxy-2-chlorophenyl]methyl)aminomethylimidazole; or

1-Butyl-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2,3-dihydrobenzo[b] furan-5-yl]aminomethylimidazole.

27 A compound according to Claim 1, which is

1-(1-Butyl)2-(2-methoxyphenyl)-4-bromo-5-(N-[4-dimethylaminophenylmethyl]-N-phenyl)aminomethylimidazole.

28 A compound according to Claim 1, which is 2-{[5-({Butyl[(1-butyl-2,4-diphenylimidazol-5-yl)methyl]amino}methyl)-2-pyridyl]amino}ethan-1-ol

29 A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

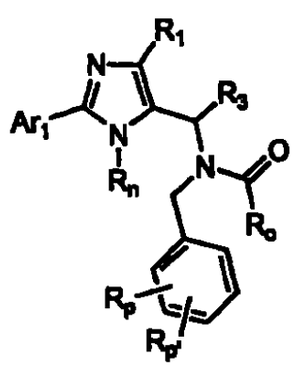
30 The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of autoimmune or inflammatory diseases

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31 The use of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, in the treatment of autoimmune or inflammatory disorders

32 A method of inhibiting leukocyte chemotaxis, which comprises contacting a compound of Claim 1 with white blood cells, wherein the compound is present in an amount effective to produce a concentration sufficient to inhibit chemotaxis of white blood cells in vitro.

33 A compound of the formula



where

R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 is hydrogen or C_1-C_7 alkyl,

Ar_1 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; or

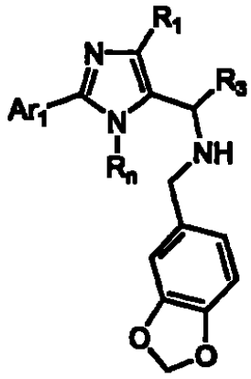
Ar_1 is 2-thienyl or pyridyl, each of which is optionally substituted with halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, or trifluoromethyl,

R_n is hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl,

R_n is C_1-C_8 alkyl, or phenyl or benzyl where the phenyl portion of each is optionally substituted with up to three four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; and

each R_p is hydrogen, halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy

34 A compound of the formula



wherein

R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 is hydrogen or C_1-C_7 alkyl,

Ar_1 is phenyl which may be substituted with up to four substituents independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy; or

Ar_1 is 2-thienyl or pyridyl, each of which is optionally substituted with halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, or trifluoromethyl, and

R_n is hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

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ARYL CYCLOALKYLIMIDAZOLES

BACKGROUND OF THE INVENTION

1 Field of the Invention

This invention relates to certain heterocyclic derivatives which when appropriately substituted, are modulators of human complement C5a receptors This invention also relates to pharmaceutical compositions comprising such compounds It further relates to the use of such compounds in treating a variety of inflammatory and immune system disorders Additionally, this invention relates to the use such compounds as probes for the localization of C5a receptors

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2 Description of Related Art

Inflammation is the normal physiological response to cellular injury - microbial infection, physical or chemical trauma, or invasion of cancerous cells While necessary to remove infectious particles and damaged tissue, inflammation can also cause pain and further tissue damage Pathogenic inflammation is associated with various diseases, and is a hallmark of autoimmune disease

Proteins of the complement cascade play a key role in the mediation of inflammation This system of more than 20 interacting soluble and membrane-bound proteins undergoes a series of proteolytic reactions that set in motion a number of important immune functions including the recruitment of leukocytic cells to sites of injury and/or infection Additionally, proteins of the complement system mediate changes in vascular permeability and blood flow, target cells for opsonization, and effect formation of the membrane attack complex, which mediates the immune lysis of foreign cells

C5a, a 74 amino acid peptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement enzyme C5 convertase The anaphylatoxic effects of the C5a peptide are mediated through the C5a receptor, a 52 kD membrane bound G-coupled protein receptor C5a is a potent chemoattractant for polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to the site of cellular injury Additionally, C5a stimulates the release of inflammatory mediators (e g , histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes, C5a also promotes the production of activated oxygen radicals and the contraction of smooth muscle

Considerable experimental evidence implicates increased levels of C5a in a number of autoimmune diseases and inflammatory and related disorders Such autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus, psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, and immunovasculitis Such inflammatory and related conditions include neutropenia, sepsis, septic shock, artherosclerosis, Alzheimer's disease, vascular occlusion, post-surgical vascular reocclusion, stroke, coronary thrombosis, and myocardial infarction lung injury, and acute respiratory distress syndrome (ARDS), tissue graft rejection, hyperacute rejection of transplanted organs, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephris and pulmonary hemorrhage), myasthenia gravis, pathologic sequellae associated with insulin-dependent diabetes mellitus, glomerulonephristis, ischemic heart disease, inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (e g , during hemodialysis or via a heart-lung machine, for example, in association with heart surgery such as coronary artery bypass grafting or heart valve replacement) such as extracorporeal post-dialysis syndrome or in association with contact with other artificial vessel or

container surfaces (e g , ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, and the like) Antagonists that block the binding of C5a to its receptor or which modulate signal transduction associated with C5a-receptor interactions can inhibit the pathogenic chemotaxis associated with such inflammatory and autoimmune conditions Indeed, certain modified C5a peptides have been identified as C5a antagonists and have been shown to block a number of C5a mediated actions including neutrophil chemotaxis, neutropenia and superoxide formation

SUMMARY OF THE INVENTION

The present invention provides novel substituted 1-alkyl-2-aryl-4,5-cycloalkylimidazoles The invention also provides novel compounds of Formula I, shown below, that bind specifically, and preferably with high affinity, to C5a receptors Preferred C5a receptors are mammalian receptors, including human C5a receptors and may either be cloned, recombinantly expressed receptors or naturally expressed receptors

Novel intermediates useful for synthesizing compounds of the invention are also provided

The invention also provides pharmaceutical compositions comprising compounds of Formula I The compounds are particularly useful in the treatment of C5a-mediated

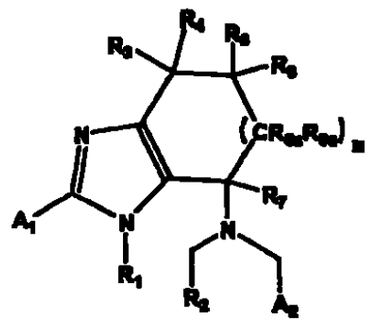
inflammation, e g , inflammation associated with various inflammatory and immune system disorders The invention further comprises a method of treating a patient in need of such anti-inflammatory treatment with a sufficient concentration of a compound of the invention A preferred concentration is one sufficient to inhibit white blood cell chemotaxis in vitro Treatment of humans, domesticated companion animals (pets) or livestock animals suffering such conditions with an effective amount of a compound of the invention is contemplated by the invention

In a separate aspect, the invention provides methods of using compounds of this invention as positive controls in assays for receptor activity and using appropriately labeled compounds of the invention as probes for the localization of receptors, particularly C5a receptors, in tissue sections

The invention provides compounds and compositions that are useful as inhibitors of C5a-mediated chemotaxis (e g , they may be used as standards in assays of such chemotaxis) The invention additionally comprises methods of inhibiting C5a-mediated chemotaxis, preferably leukocyte chemotaxis, the methods comprising contacting white blood cells with a chemotaxis-inhibitory concentration of a compound of the invention Preferably the concentration is sufficient to inhibit chemotaxis of white blood cells in an *in vitro* chemotaxis assay, so that the

levels of chemotaxis observed in a control assay (e g , one to which a compound of the invention has not been added) are significantly higher (significantly here measured as $p<0.05$ using a conventional parametric statistical analysis method) than the levels observed in an assay to which one or more compounds of the invention have been added

Accordingly, a broad embodiment of the invention is directed to compounds of Formula I



Formula I

or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl (i e cyclopentylmethyl), or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

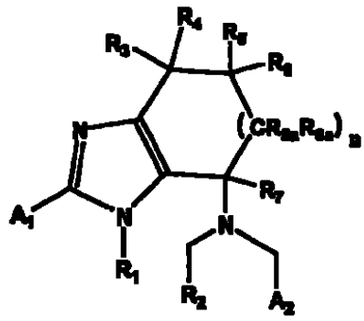
A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or

unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

DETAILED DESCRIPTION OF THE INVENTION

The invention provides novel compounds of Formula I, shown above that bind to specific cellular receptors. Preferably the receptors are cell surface receptors, more preferably G-protein coupled receptors, and most preferably the receptors are C5a receptors Preferred compounds of the invention are those of Formula IA



Formula IA

or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

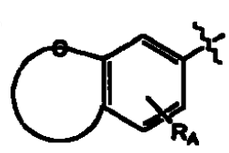
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each of which may be substituted or unsubstituted, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached may form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, alkyl, alkoxy, cyano, amino, mono- or dialkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-trifluoromethyl, trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined below, or

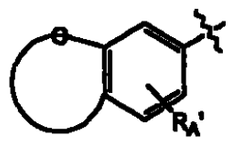
A_1 is thiophene or pyridine which is unsubstituted or may be substituted with alkyl, halogen, alkoxy, amino or mono or dialkylamino,

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from

halogen, alkyl, alkoxy, cyano, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-

pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy, or $-XR_B$, wherein X and R_B are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

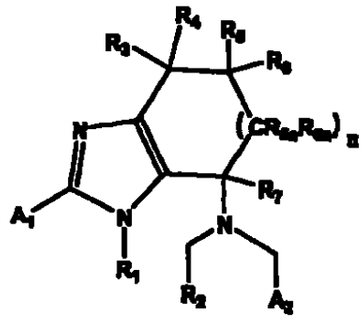
X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from

oxo, hydroxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl),

-N(alkyl)C(O)(alkyl), -NHS(O)$_x$(alkyl), -S(O)$_x$(alkyl), -S(O)$_x$NH(alkyl), -S(O)$_x$N(alkyl)(alkyl), (where x is 0, 1, or 2)

Also preferred are compounds of Formula IB:



Formula IB

or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl;

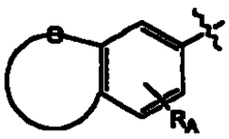
R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy,

halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group (i e an oxygen containing small ring such as furan, dioxolane, dioxane or the like, fused to phenyl) of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, and C_1-C_7 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_8$, wherein X and R_8 are as defined below, or

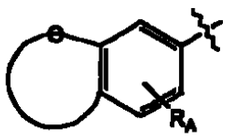
A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino; and

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-

azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_B$, wherein X and R_B are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NHC(O)(C_1$-C_4 alkyl),

-N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -NHS(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$NH(C_1-C_4 alkyl), -S(O)$_x$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

Particularly preferred compounds of Formula IB include those for which

R_3 and R_4 are the same or different and represent hydrogen or methyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl, and

n, R_1, R_2, R_7, A_1, and A_2 are as defined above for Formula IB

More preferred compounds of Formula IB include those wherein

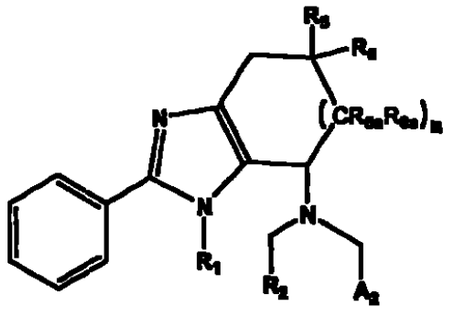
R_3 and R_4 hydrogen,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl, and

n, R_1, R_2, R_7, A_1, and A_2 are as defined above for Formula IB

Other preferred compounds of the invention are compounds of Formula II



Formula II

or a pharmaceutically acceptable salt thereof, wherein

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

R_1, R_2, A_2, and n are as defined above for Formula IB

Particularly preferred compounds of Formula II include those wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

R_2, A_2, and n are as defined above for Formula IB

Additional preferred compounds of Formula II include those wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

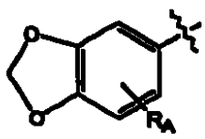
A_2, and n are as defined above for Formula IB

Yet more preferred compounds of Formula II include those wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is phenyl, which may be unsubstituted or substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

A_2 is phenyl which is unsubstituted or substituted with up to four groups independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined for Formula IB, above,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

n is as defined for Formula IB, above

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Preferred compounds of Formula II also include those wherein

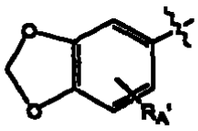
R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{6a} and R_{6a} are the same or different, and are independently selected at each occurrence from and hydrogen and methyl, and

A_2 is a bicyclic oxygen containing group of the formula

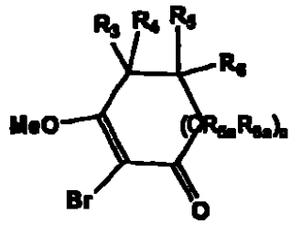


wherein R_A' is as defined above for Formula IB, and

n is as defined for Formula IB.

For all preferred compounds of the invention the pharmaceutically acceptable salts thereof are included as part of the invention

Also provided are novel intermediates useful for synthesizing compounds of the invention and methods of synthesizing compounds of the invention using such intermediates Specifically provided are compounds of Formula III



Formula III

wherein

n is an integer from 0 to 3,

R_3 and R_4 are the same or different and represent hydrogen or alkyl; or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkoxy, or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring, and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, hydroxy, halogen, alkoxy, and alkyl

Preferred compounds of Formula III are those where

n is an integer from 0 to 3,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms, and

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen and C_1-C_7 alkyl Such compounds are known as compounds of Formula IIIA

More preferred compounds of Formula III are those where

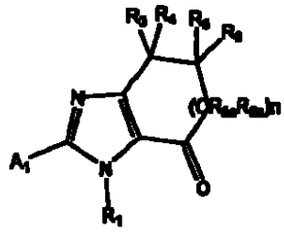
n is an integer from 0 to 3,

R_3 and R_4 are hydrogen, and

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurence represent hydrogen and methyl Such compounds are known as compounds of Formula IIIB

Also provided as intermediates are compounds of Formula IV



Formula IV

wherein

n is an integer from 0 to 3,

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl (i e cyclopentylmethyl), or haloalkyl, each of which may be substituted or unsubstituted,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, hydroxy, halogen, alkoxy or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, hydroxy, halogen, alkoxy and alkyl, and

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having

from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

Preferred intermediates of Formula IV include those compounds in which:

n is an integer from 0 to 3;

R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms, and

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen or C_1-C_7 alkyl, and

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_B$, wherein X and R_B are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

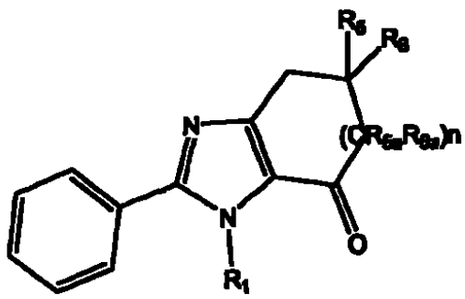
R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NHC(O)(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$C(O)(C_1$-C_4 alkyl), $-NHS(O)_x(C_1$-C_4 alkyl), $-S(O)_x(C_1$-C_4 alkyl), $-S(O)_xNH(C_1$-C_4 alkyl), $-S(O)_xN(C_1$-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1,

or 2)

Such compounds are known as compounds of Formula IVA

Especially preferred intermediates of Formula IV are compounds of Formula IVB



Formula IVB

wherein

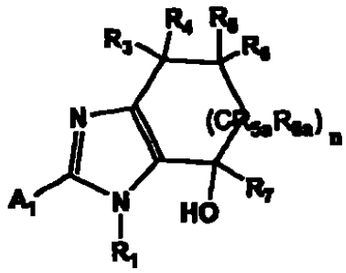
n is an integer from 0 to 3,

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and C_1-C_7 alkyl,

Other intermediates included in the invention are those of Formula V



Formula V

wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, hydroxy, halogen, alkoxy or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, hydroxy, halogen, alkoxy and alkyl;

R_7 represents hydrogen or alkyl, and

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

Preferred intermediates of Formula V include those compounds in which

n is an integer from 0 to 3,

R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and and are independently selected at each occurrence from hydrogen and C_1-C_7 alkyl;

R_7 represents hydrogen or alkyl, and

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or -XR_8, wherein X and R_8 are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_c-, -O-, -$S(O)_m$-, -NH-, -NR_c-, -C(=O)NH-, -$C(=O)NR_c$-, -$S(O)_mNH$-, -$S(O)_mNR_c$-, -NHC(=O)-, -$NR_cC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and -$NR_cS(O)_m$- (where m is 0, 1, or 2), and

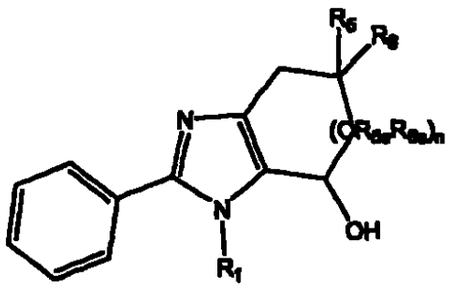
R_8 and R_c, which may be the same or different, are independently selected at each occurrence from the group consisting of

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, -O(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NHC(O)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)C(O)(C_1-C_4 alkyl), -NHS(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$(C_1-C_4 alkyl), -S(O)$_x$NH(C_1-C_4 alkyl), -S(O)$_x$N(C_1-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

Such compounds are known as compounds of Formula VA

Especially preferred intermediates of Formula V are compounds of Formula VB



Formula VB

wherein

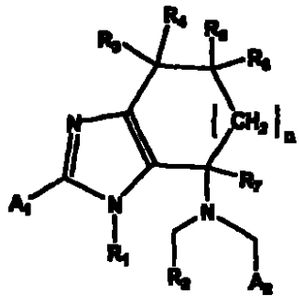
n is an integer from 0 to 3,

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

R_3 and R_4 are the same or different and represent hydrogen or methyl,

R_{3a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl

The invention also includes a process for preparing a compound of the formula



wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

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R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, alkoxy, or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, alkoxy, or alkyl,

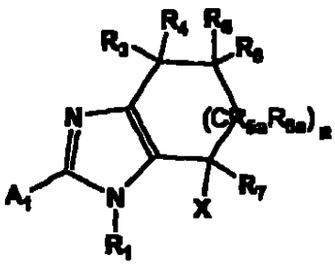
R_7 represents hydrogen or alkyl,

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

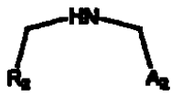
the process comprising

reacting a compound of the formula



wherein X is halogen or sulfonate ester,

in a suitable solvent in the presence of a suitable base with a secondary amine of the formula



Suitable solvents include dimethyl chloride, tetrahydrofuran, dimethylformamide and the like Suitable bases include potassium carbonate, triethylamine, N-methylmorpholine and the like Other suitable solvents and bases that may be used in this process will be readily apparent to those of ordinary skill in the art to which it pertains

In a preferred embodiment of the above process,

X is halogen or sulfonate ester,

and the variables n, A_1, A_2, R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are defined as follows

n is an integer from 0 to 3, and

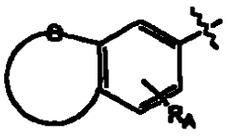
R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_6cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, and C_1-C_7 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

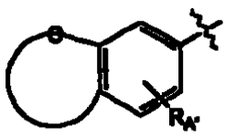
halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or

$-XR_8$, wherein X and R_8 are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino, and

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined below, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

$-NR_cC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_cS(O)_m-$ (where m is 0, 1, or 2), and

R_a and R_c, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from:

oxo, hydroxy, $-O(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)(C_1-C_4 alkyl), $-NHC(O)($ C_1-C_4 alkyl), $-N(C_1-C_4$ alkyl)$C(O)($ C_1-C_4 alkyl), $-NHS(O)_x(C_1-C_4$ alkyl), $-S(O)_x(C_1-C_4$ alkyl), $-S(O)_xNH(C_1-C_4$ alkyl), $-S(O)_xN(C_1-C_4$ alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

In certain situations, the compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms These compounds can be, for example, racemates or optically active forms In these situations, the single enantiomers, i e , optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates Resolution of the racemates can be accomplished, for example, by conventional methods such

as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds of Table 1 and their pharmaceutically acceptable salts Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0 - 4, and the like Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts

The present invention also encompasses the acylated prodrugs of the compounds of Formula I Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compound encompasses by Formula I

As indicated above, various substituents of the various formulae may be "substituted or unsubstituted", including A_1, A_2, R_1, and R_2 of Formula I, and such substituents as recited in the sub-formulae such as Formulae II and the like When substituted, those substituents (A_1, A_2, R_1, and R_2) may be substituted by other than hydrogen at one or more available positions, typically

1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein Suitable groups that may be present on a "substituted" A_1, A_2, R_1, and R_2 group or other substituent include e g halogen such as fluoro, chloro, bromo and iodo, cyano, hydroxyl, nitro; azido, alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like, carboxamido, alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms, alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, aryloxy such as phenoxy, alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, carbocyclic aryl having 6 or more carbons, particularly phenyl (e g an Ar group being a substituted or unsubstituted biphenyl

moiety), aralkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group, aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group, or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e g coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl

When "araalkyl" is specified in the present invention the point of attachment is the alkyl group

By the term "C_1-C_x alkyl" in the present invention is meant straight or branched chain alkyl groups having 1 to x carbon atoms, generally up to 6 or 7 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl Preferred C_1-C_6 alkyl groups are methyl, ethyl, propyl, butyl, pentyl and cyclopentyl

By the term "alkyloxy" is meant the group -O-R wherein R is alkyl as defined above

The term "C_1-C_x alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through

an oxygen bridge Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy

The term "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl

The term "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl

The term "Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl

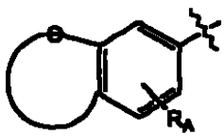
In the term "(C_{3-z} cycloalkyl)C_{1-y} alkyl the point of attachment is on the alkyl group This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl, cyclohexylmethyl

The term "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w =1 to (2v+1) Examples of haloalkyl include, but are not limited to,

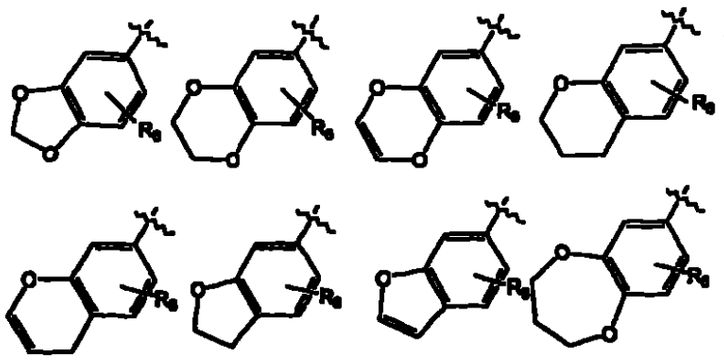
trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl

By the term "halogen" is meant fluorine, chlorine, bromine or iodine

Examples of bicyclic oxygen containing groups of the formula

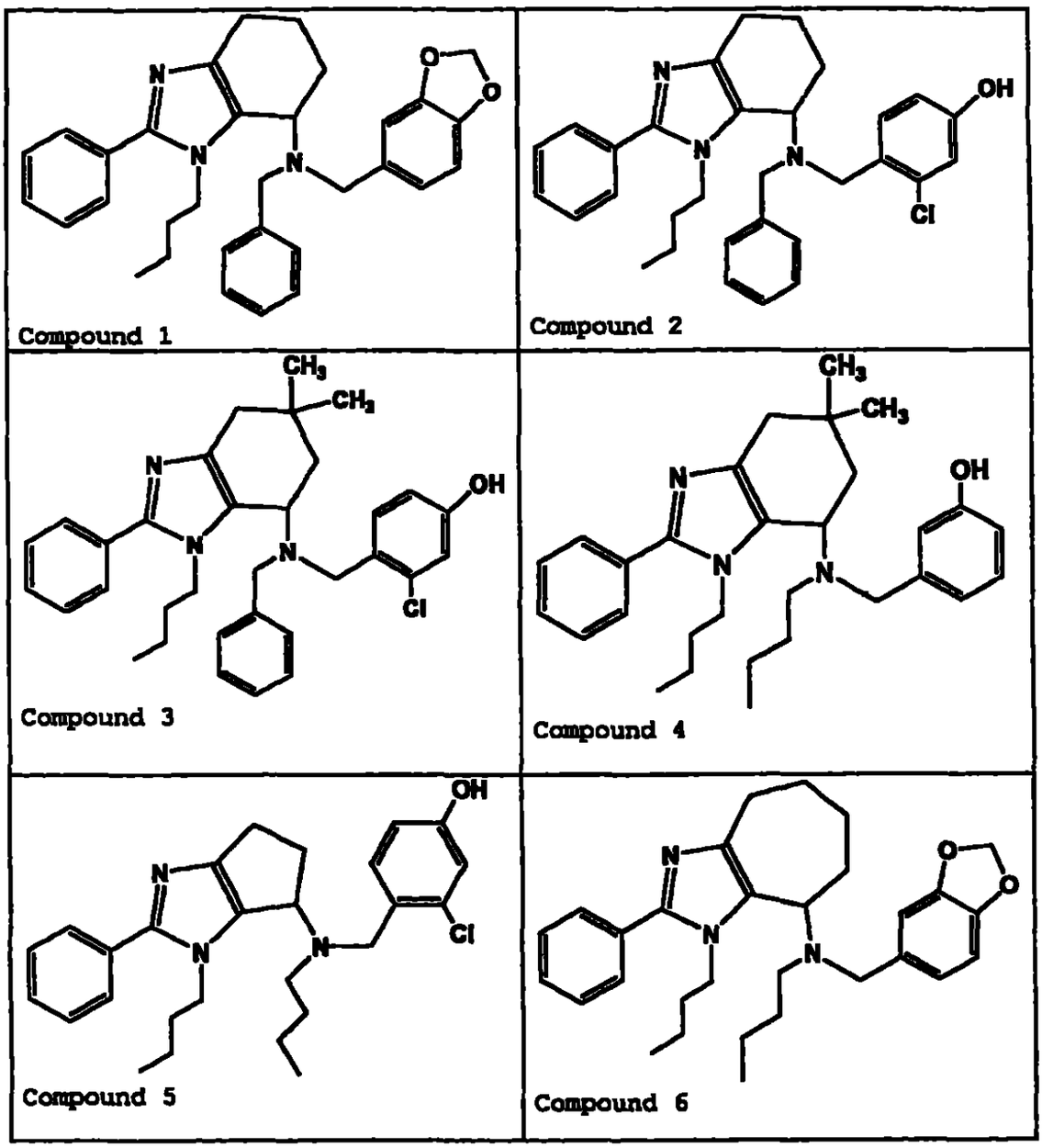


include the following



Representative compounds of the invention are shown in Table 1

1070
1014



The invention also includes methods for the treatment or prevention of various inflammatory and immune system disorders, such as for example rheumatoid arthritis and Crohn's disease, which comprises administering to a patient in need of such

1015

treatment a compound of the invention The interaction of compounds of the invention with C5a receptors is shown by the inhibition of C5a-mediated chemotaxis e g , as described in Example 5 While not wishing to be bound by any particular theory of operation, it is believed that this interaction results in the pharmacological activity of these compounds This invention includes compounds that inhibit C5a mediated chemotaxis Preferred compounds exhibit EC_{50} values of less than 1 μM in an assay of C5a mediated chemotaxis, more preferred compounds exhibit EC_{50} values of less than 500 nM, and most preferred compounds exhibit EC_{50} values of less than 250 nM

This invention also includes compounds that act as are selective modulators of G-coupled protein receptors, especially the C5a receptor Preferably, compounds of this invention do not bind to dopamine receptors Most preferably compounds of this invention do not exhibit binding constants less than 1 μM at dopamine receptors in a standard radioligand binding assay for dopamine binding activity (US patent no 5,159,083 is hereby incorporated by reference for its teachings in regard to such assays at col 8)

The present invention also pertains to methods of inhibiting the binding of C5a to C5a receptors which methods involve contacting a compound of the invention with cells expressing C5a receptors, wherein the compound is present at a concentration

sufficient to inhibit C5a binding to C5a receptors *in vitro*. This method includes inhibiting the binding of C5a to C5a receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of C5a to C5a receptors *in vitro*. In one embodiment, such methods are useful in treating physiological disorders associated with excess concentrations of C5a. The amount of a compound that would be sufficient to inhibit the binding of a C5a to the C5a receptor may be readily determined via a C5a receptor binding assay, or from the EC_{50} of a C5a receptor functional assay, such as the standard assay of C5a receptor mediated chemotaxis described in Example 5. The C5a receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of leukocytes or from cells expressing cloned human C5a receptors, e.g. human promonocytic U937 cells.

The present invention also pertains to methods for altering the activity of C5a receptors, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white blood cells *in vitro*. This method includes altering the activity of C5a receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the chemotactic responses to C5a of white blood cells *in vitro*. The amount of a compound that

would be sufficient to alter the chemotactic activity of C5a receptors may be determined via an assay of C5a receptor mediated chemotaxis, such as the standard assay described in Example 5

The C5a receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the C5a receptor

Labeled derivatives the C5a receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT)

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred The term parenteral as used herein includes injections and the like, such as subcutaneous, intradermal, intravascular (e g , intravenous), intramuscular, intrasternal, spinal, intrathecal, and like injection or infusion techniques, with subcutaneous, intramuscular and intravascular injections or infusions being preferred In addition, there is provided a pharmaceutical formulation comprising a compound of general

Formula I and a pharmaceutically acceptable carrier One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, corn starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc The tablets may be uncoated or they may be

coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene

sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present

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Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may

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be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides In addition, fatty acids such as oleic acid find use in the preparation of injectables

The compounds of general Formula I may also be administered in the form of suppositories e g , for rectal administration of the drug These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal tempefature and will therefore melt in the rectum to release the drug Such materials are cocoa butter and polyethylene glycols

Compounds of general Formula I may be administered parenterally, preferably in a sterile non-toxic, pyrogen-free medium The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle

Dosage levels of the order of from about 0 1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0 5 mg to about 7 g per patient per day) The amount of active ingredient

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that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient

Frequency of dosage may also vary depending on the compound used and the particular disease treated However, for treatment of most disorders, a dosage regimen of 4 times daily, three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i e , other drugs being administered to the patient), the severity of the particular disease undergoing therapy, and other factors, including the judgment of the prescribing medical practitioner

Preferred compounds of the invention will have favorable pharmacological properties Such properties include, but are not limited to bioavailability (e g , oral bioavailibilty), low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lifes Distribution in the body to sites of complement

activity is also desirable, e g , compounds to treat compounds used to treat CNS disorders will preferably penetrate the blood brain barrier, while low brain levels of compounds used to treat periphereal disorders are often preferred

Assays may be used to predict these desirable pharmacological properties Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers Toxicity to cultured hepatocyctes may be used to predict compound toxicity Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously

Serum protein binding may be predicted from albumin binding assays Such assays are described in a review by Oravcová, et al (Journal of Chromatography B (1996) volume 677, pages 1-27)

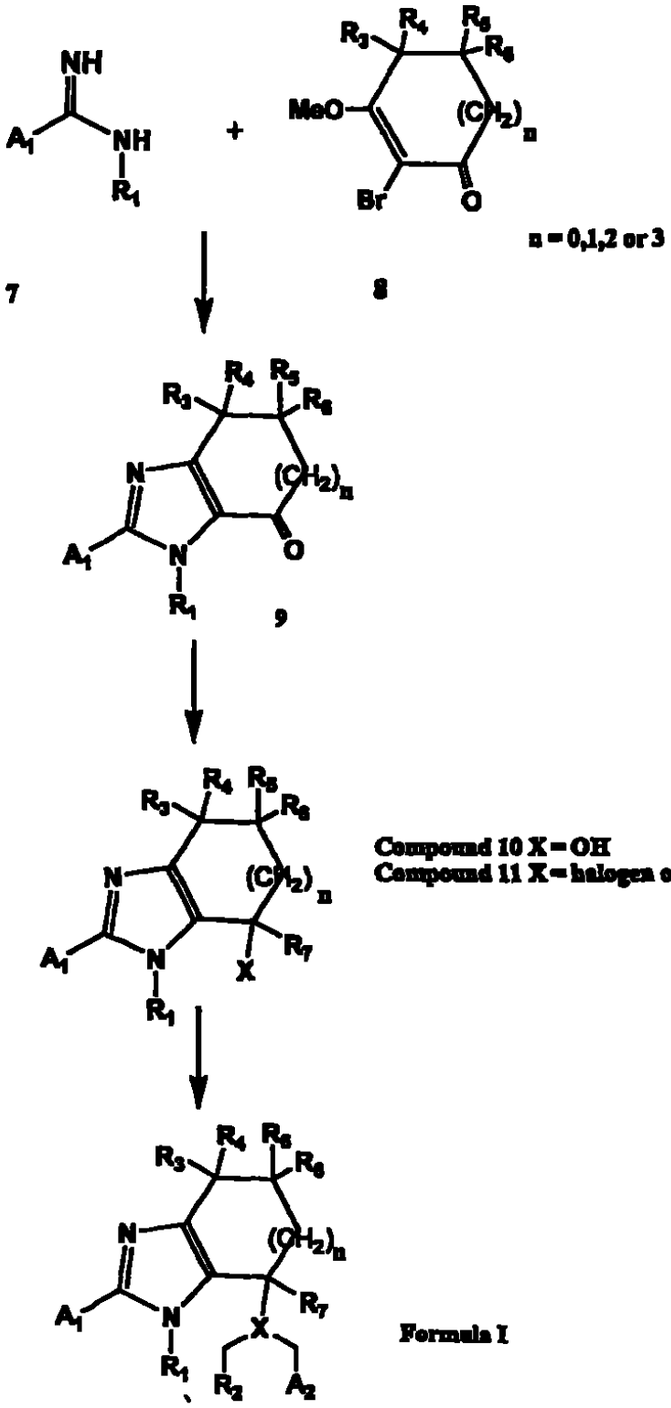
Compound half-life is inversely proportional to the frequency of dosage required for the effective administration of a compound *In vitro* half-lifes of compounds may be predicted, e g , from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127)

The present invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to C5a receptor modulation, e g , any of the inflammatory or

autoimmune disorders discussed above as the ``background of the invention'' including but not limited to arthritis, ARDS, and Alzheimer's Disease The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one C5a receptor modulator as described supra and instructions for its use for the treatment of a disorder responsive to C5a receptor modulation

An illustration of the preparation of compounds of the present invention is given in Scheme 1 Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention Within Scheme 1 the variables n, A_1, A_2, R_1, R_2, R_3, R_4 R_5, R_6 and R_7 are defined as previously described for Formula I

Scheme 1. Preparation of Compounds of Formula I



As shown in Scheme 1, an appropriately substituted arylamidine 7 is condensed with an appropriately substituted 2-halo-3-alkoxyenone 8 to provide a 2-aryl-4,5-cycloalkylimidazole 9 The ketone functionality of 9 can be either reduced (R_7 = H) or treated with the appropriate by treatment with the appropriate organometallic (for cases where R_7 is alkyl) to give the cyclic alcohol 10 Compounds of general formula 11 can be prepared from 10 by one of several methods described in the chemical literature, for instance, by treatment with thionyl chloride or by treatment with an alkyl or arylsulphonyl chloride in the presence of base

Compounds of formula 11 can then be transformed into compounds of general Formula I by direct treatment with the appropriate secondary amine Alternatively, the X functionality of 11 may be transformed into a tertiary amine in a stepwise manner In this case, 11 would be treated with a primary amine to provide an intermediate secondary amine This, in turn, could be alkylated to give compounds of general Formula I

Scheme 2 is a graphical representation of the preparation of a specific compound of this invention (Compound 5) according to the general route described graphically in Scheme 1 The preparation of Compound 5 and the subsequent demonstration of

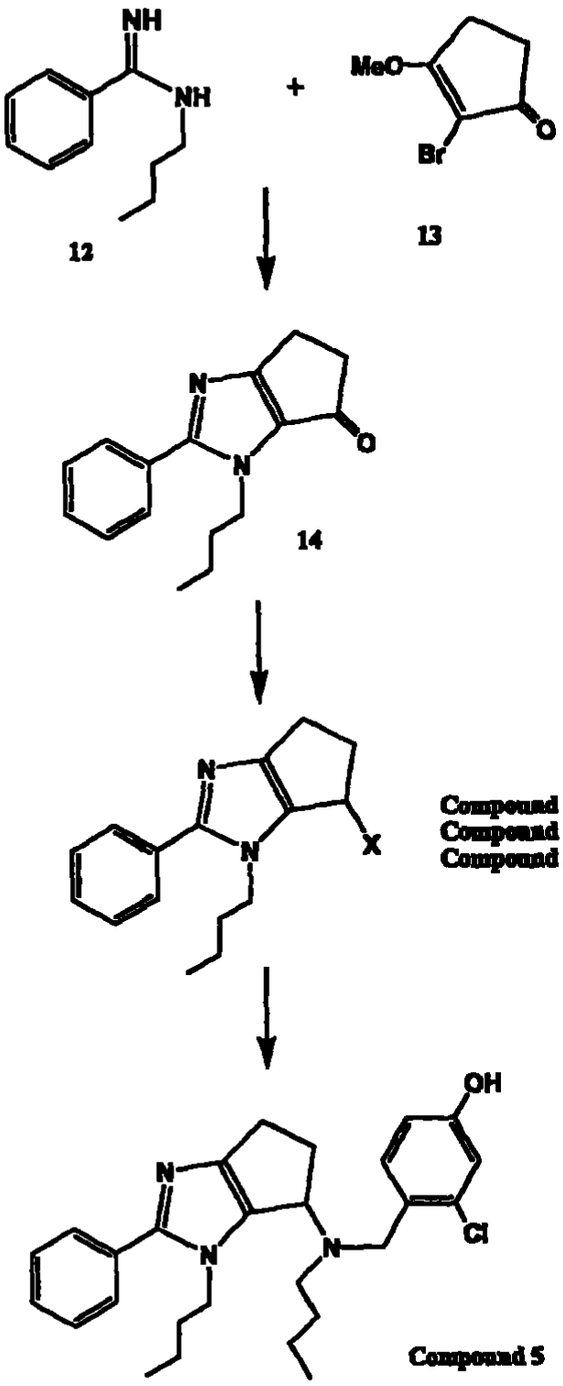
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its ability to inhibit C5a mediated chemotaxis represents a reduction to practice of the described invention

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Scheme 2. Preparation of Compound 5



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The invention is further illustrated by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them

EXAMPLE I

Preparation of 4-{[butyl{1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol (Compound 5, Table 1)

N-(n-butyl)-benzamidine (12) To a solution of methyl benzimidate hydrochloride (12 g, 0 07 mole) in dimethylformamide (DMF, 20 mL) was added 7 ml of triethylamine at 0 °C After 2 h the reaction was filtered to remove triethylamine hydrochloride To the filtrate was added 3 68 g of 1-butylamine and the mixture heated to 60 °C for 6 h After cooling the mixture was partitioned between ethyl acetate and water The organic layer was washed with brine, dried over sodium sulfate and concentrated to provide 13 28 g of the amidine as a yellow oil ^{1}H NMR ($CDCl_3$) 7 55 (m, 2H), 7 4 (m, 3H), 3 37 (bm, 2H), 1 62 (m, 2H), 1 42 (m, 2H), 0 95 (t, J = 7 Hz, 3H)

2-Bromo-3-methoxycyclopentenone (13) was prepared via the method of Curran et al JACS, vol 112, page 5601 To a suspension of 1,3-cyclopentanedione (10 g) in chloroform (700 ml) was added a N-bromosuccinimide (18 2 g). The mixture was refluxed for 2 h, cooled and concentrated Methanol (700 mL) and p-toluenesulfonic acid (1 g) were added and the solution was refluxed overnight The mixture was concentrated to 100 ml, diluted with methylene chloride (500 mL) and poured into water The aqueous layer was discarded and the organic layer was washed with water (3 X 100 mL), dried (Na_2SO_4) and concentrated The residue was crystallized from ethyl acetate to give 13 as tan crystals (1 67 g)

1-Butyl-2-phenyl-4,5-dihydrocyclopenty[1,2-d]imidazol-6-one (Compound 14, Scheme 2) To a mixture of amidine 12 (3 52 g, 20 mmol) and enone 13 (4.58 g, 24 mmol) in chloroform (40 mL) and water (5 mL) was added solid potassium carbonate (3 32 g, 24 mmol) The resulting mixture was refluxed overnight After cooling, the mixture was washed with water, dried (Na_2SO_4) and concentrated Purification on silica gel eluting with 25% ethyl acetate/hexane gave the desired product 14 (3 0 g)

LC-MS (M^++1) 255

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^{1}H-NMR (δ, $CDCl_3$) 0 84 (t, J = 7 6 Hz, 3H), 1 23 (dt, J = 7 0, 7 6 Hz, 2H), 1 81 (m, 2H), 2 95 (m, 4H), 4 13 (t, J = 7 6 Hz, 2H) 7 5-7 45 (m, 3H), 7.76-7 6 (m, 2H) ppm

1-Butyl-2-phenyl-4,5-dihydrocyclopenty[1,2-d]imidazol-6-ol (Compound 15, Scheme 2) To a solution of 14 (2 68 g) in methanol (20 mL) was added sodium borohydride (1 5 equiv) and the mixture stirred overnight The mixture was concentrated, diluted with chloroform and washed with 0 5 N NH_4Cl solution The organic layer was dried (Na_2SO_4) and concentrated to provide the desired product 15

LC-MS (M + 1) 257

Butyl(1-butyl-2-phenyl-4,5,6-trihydrocyclopentyl[3,2-d]imidazol-6-yl))amine (Compound 17, Scheme 2) Compound 15 (2 g) was dissolved in chloroform (20 mL) and thionyl chloride (5 mL) and the resulting solution was stirred at room temperature overnight The solvent and excess thionyl chloride was evaporated and the crude chloride 16 was dissolved in n-butylamine (10 mL) After 2 h, the excess butylamine was evaporated, the residue dissolved in ethyl acetate and the organic solution washed with 5% NaOH solution and water The organic layer was dried and concentrated The organic residue was purified by column

chromatography on silaica gel eluting with 10% CH_3OH in $CHCl_3$ to provide the desired secondary amine 17 in 82% yield.

LC-MS (M+1) 312

^{1}H-NMR (chemical shift, $CDCl_3$) 0 83 (t, J = 7 2 Hz, 3H), 0 9 (t, J = 7 2 Hz, 3H), 1 23 (q, J = 7 2 Hz, 2H), 1 35 (q, J = 7 2 Hz, 2H), 1 46 (m, 2H), 1 70 (m, 2H), 2 24 (m, 1H), 2 55-2 66 (m, 4H), 2 73-2 80 (m, 2H), 3 97-4 04 (m, 2H), 4 30 (d, J = 5 6 Hz, 1H), 7 37-7 44 (m, 3H), 7 55-7 57 (m, 2H)

4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol (Compound 5, Table 1) To a solution of compound 17 (50 mg) in 1,2-dichloroethane (2 mL) and 2-chloro-4-hydroxybenzaldehyde (30 mg) was added sodium triacetoxyborohydride (100 mg) The resulting mixture was allowed to stir overnight After washing with 0 5 ammonium chloride solution, the organic layer was dried (Na_2SO_4) and concentrated. Purification using preparative thin layer chromatography eluting with 5% $CH_3OH/CHCl_3$ provided the desired product 5 as an oil (21 mg)

LC-MS (M+1) 452, (M-1) 450

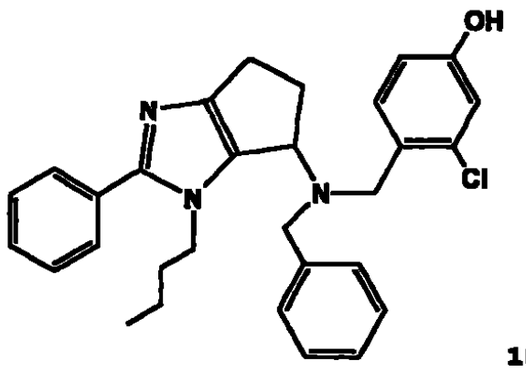
^{1}H-NMR (chemical shift, $CDCl_3$) 0 74 (t, J = 7 2 Hz, 3H), 0 83 (t, J = 7 2 Hz, 3H), 1 11 (q, J = 7 2 Hz, 2H), 1 21-1 33 (m, 2H), 1 41-1 51 (m, 4H), 2 34-2 44 (m, 3H), 2 51-2 57 (m, 1H), 2 60-2 67 (m, 1H), 2 69-2 75 (m, 1H), 3 38 (d, J = 7 6 Hz, 1H), 3 47

(d, J = 13 6 Hz, 1H), 3 65 (d, J = 13 6 Hz, 1H), 3 78-3 96 (m, 1H), 6 62 (dd, J = 8,2 Hz, 1H), 6 78 (d, J = 2 Hz, 1H), 7 07 (d, J = 8 Hz, 1H), 7 35-7 41 (m, 3H), 7 45-7 48 (m, 2H)

Example II

2-Aryl-4,5 cycloalkylimidazoles

The following compounds were prepared essentially according to the procedures described in Example I



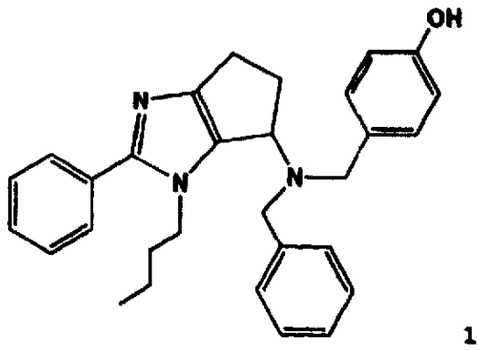
18

4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino]methyl}-3-chlorophenol (compound 18)

LC-MS (M^++1) 486 (M-1) 484

^{1}H-NMR (chemical shift, $CDCl_3$) 0 69 (t, J = 7 Hz, 3H), 1 02-1 08 (m, 2H), 1 32-1 40 (m, 2H), 2 38-2 43 (m, 1H), 2 63-2 69 (m, 2H), 2 75-2 80 (m, 1H), 3 21 (d, J = 13 6 Hz, 1H), 3 60 (s, 2H), 3 69-3 76 (m, 2H), 3 81-3 88 (m, 1H), 4 36 (d, J = 8 Hz, 1H), 6 61

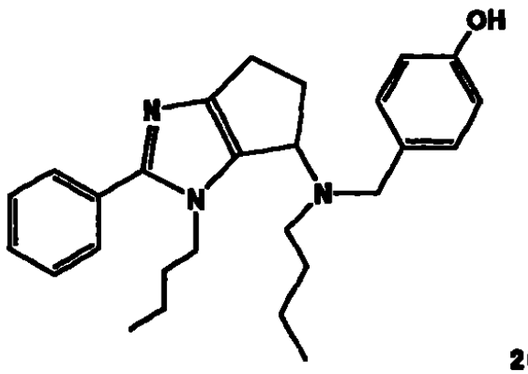
(dd, J = 8.8, 2.4 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 7.19-7.23 (m, 1H), 7.25-7.26 (m, 4H), 7.32-7.41 (m, 5H). ppm.



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4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino] methyl}phenol (compound 19)

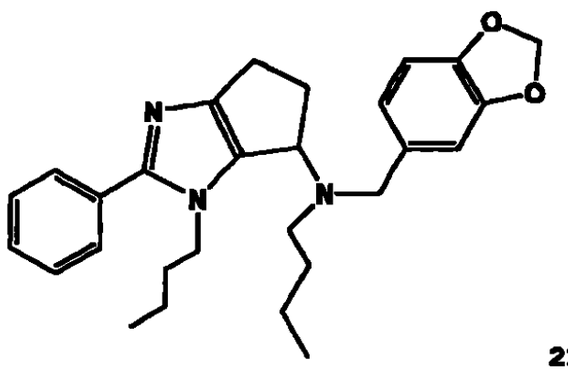
^{1}H-NMR (chemical shift, $CDCl_3$): 0.75 (t, J = 7 Hz, 3H), 1.12-1.16 (m, 2H), 1.43-1.51 (m, 2H), 2.34-2.43 (m, 1H), 2.59-2.69 (m, 2H), 2.75-2.79 (m, 1H), 3.30 (d, J = 13.6 Hz, 1H), 3.38 (d, J = 13.6 Hz, 1H), 3.65 (d, J = 13.6 Hz, 1H), 3.74 (d, J = 13.6 Hz, 1H), 3.81-3.96 (m, 1H), 4.42 (d, J = 7 Hz, 1H), 6.73 (d, J = 8 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.19-7.47 (m, 10H) ppm.



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4-({[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}phenol (Compound 20)

^{1}H-NMR (chemical shift, $CDCl_3$) 0 79 (t, J = 7 2 Hz, 3H), 0 84 (t, J = 7 2 Hz, 3H), 1 74 (q, J = 7 2 Hz, 2H), 1 30-1 38 (m, 2H), 1 43-1 58 (m, 4H), 2 31-2 40 (m, 2H), 2 43-2 53 (m, 2H), 2 60-2 73 (m, 2H), 3 26 (d, J = 13 6 Hz, 1H), 3 64 (d, J = 13 6 Hz, 1H), 3 79-3 95 (m, 2H), 4 42 (d, J = 8 Hz, 1H), 6 71 (d, J = 8 4 Hz, 1H), 6 77 (d, J = 8 4 Hz, 1H), 7 05 (d, 8 4 Hz, 1H), 7 15 (d, J = 8 4 Hz, 1H), 7 34-7 41 (m, 3H), 7 46-7 49 (m, 2H)

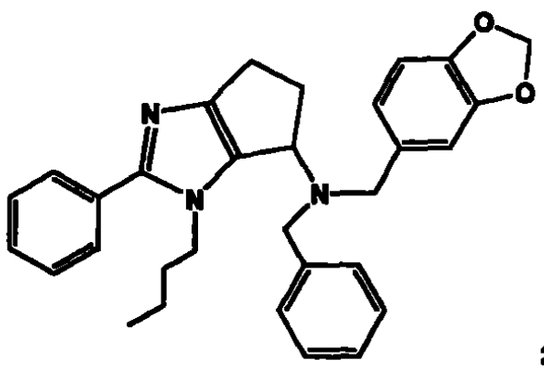


21

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))amine (Compound 21)

LC-MS (M^++1) 446

^{1}H-NMR (chemical shift, $CDCl_3$) 0 82 (t, J = 7 Hz, 3H), 0 85 (t, J = 7 2 Hz, 3H), 1 21-1 26 (m, 3H), 1 28-1 37 (m, 1H), 1 41-1 48 (m, 2H), 1 55-1 61 (m, 2H), 2 31-2 53 (m, 4H), 2 60-2 75 (m, 2H), 3 26 (d, J = 14 Hz, 1H), 3 67 (d, J = 13 5 Hz, 1H), 3 88-4 01 (m, 2H), 4 31 (dt, J = 7, 2 Hz, 1H), 5 90 (dd, J = 7, 2 Hz, 2H), 6 72 (s, 2H), 6 82 (s, 1H), 7.34-7 43(m, 3H), 7.52-7 55 (m, 2H)



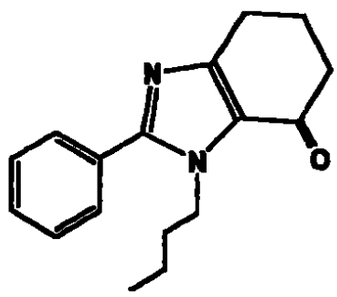
22

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))benzylamine (Compound 22)

LC-MS (M^++1) 480

^{1}H-NMR (chemical shift, $CDCl_3$) 0 79 (t, J = 7 Hz, 3H), 1 14-1 21 (m, 2H), 1 49-1 53 (m, 2H), 2 34-2 44 (m, 1H), 2 60-2 72 (m, 2H), 2 76-2 84 (m, 1H), 3 31 (d, J = 14 Hz, 1H), 3 37 (d, J = 13 6 Hz,

1H), 3 67 (d, J = 13 6 Hz, 1H), 3 76 (d, J = 14 Hz, 1H), 3 88-4 02 (m, 2H), 4 44 (dt, J = 7, 2 Hz, 1H), 5 92 (dd, J = 4, 2 Hz, 2H), 6 76 (s, 2H) 6.84 (d, J = 2 Hz, 1H), 7 22-7 42 (m, 8H), 7 48-7 52 (m, 2H)



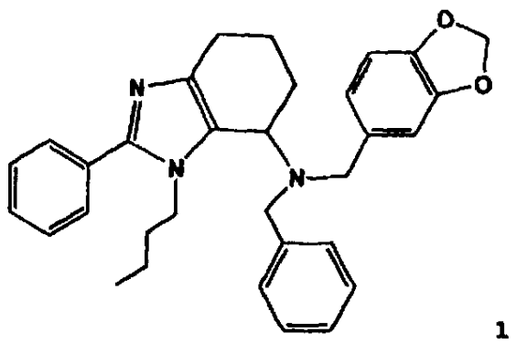
23

3-Butyl-2-phenyl-3, 5, 6, 7-tetrahydrobenzimidazol-4-one (Compound 23)

^{1}H-NMR (chemical shift, $CDCl_3$) 0 83(t, J = 7 2 Hz, 3H), 1 23 (q, J = 7 Hz, 2H), 1 66-1 74 (m, 2H), 2 14-2 20 (m, 2H), 2 54-2 57 (m, 2H), 2 87-2.92 (m, 2H), 4 29 (d, J = 8 Hz, 2H), 7 46-7 50 (m, 3H), 7 58-7 60 (m, 2H)

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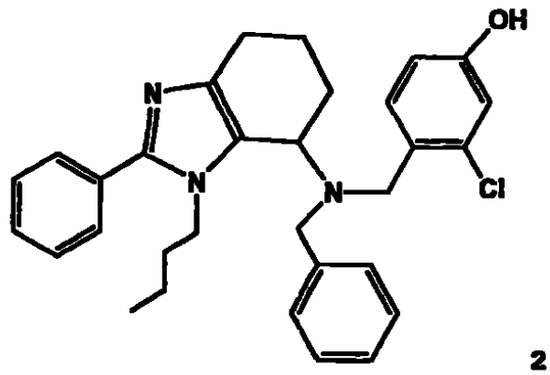
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(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(3-butyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl)}benzylamine

(Compound 1, Table 1)

LC-MS (M^++1): 494.

^{1}H-NMR (chemical shift, $CDCl_3$): 0.60 (t, J = 7 Hz, 3H), 0.80-0.90 (m, 2H), 1.03-1.13 (m, 2H), 1.83-1.87 (m, 1H), 1.93-1.99 (m, 1H), 2.20-2.27 (m, 1H), 2.56-2.62 (m, 1H), 2.69-2.76 (m, 1H), 3.38 (d, J = 13.2 Hz, 1H), 3.42 (d, J = 13.2 Hz, 1H), 3.78 (d, J = 12.8 Hz, 1H), 3.88 (d, J = 12.8 Hz, 1H), 3.95-4.07 (m, 2H), 4.47-4.54 (m, 1H), 5.29 (s, 1H), 5.92 (s, 2H), 6.73 (s, 2H), 6.75 (s, 1H), 7.24-7.44 (m, 8H), 7.52-7.54 (m, 2H).

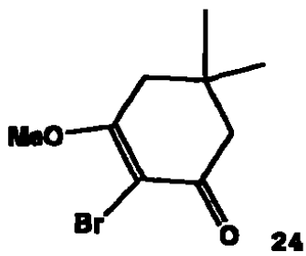


2

4-{[(3-Butyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazoly-4-yl))benzylamino]methyl}-3-chlorophenol (Compound 2, Table 1)

LC-MS (M^++1) 500, (M^+-1) 498

^{1}H-NMR (chemical shift, $CDCl_3$) 0 52 (t, J = 7 Hz, 3H), 0 68-0 76 (m, 2H), 1 01-1 14 (m, 2H), 1 67-1 72 (m, 1H), 1 88-2 00 (m, 2H), 2 53-2 82 (m, 2H), 3 46-3 49 (m, 1H), 3 65-3 74 (m, 2H), 3 79-4 02 (m, 4H), 4 40-4 46 (m, 1H), 6 58 (dd, J = 12, 3 Hz, 1H), 6 74 (d, J = 3 Hz, 1H), 6 98 (d, J = 12 Hz, 1H), 7 24-7 44 (m, 8H), 7 54-7.58 (m, 2H)

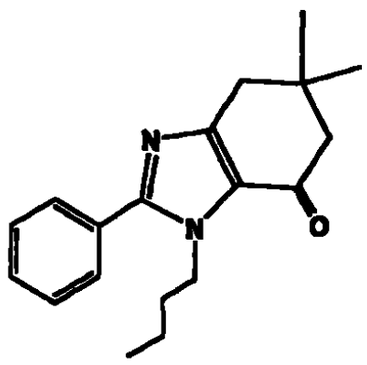


24

2-Bromo-3-methoxy-5,5-dimethylcyclohex-2-en-1-one (Compound 24)

LC-MS (M+1) 234 8,

^{1}H-NMR (chemical shift, $CDCl_3$) 1 14 (6H, s), 2 42 (2H, s), 2 57 (2H, s), 3 95 (3H, s)

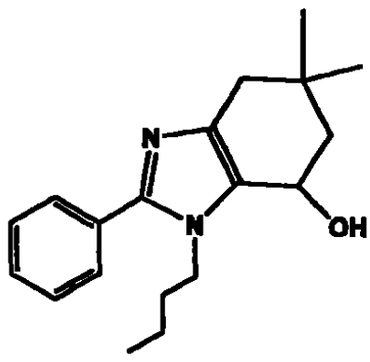


25

3-Butyl-6,6-dimethyl-2-phenyl-3,5,6,7-tetrahydrobenzimidazol-4-one (Compound 25)

LC-MS (M+1) 297 3,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 82 (3H, t, J = 7 6 Hz), 1 16 (6H, s), 1 21 (2H, m, J = 7 6 Hz), 2 42 (2H, s), 2 77 (2H, s), 4 29 (2H, t, J = 7 6 Hz), 7 45-7 50 (3H, m), 7 57-7 61 (2H, m) ppm



26

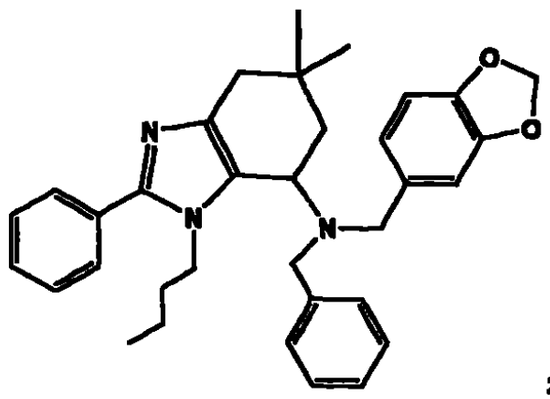
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3-Butyl-6,6-dimethyl-2-phenyl-3,4,5,6,7-pentahydrobenzimidazol-4-ol (Compound 26)

LC-MS (M+1) 299 3

^{1}H-NMR (chemical shift, $CDCl_3$) 0 76 (3H, t, J = 7 2 Hz), 0 92 (3H, s), 1 07 (3H, s), 1 12 (2H, m, J = 7 2 Hz), 1 58 (3H, m), 1 86 (1H, dd, J = 13 2, 6 8 Hz), 2 34 (1H, d, J = 16 Hz), 2 47 (1H, d, J = 16 Hz), 3 96 (1H, m), 4 20 (1H, m), 4 81 (1H, t, J = 6 8 Hz), 7 35-7.42 (3H, m), 7 49-7 52 (2H, m) ppm

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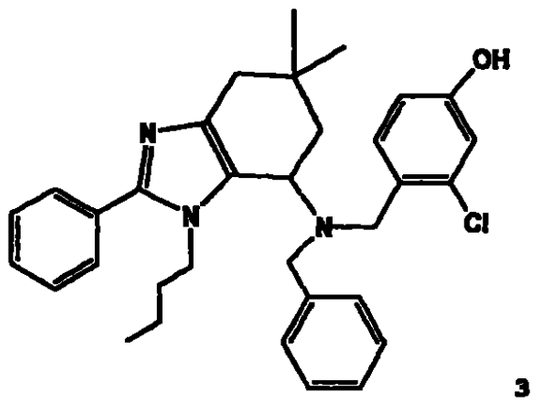


27

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2H-benzo[3,4-d]1,3-dioxolan-5-ylmethyl)benzylamine (Compound 27)

LC-MS (M+1) 522 4,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 58 (3H, m), 0 81 (5H, m), 0 98-1 20 (5H, m), 1 68-1 84(2H, m), 2 38 (1H, d, J = 16 Hz), 2 55 (1H, d, J = 16 Hz), 3 26-3 49 (2H, m), 3 67-3 80 (2H, m), 3 96-4 10 (2H, m), 4 70 (1H, br), 5 93 (2H, br), 6 76 (3H, m), 7 24-7 43 (8H, m), 7 53 (2H, d, J = 6 8 Hz) ppm

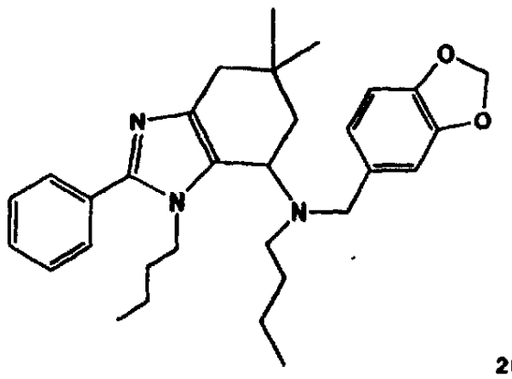


3

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4-hydroxybenzyl)benzylamine (Compound 3, Table 1)

LC-MS (M+1) 528 4,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 49-1 26 (11H, m), 1 76-2 50 (6H, m), 3 33-4 69 (7H, m), 6 30-6 76 (3H, m), 7 09-7 45 (10H, m) ppm

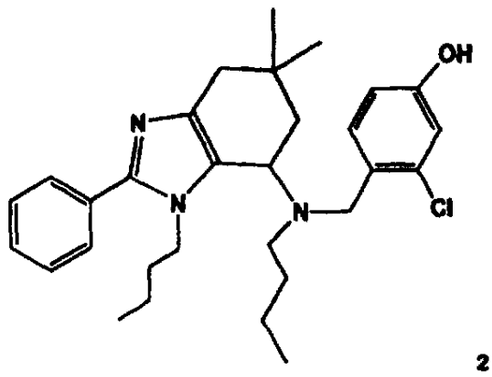


28

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2H-benzo[d]1,3-dioxolen-5-ylmethyl)butylamine (Compound 28):

LC-MS (M+1): 488.5;

^{1}H-NMR (chemical shift, $CDCl_3$): 0.60-1.14 (14H, m), 1.23-1.33 (2H, m), 1.34-1.57 (3H, m), 1.71-1.82 (2H, m), 2.21-2.54 (4H, m), 3.17-4.81 (6H, m), 5.93 (2H, m), 6.5-6.88 (3H, m), 7.34-7.43 (3H, m), 7.53 (2H, d, J = 7.2 Hz) ppm.

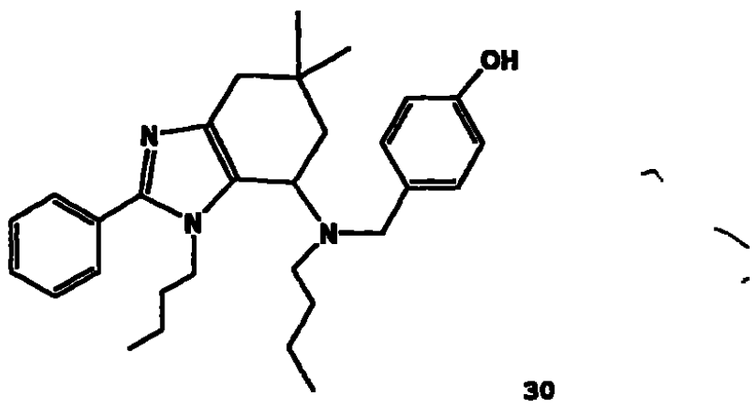


29

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4-hydroxybenzyl)butylamine (Compound 29):

LC-MS (M+1) 494 5

^{1}H-NMR (chemical shift, $CDCl_3$) 0 48-0 92 (11H, m), 1 10 (3H, m), 1 24-1 34 (3H, m), 1 55 (3H, m), 1 85 (1H, m), 2 30-2 65 (4H, m), 3 56-4 19 (5H, m), 4 68 (1H, m, J = 7 2 Hz), 6 43-7 13 (3H, m), 7 35 (3H, m), 7 46 (2H, m) ppm

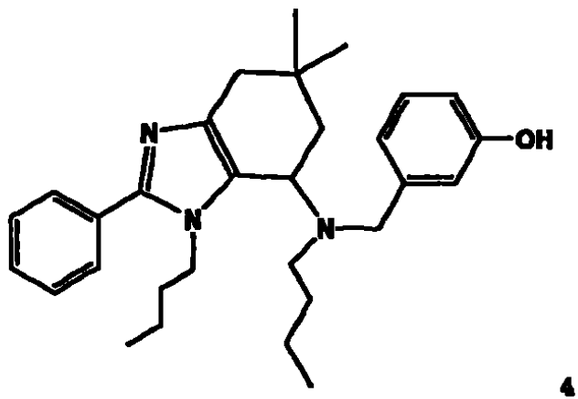


30

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(4- hydroxybenzyl)butylamine (Compound 30)

LC-MS (M+1) 460 5;

^{1}H-NMR (chemical shift, $CDCl_3$) 0 57-1 11 (14H, m), 1 25-1 69 (7H, m), 2 24-2 57 (4H, m), 3 20-4 78 (6H, m), 6 66-6 76 (2H, m), 6 94 (1H, m), 7 16 (1H, m), 7 36 (3H, m), 7 49 (2H, m) ppm

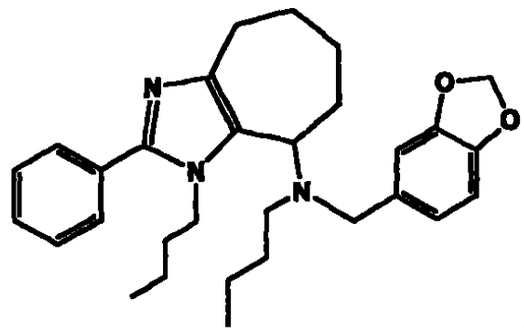


4

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(3-hydroxybenzyl)butylamine (Compound 4, Table 1)

LC-MS (M+1) 460 7,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 53-1 13 (14H, m), 1 25-1 74 (7H, m), 2 22-2 56 (4H, m), 3 09-4 78 (6H, m), 6 49-6 84 (3H, m), 7 06 (1H, t, J = 7 6 Hz), 7 34 (3H, m), 7 47 (2H, m) ppm



6

(1-Butyl-2-phenyl-4,5,6,7,8-pentahydrocyclohepta[3,2-d]imidazol-8-yl)(2H-benzo[d]1,3-dioxolen-5-ylmethyl)butylamine (Compound 6, Table 1)

LC-MS (M+1) 474 5,

^{1}H-NMR (chemical shift, $CDCl_3$) 0 73 (3H, t, J = 7 6 Hz), 0 79 (3H, t, J = 7 6 Hz), 1 02 (2H, m), 1 15 (2H, m), 1 25-1 48 (6H, m), 1 72 (2H, m), 1 89 (2H, m), 2 48-2 63 (2H, m), 2 89 (2H, br), 3 42 (1H, d, J = 13 2 Hz), 3 73 (1H, d, J = 13 2 Hz), 3 83-3 91 (1H, m), 3 95 (1H, m), 4 17 (1H, m), 5 92 (2H, s), 6 68-6 75 (3H, m), 7 38-7 44 (3H, m), 7 52 (2H, d, J = 8 0 Hz) ppm

Example 3

Assay for C5a Receptor Mediated Chemotaxis

This assay is a standard assay of C5a receptor mediated chemotaxis

Human promonocytic U937 cells are treated with dibutyryl cAMP for 48 hours prior to performing the assay The cells are pelleted and resuspended in culture media containing 0 1% fetal bovine serum (FBS) and 10 ug/ml calcein AM (a fluorescent dye) This suspension is then incubated at 37 °C for 30 minutes such that the cells take up the fluorescent dye The suspension is then centrifuged briefly to pellet the cells, which are then resuspended in culture media containing 0 1% FBS at a concentration of approximately 3 x 10^6 cells/mL. Aliquots of this cell suspension are transferred to clean test tubes, which contain vehicle (1% DMSO) or varying concentrations of a compound of interest, and incubated at room temperature for at least 30 minutes The chemotaxis assay is performed in ChemoTx 101-8, 96

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well plates The bottom wells of the plate are filled with varying concentrations of human C5a (0-10 nM) The top wells of the plate are filled with cell suspensions (compound or vehicle-treated) The plate is then placed in a tissue culture incubator for 60 minutes The top surface of the plate is washed with PBS to remove excess cell suspension The number of cells that have migrated into the bottom well is then determined using a fluorescence reader Chemotaxis index (the ratio of migrated cells to total number of cells loaded) is then calculated for each compound concentration to determine an EC_{50} value

As a control to insure that cells retain chemotactic ability in the presence of the compound of interest, the bottom wells of the plate may be filled with varying concentrations chemoattractants that do not mediate chemotaxis via the C5a receptor, e g zymosan-activated serum (ZAS), N-formylmethionyl-leucyl-phenylalanine (FMLP) or leukotriene B4(LTB4)

Compounds of the accompanying Examples exhibit EC_{50} values of less than 1 μM in the above assay for C5a mediated chemotaxis Data is shown for several representative compounds of this invention in Table 2

TABLE 2	
Compound Number	EC_{50}
1	642 nM
2	22 nM
5	450 nM
6	148 nM

Example 4
Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I) Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds Such suppliers include Amersham Corporation, Arlington Heights, IL, Cambridge Isotope Laboratories, Inc Andover, MA, SRI International, Menlo Park, CA, Wizard Laboratories, West Sacramento, CA, ChemSyn Laboratories, Lexena, KS, American Radiolabeled Chemicals, Inc , St Louis, MO, and Moravek Biochemicals Inc , Brea, CA

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Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate

Example 5

Use of compounds of the invention as probes for C5a receptors in cultured cells and tissue samples

Receptor autoradiography (receptor mapping) of NK-3 receptors in cultured cells or tissue samples is carried out in vitro as described by Kuhar in sections 8 1 1 to 8 1 9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference

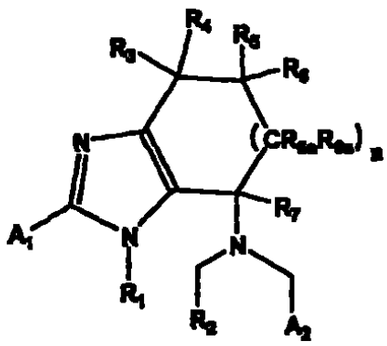
The invention and the manner and process of making and using it are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims To particularly point out and distinctly claim the subject matter regarded as the invention, the following claims conclude the specification

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What is claimed is

1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

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R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring;

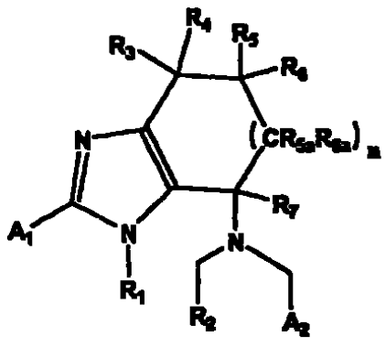
R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

2 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

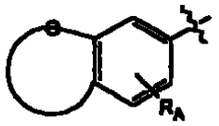
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each of which may be substituted or unsubstituted, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



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wherein R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached may form a cycloalkyl ring,

R_{5a} and R_{5b} are the same or different and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy,

R_7 represents hydrogen or alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

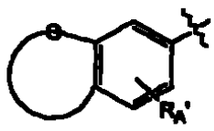
halogen, alkyl, alkoxy, cyano, amino, mono- or dialkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-trifluoromethyl, trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined below, or

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A_1 is thiophene or pyridine which is unsubstituted or may be substituted with alkyl, halogen, alkoxy, amino or mono or dialkylamino,

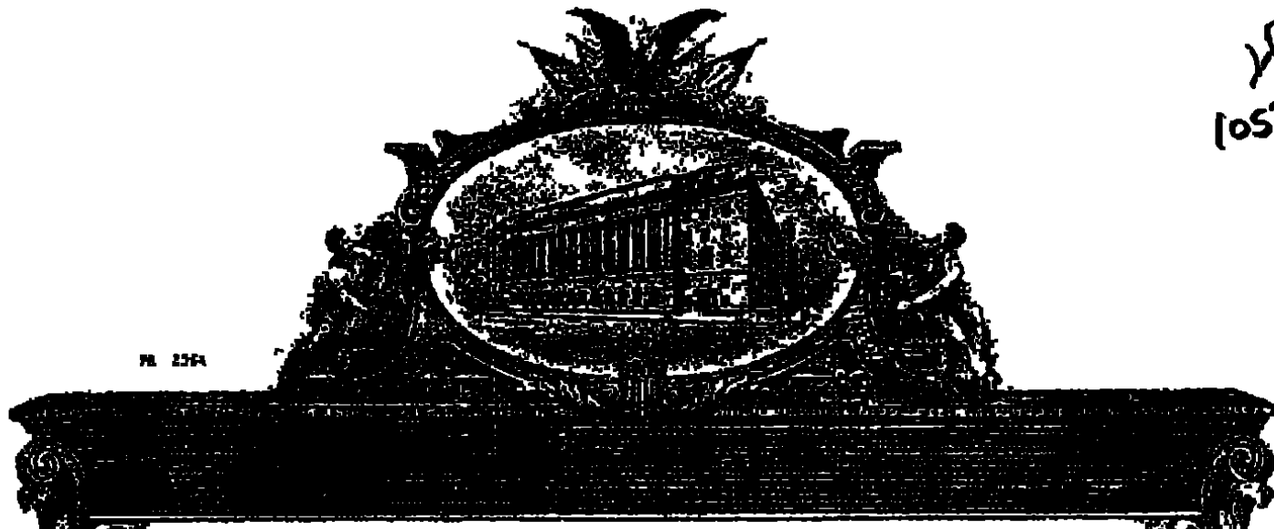
A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from halogen, alkyl, alkoxy, cyano, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy, or $-XR_a$, wherein X and R_a are as defined below, or

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

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LOS ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS A QUIENES LA PRESENTE CONCIERNE
DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

26 de diciembre de 2000

LA PRESENTE ES PARA CERTIFICAR QUE LA ANEXA A ESTA ES UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA MAS ADELANTE QUE SATISFACEN LOS REQUISITOS PARA QUE SE OTORGUE UNA FECHA DE PRIORIDAD BAJO 35 USC 111..

SOLICITUD NUMERO 60/224,036

FECHA DE PRESENTACION *9 de agosto de 2000*



Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS

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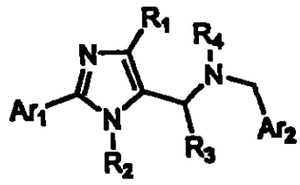
PARTE (1) DE (2) PARTES **E BORNETT**

Funcionario Certificador

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REIVINDICACIONES

1 Un compuesto de fórmula



o una sal farmacéuticamente aceptable de la misma, donde

R_1 es hidrógeno, C_1-C_7alquilo, halógeno o fenilo opcionalmente substituido con C_1-C_6alquilo, C_1-C_6alcoxi, halógeno, hidroxi, amino, o mono- o di (C_1-C_6)alquilamino,

R_2 es C_1-C_8alquilo o C_3-C_8cicloalquilo,

R_3 es hidrógeno o C_1-C_7 alquilo,

R_4 es C_1-C_8 alquilo o C_3-C_8 cicloalquilo, o

R_4 es arilalquilo donde el grupo arilo es fenil, 2-,3-, o 4-pirimidinilo, 2-o 3-dihidrobenzofuranilo, 2-,3-, o 4-cromanilo, 2-,4-,5-,6-,o 7-benzodioxanilo o 1-,2-, o 3-indolilo, cada uno de los cuales puede estar substituido hasta por cuatro grupos independientemente seleccionados de halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono o di(C1-C6)alquilamino, hidroxi, acetoxi, 3,4 metilendioxi, trifluorometil y trifluorometoxi, o

Ar_1 es fenilo el cual puede estar substituido con hasta cuatro substituyentes independientemente seleccionados de halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono-o di (C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometil, y trifluorometoxi, o

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Ar_1 es 2-tienilo o piridilo, cada uno de los cuales puede estar substituido con halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono o di(C_1-C_6)alquilamino, o trifluorometil,

Ar_2 es fenilo el cual puede estar substituido hasta por cuatro substituyentes independientemente seleccionados de halógeno, C_1-C_7 alquilo, C_1-C_7alcoxi, ciano, amino, mono- o di (C_1-C_6)alquilamino, 1-acetidinilo, 1-pirolidinilo,1-piperidilo, nitro, hidroxi, trifluorometilo, trifluorometoxi, y 3,4 metilendioxi, o

Ar_3 es 1 o 2 naftilo, 1,2,o 3-indolilo, 2,3-dihidroindolilo, 1,2,3,4-tetrahidroquinolilo, 1-o2-bencimidazolilo, 1-4benzodioxano-6ilo, 2-,3-, o4-piridilo, quinolilo, 2-o-tienilo, 2-o-3-benzo[b]tiofenilo, 2,3-dihidrobenzofuranilo o 2-,3-,o 4-cromanilo, cada uno de los cuales puede estar substituido hasta por cuatro grupos seleccionados independientemente de halógeno, C_1-C alquilo, C_1-C_7 alcoxi, ciano, amino, mono- o di(C_1-C_6)alquilamino, 1-acetidinilo, 1-pirolidinilo, 1-piperidilo, nitro, hidroxi, acetoxi, trifluorometilo, trifluorometoxi

2 Un compuesto de acuerdo a la reivindicación 1, donde R_3 es hidrógeno o metilo y R_4 es bencilo o feniletilo

3 Un compuesto de acuerdo a la reivindicación 2, donde

R_1 es hidrógeno o metilo,

Ar_1 es fenilo opcionalmente substituido hasta con tres grupos seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_6alcoxi, ciano, amino, mono o di(C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi, y

Ar_2 es fenilo el cual puede estar sustituido hasta con tres grupos independientemente seleccionados de halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono- o di(C_1-C_6)alquilamino, 1-acetidinilo, 1-pirrolidinilo, 1-piperidinilo, nitro, hidroxi,trifluorometilo, trifluorometoxi o 3,4-metilendioxi

4 Un compuesto de acuerdo a la reivindicación 3, donde

Ar_1 es fenilo, y

Ar_2 es fenilo opcionalmente sustituido hasta con tres grupos seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7alcoxi, ciano, amino, nitro, hidroxi, trifluorometilo, o trifluorometoxi

5 Un compuesto de acuerdo a la reivindicación 3, donde

Ar_1 es fenilo, y Ar_2 es fenilo el cual puede ser substituido hasta por tres substituyentes seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7alcoxi, ciano, amino, nitro, hidroxi, trifluorometilo, y trifluorometoxi y es substituidos por al menos un miembro del grupo que consiste de mono-o di(C_1-C_6)alquilamino, 1-acetidinilo, 1-pirolidinilo, 1-piperidinilo, 1-piperidilo y 3,4-metilendioxi

6 Un compuesto de acuerdo con la reivindicación 3, donde

R_1 es hidrógeno o metilo,

Ar_1 es fenilo sustituido hasta con tres sustituyentes seleccionados independientemente de un grupo consistente de

Halógeno, una cadena larga o ramificada de alquilo que tienen de 1 a 7 átomos de carbono, una cadena larga o ramificada de alquiloxi que tiene

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1 a 7 átomos de carbono, ciano, amino, alquilamino, dialquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo y trifluorometoxi, y

Ar_2 es fenilo el cual puede estar sustituido hasta con tres sustituyentes seleccionados independientemente del grupo que consiste de

Flúor, cloro, bromo, yodo, una cadena larga o ramificada de alquilo que tiene de 1 a 7 átomos de carbono, una cadena larga y ramificada de alquiloxi que tiene 1 a 7 átomos de carbono, ciano, amino, alquilamino, dialquilamino, 1-acetidinilo, 1-pirolidinilo, 1-piperidilo, nitro, hidoxi, trifluorometilo, trifluorometoxi y 3,4-metilendioxi

7 Un compuesto de acuerdo a la reivindicación 2, donde

R_1 es hidrógeno o metilo

Ar_1 es fenilo, el cual puede ser adicionalmente sustituido hasta con tres sustituyentes seleccionados independientemente del grupo consistente de

Halógeno, un alquilo de cadana larga o ramificada que tiene 1 a 7 carbonos, una cadena larga o ramificada de alquiloxi que tiene 1 a 7 átomos de carbono, ciano, amino, alquilamino, dialquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo y trifluorometoxi, y

Ar_2 es 1 o 2-naftilo, indolilo, 2,3-dihidroindolilo, 1,2,3,4-tetrahidroquinolilo, bencimidazol, 14-benzodioxan-6-ilo, 2-piridilo, 3-piridilo, 4-piridilo,quinolilo, tiofeno, benzo[b]tofeno, 2,3-dihirobenzofurano o cromano el cual puede estar adicionalmente substituido hasta por cuatro substituyentes seleccionados independientemente de un grupo consistente de

Flúor, cloro, bromo, Yodo, un alquilo de cadena larga o ramificada que tiene 1-7 átomos de carbono, un alquiloxi de cadena larga o ramificada

que tiene de 1 a 7 átomos de carbono, ciano, amino, alquilamino, dialquilamino, 1-acetidinilo, 1-pirolidinilo, 1-piperidinilo, nitro, hidroxi,acetoxi, trifluorometilo y trifluorometoxi

8 Un compuesto de acuerdo a la reivindicación 7, donde

Ar_1 es fenilo

9 Un compuesto de acuerdo a la reivindicación 7, donde

Ar1 es fenilo el cual puede estar substituido hasta por tres substituyentes seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7alcoxi, ciano, amino, mono-o di(C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi

10 Un compuesto de acuerdo a la reivindicación 1, donde

R_3 es hidrógeno o metilo, y

R_4 es C_1-C_8 alquilo o C_3-C_8 cicloalquilo

11 Un compuesto de acuerdo a la reivindicación 7, donde

Ar_1 es fenilo, y

Ar_2 es fenilo el cual puede estar substituido hasta con cuatro sustituyentes seleccionados independientemente de un grupo que consiste de halógeno, C_1-C_7 alquilo, C_1-C_7alcoxi, ciano, amino, mono-o di(C_1-C_7)alquilamino, 1-acetidinilo, 1-pirolidinilo, 1-piperidinilo, nitro, hidroxi, trifluorometilo, trifluorometoxi y 3,4-metilendioxi

12 Un compuesto de acuerdo a la reivindicación 1, donde

R_3 es hidrógeno o metilo, y

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R_4 es arilalquilo donde la porción arilo está substituida hasta por cuatro substituyentes seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono o di(C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi

13 Un compuesto de acuerdo a la reivindicación 12, donde

Ar_1 es fenilo sustituido hasta con tres sustituyente seleccionados independientemente de un grupo consistente de halógeno, C_1-C_7 alcoxi, C_1-C_7 alcoxi, ciano, amino, mono-o di(C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo y trifluorometoxi, y

Ar_2 es fenilo susbstituido hasta con tres susbstituyentes seleccionados independientemente de un grupo consistente de halógeno, C_1-C_7 alquilo, C_1-C_7alcoxi, ciano, amino, mono- o di(C_1-C_6)alquilamino, 1-acetidinilo, 1-pirrolidinilo, 1-piperidilo, nitro, hidroxi, trifluorometilo, trifluorometoxi, y 3,4-metilendioxi

14 Un compuesto de acuerdo a la reivindicación 12, donde

Ar_1 es fenilo, y

Ar_2 es fenilo sustituido hasta con cuatro sustituyente seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono-o di(C_1-C_6)alquilamino, 1-acetidinilo, 1-pirolidinilo, 1-piperidilo, nitro, hidroxi, trifluorometilo, trifluorometoxi y 3,4 metilendioxi

15 un compuesto de acuerdo a la reivindicación 12, donde

Ar_1 es fenilo, y

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Ar_1 es 1 o 2-naftilo, 1-,2-, o 3-indolilo, 2,3-dihidroindolilo, 1,2,3,4-tetrehidroquinolilo, 1-,2-,o 3-bencimidazol, 1,4-benzodioxan-6-ilo, 2-,3-, 4-piridilo, 2-,3-, o 4-quinolilo, 2- o 3-tienilo, 2- o 3-benzo[b]tiofenilo, 2- o 3-(2,3-dihidrobenzofuranilo) o 2-,3-, o 4-cromanilo, cada uno de los cuales es opcionalmente substituido hasta por cuatro substituyentes independientemente seleccionados de halógeno, C_1-C_7, C_1-C_7 alcoxi, ciano, amino, mono, o di(C_1-C_6)alquilamino, 1-acetidinilo, 1-pirolidinilo,1-piperidilo, nitro, hidroxi, acetoxi, trifluorometilo y trifluorometoxi

16 Un compuesto de acuerdo a la reivindicación 1, donde Ar_1 es 2-tienilo o piridilo

17 Un compuesto de acuerdo a la reivindicación 1, el cual es
1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[quinol-6-metil])aminometilimidazol,
1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[indan-2-il])aminometilimidazol, o
1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[{1-metilindol-5-il}metil])aminometilimidazol

18 Un compuesto de acuerdo a la reivindicación 1, el cual es
1-(1-butil)-2-(2-tienil)-5-(N-[3,4-metilendioxifenil]metil-N-fenilmetil]aminometilimidazol

19 Un compuesto de acuerdo a la reivindicación 1, el cual es

1-(1-butil)-2-fenıl-5-(N-[4-metoxifenılmetil]-N-fenılmetıl)amınometıl-imidazol,

1-(1-butıl)-2-fenil-5-(N-[1-(S)-fenıletıl]-N-fenılmetil) amınometil-imidazol,

1-(1-butıl)-2-fenil-5-(N-[1-(R)-fenıletıl]-N-fenilmetil) aminometıl-ımidazol,

1-(1-butıl)-2-fenil-5-(N-[3,4-metilendioxifenilmetıl]-N-[2-feniletil]) amınometıl-ımidazol,

1-(1-butıl)-2-fenıl-5-(N-[3,4,5-trimetoxıfenilmetil]-N-fenılmetıl) aminometil-imidazol,

1-(1-butıl)-2-fenil-5-(N-fenılmetıl-N-[3,4dımetoxıfenilmetil]) aminometil-ımıdazol,

1-(1-butıl)-2-fenil-5-(N-[3-metil-4-amınofenilmetıl]-N-fenilmetil) amınometil-imidazol,

1-(1-butil)-2-fenıl-5-(N-[2,3-dıclorofenilmetıl]-N-fenilmetil) amınometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[3,4-diclorofenılmetıl]-N-fenılmetıl) aminometil-ımıdazol,

1-(1-butil)-2-fenıl-5-(N-[3,4-dıfluorofenilmetıl]-N-fenilmetıl) aminometil-ımıdazol,

1-(1-butil)-2-fenil-5-(N-[4-etoxifenılmetil]-N-fenilmetil) amınometil-imıdazol,

1-(1-butıl)-2-fenil-5-(N-[4-metoxifenılmetıl]-N-fenilmetil) aminometıl-ımidazol,

1-(1-butıl)-2-fenil-5-(N-[3-metoxıfenilmetil]-N-fenilmetil) amınometıl-imidazol,

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1-(1-butil)-2-fenil-5-(N-[2-cloro-4-fluorofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[2,6-diclorofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[2-cloro-4-hidroxifenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[2-fluoro-6-clorofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[2,4-diclorofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-clorofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-hidroxifenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-trifluorometoxifenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[2-cloro-3,4dimetoxifenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-nitrofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-aminofenilmetil]-N-fenilmetil) aminometil-imidazol,

20 Un compuesto de acuerdo a la reivindicación 1, el cual es

1-(1-butil)-2-fenil-4-metil-5-(N-[3,4-metilendioxyfenil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[3,4-metilendioxyfenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[3,4-metilendioxyfenilmetil]-N-fenilmetil) aminoetil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-dimetilaminofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-metilaminofenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[6-cloro-3,4-metilendioxyfenilmetil]-N-fenilmetil) aminometil-imidazol,

1-(1-butil)-2-fenil-5-(N-[4-{1-pirrolidinil}fenilmetil]-N-fenilmetil) aminometil-imidazol, o

1-(1-butil)-2-fenil-5-(N-[4-dietilaminofenilmetil]-N-fenilmetil) aminometil-imidazol,

21 Un compuesto de acuerdo a la reivindicación 1, el cual es

1-(1-butil)-2-(4-fluorofenil)-5-(N-[3,4-metilendioxifenilmetil]-N-fenilmetil)aminometilimidazol,

1-(1-butil)-2-(2-metoxifenil)-5-(N-[3,4-metilendioxifenilmetil]-N-fenilmetil)aminometilimidazol,

1-(1-butil)-2-(2-metoxifenil)-5-(N-[4-dimetilaminofenilmetil]-N-fenilmetil)aminometilimidazol,

1-(1-butil)-2-(2-metilfenil)-5-(N-[3,4-metilendioxifenilmetil]-N-fenilmetil)aminometilimidazol,

1-(1-butil)-2-(3-fluorofenil)-5-(N-[3,4-metilendioxifenilmetil]-N-fenilmetil)aminometilimidazol,

1-(1-butil)-2-(3-metoxıfenıl)-5-(N-[3,4-metilendıoxifenilmetil]-N-fenılmetıl)amınometılimidazol,

1-(1-butil)-2-(3-fluorofenıl)-5-(1-[N-{4-hidroxi-2-clorofenıl}metil-N-fenılmetil]amino)etilimıdazol,

1-(1-butıl)-2-(4-fluorofenil)-5-(1-[N-{3,4-metılendioxifenil}metil-N-fenilmetil]amıno)etılimidazol,

1-(1-butil)-2-(4-fluorofenil)-5-(N-[2-cloro-4-hidroxifenılmetıl]-N-fenilmetil)aminometilimidazol,

1-(1-butil)-2-(3-fluorofenıl)-5-(N-[2-cloro-4-hidroxifenılmetıl]-N-fenilmetil)amınometılimıdazol,

1-(1-butil)-2-(3-fluorofenıl)-5-(N-[2,3-diclorofenilmetıl]-N-fenilmetil)amınometılımidazol,

1-(1-butil)-2-(3-fluorofenıl)-5-(N-[4-dimetılaminofenılmetil]-N-fenilmetıl)aminometilımıdazol, o

1-(1-butıl)-2-(3-fluorofenıl)-5-[N-{2-cloro-4-hidroxıfenılmetıl}-N-fenilmetil]amıno)etılimidazol

22 Un compuesto de acuerdo a la reıvındıcacıón 1, el cual es

1-(1-propil)-2-fenıl-5-(N-[1,4-benzodıoxan-6-ilmetil]-N-fenılmetil)amıno-metılimidazol,

1-(1-Butil)-2-fenıl-5-(N-[ındol-4-ılmetıl]-N-fenıletil)aminometilimıdazol,

1-(1-pentıl)-2-fenil-5-(N-[ındol-5-ilmetil]-N-feniletil)amınometilimidazol,

1-(1-Butıl)-2-fenil-5-(N-[indol-5-ılmetil]-N-feniletıl)amınometilimidazol,

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1-(1-propil)-2-fenil-5-(N-[indol-5-ilmetil]-N-feniletil)aminometilimidazol,

1-(1-pentil)-2-fenil-5-(N-[1,4-benzodioxan-6-ilmetil]-N-feniletil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-(benzo[b]tiofen-5-ilmetil]-N-feniletil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[piridin-2-ilmetil]-N-feniletil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[piridin-3-ilmetil]-N-feniletil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[piridin-4-ilmetil]-N-feniletil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[2aminopiridin-5-ilmetil]-N-feniletil)aminometilimidazol, o

1-(1-Butil)-2-fenil-5-(N-[2,3-dihidrobenzo[b]furan-5-ilmetil]-N-feniletil)aminometilimidazol,

23 Un compuesto de acuerdo a la reivindicación 1, el cual es

1-(1-butil)-2-(4-fluorofenil)-5-(N-[1,4-benzodioxan-6-il]metil-N-fenilmetil)amino metilimidazol,

1-(1-butil)-2-(2-fluorofenil)-5-(N-[1,4-benzodioxan-6-il]metil-N-fenilmetil)amino metilimidazol,

1-(1-butil)-2-(2-metoxifenil)-5-(N-[nafta-2-ilmetil]-N-fenilmetil)amino metilimidazol,

1-(1-butil)-2-(3-fluorofenil)-5-(N-[naft-2-ilmetil]-N-fenilmetil)amino metilimidazol, y

1-(1-butil)-2-(3-fluorofenil)-5-(N-[4-{1-pirolidin]fenilmetil]-N-fenilmetil)amino metilimidazol,

24 Un compuesto de acuerdo a la reivindicación 1, el cual es

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-etil)aminometil-imidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4-metilendioxifenilmetil]-N-1-propil)aminometil-imidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4-metilendioxifenilmetil]-N-[1-butil])aminometil-imidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4-metilendioxifenilmetil]-N-cicloheptilmetil)aminometil-imidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-isobutil)aminometil-imidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[2-ciclopentiletil]aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[3-ciclopentilpropil]aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[1-n-octil])aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-ciclopropilmetil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-ciclopentilmetil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-ciclohexilmetil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-t-amil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[1-{3-metil}butil])aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[1-{2,2-dimetil}butil)aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-metil)aminometilimidazol,

1-(1-Butil)-2-fenilo-4-bromo-5-(N-fenilmetil-N_[1-butil])aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[2,3-diclorofenilmetil]-N-[1-butilo])aminometilimidazol,

1-(1-Butil)-2-fenil-4-bromo-5-(N-[2,3-diclorofenilmetil]-N-[1-butil])aminometilimidazol,

1-(1-Butil)-2-fenil-4-cloro-5-(N-fenilmetil-N-[1-butil])aminometilimidazol,

1-(1-Butil)-2,4-difenil-5-(N-fenilmetil-N-[1-butil]aminometilimidazol,

1-(1-Butil)-2-fenil-5-(N-[2-cloro-4-hidroxifenilmetil]-N-[1-butil]aminometilimidazol, o

1-(1-Butil)-2-fenil-4-metil-5(N-fenilmetil-N-[1-butil]aminometilimidazol

25 Un compuesto acuerdo con la reivindicación 1, la cual es

1-(1-butil)-2-(2-metoxifenil)-5-(N,N-di[3,4-metilendioxifenilmetil])aminometilimidazol,

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1-(1-butil)-2-(4-fluorofenil)-5-(N,N-di[3,4-metilendioxifenilmetil])aminometilimidazol,

1-(1-butil)-2-(2-metilfenil)-5-(N,N-di[3,4-metilendioxifenilmetil])aminometilimidazol,

1-(1-butil)-2-(2-metilfenil)-5-(N,N-di[3,4-metilendioxifenilmetil])aminometilimidazol,

1-(1-butil)-2-(4-fluorofenil)-5-(1-N,N-di[3,4-metilendioxifenilmetil])aminometilimidazol,

26 Un compuesto de acuerdo a la reivindicación 1, el cual es

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifeniletil]-N-[3,4-diclorofenil]-metil)aminometilimidazol,

1-(1-butil)-2-fenil-5-(N,N-di[3,4-metilendioxifenilmetil]aminometilimidazol,

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[3,4-metoxifenil]-metil)aminometilimidazol,

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[4-{1-propil}fenil]-metil)aminometilimidazol,

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[3,4-diclorofeniletil)aminometilimidazol,

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenil]metil-N-[4-nitrofenilmetil]aminometilimidazol,

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[4-{1-propiloxy}fenil-metil])aminometilimidazol,

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[2,3-diclorofenilmetil])aminometilimidazol,

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1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifenilmetil]-N-[3,4-dimetilfenilmetil])aminometilimidazol,

1-(1-butil)-2-fenil-5-(N-[3,4metilendioxifénilmetil]-N-[2-tiofenilmetil])aminometilimidazol,

1-(1-butil)-2-fenil-5-(n-[3,4metilendioxifenilmetil]-N-[indol-5-ilmetil])aminometilimidazol,

1-(1-butil)-2-fenil-5-(n-[3,4metilendioxifenilmetil]-N-[4-hidroxi-2-clorofenilmetil])aminometilimidazol,

1-(1-butil)-2-fenil-5-(n-[3,4metilendioxifenilmetil]-N-[2,3-dihidrobenceno[b]furan-5-il]aminometilimidazol,

27 Un compuesto de acuerdo a la reivindicación 1, el cual es 1-(1-butil)2-(2-metoxifenil)-4-bromo-5-(N-[4-dimetilaminofenilmetil]-N-fenil)aminometilimidazol

28 Un compuesto de acuerdo a la reivindicación 1, el cual es 2-{[5-({butil[(1-butil-2,4-difenilimidazol-5-5il)metil]amino}metil-2-piridil]amino}etan-1-ol

29 Una composición farmacéutica que comprende un compuesto de acuerdo a la reivindicación 1, o una sal farmacéuticamente aceptable del mismo

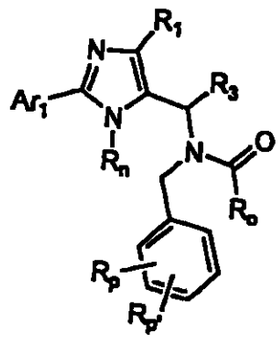
30 El uso de un compuesto de acuerdo a la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en la manufactura de un medicamento para el tratamiento de enfermedades autoinmunes o inflamatorias

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31 El uso del compuesto de acuerdo a la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en el tratamiento de desórdenes autoinmunes o inflamatorios

32 Un método para inhibir la quimiotaxis del leucocito, el cual comprende contactar el compuesto de la reivindicación con células sanguíneas blancas, donde el compuesto está presente en una cantidad efectiva para producir una concentración suficiente para inhibir la quimiotaxis de las células sanguíneas blancas in vitro

33 Un compuesto de fórmula



donde

R_1 es hidrógeno, C_1-C_7 alquilo, halógeno o fenilo opcionalmente sustituido con C_1-C_6alquilo, C_1-C_6 alcoxi, halógeno, hidroxi, amino, o mono o di(C_1-C_6)alquilamino,

R_3 es hidrógeno o C_1-C_7-alquilo,

Ar_1 es fenil el cual puede estar substituido hasta con cuatro substituyentes seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono o di(C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometil, y trifluorometoxi, o

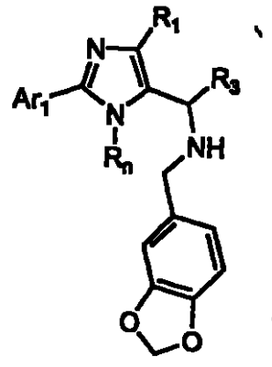
Ar_2 es 2-tienilo o piridilo, cada unode los cuales es opcionalmente substituido con halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono o di(C_1-C_6)alquilamino o trifluorometil,

R_n es hidrógeno, C_1-C_8 alquilo o C_3-C_8 cicloalquilo,

R_o es C_1-C_8alquilo, o fenilo o bencilo donde cada porción fenilo puede estar substituida hasta por tres grupos seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono o di (C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometil, y trifluorometoxi, y

Cada R_p es hidrógeno, halógeno, C_1-C_7 alquilo, C_1-$_{C7alcoxi}$, ciano, amino, mono- o di(C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4metilendioxi, trifluorometil y trifluorometoxi

34 Un compuesto de fórmula



Donde

R_1 es hidrógeno, C_1-C_7alquilo, halógeno o fenilo opcionalmente substituido con C_1-C_6 alquilo, C_1-C_6 alcoxi, halógeno, hidroxi, amino, o mono o di(C_1-C_6) alquilamino,

R_3 es hidrógeno o C_1-C_7 alquilo,

Ar_1 es fenilo el cual puede estar substituido hasta por cuatro substituyentes seleccionados independientemente de halógeno, C_1-C_7 alquilo, C_1-C_7

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alcoxi, ciano, amino, mono- o di(C_1-C_6)alquilamino, hidroxi, acetoxi, 3,4 metilendioxi, trifluorometil, y trifluorometoxi, o

Ar_1 es 2-tienilo o piridilo, cada uno de los cuales esta opcionalmente substituido con halógeno, C_1-C_7 alquilo, C_1-C_7 alcoxi, ciano, amino, mono- o di(C_1-C_6)alquilamino, o trifluorometil, y Rn es hidrógeno, C_1-C_8 alquilo o C_3-C_8 cicloalquilo

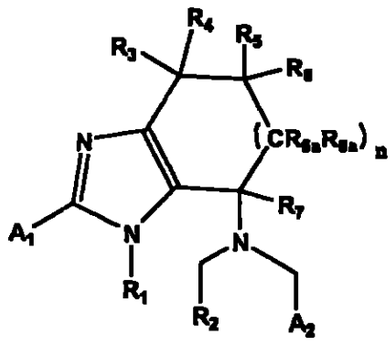
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Lo que se reivindica es

1 Un compuesto de la fórmula



o una sal farmacéuticamente aceptable del mismo, en la cual

n es un número entero de 0 a 3, y

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o

R_2 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido, o un grupo heteroaromático o heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo, o alcoxi, o

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R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

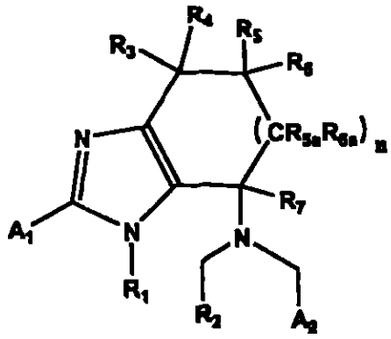
R_{5a} y R_{6b} se seleccionan independientemente cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo, y alcoxi,

R_7 representa hidrógeno o alquilo,

A_1 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido o un grupo heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos, y

A_2 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido o un grupo heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos

2 Un compuesto de la fórmula



O una sal farmacéuticamente aceptable del mismo, en la cual

n es un número entero de 0 a 3, y

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

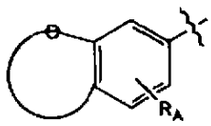
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R_2 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido; o

R_2 es fenilo, naftaleno, tiofeno o piridina cada uno de los cuales puede estar o no sustituido con:

alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino; o

R_2 es un grupo bicíclico que contiene oxígeno, de la fórmula:



en donde R_A es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino;

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo; o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo;

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo, o alcoxi; o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo;

R_{5a} y R_{6b} se seleccionan independientemente cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo, y alcoxi;

R_7 representa hidrógeno o alquilo;

A_1 es fenilo el cual puede estar o no sustituido con hasta 4 sustituyentes seleccionados independientemente de halógeno, alquilo, alcoxi, ciano, amino, mono- o dialquilamino, hidroxi,

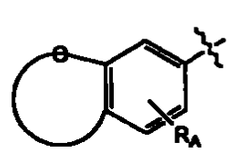
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acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo, trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_1 es tiofeno o piridina que puede estar o no sustituido con alquilo, halógeno, alcoxi, amino o mono o dialquilamino,

A_2 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar o no sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, alquilo, alcoxi, ciano, amino, mono- o dialquilamino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, alquilo (cicloalquilo), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

X está independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_C-$, $-O-$, $-S(0)_m-$, $-NH-$, $-NR_C-$, $-C(=0)NH$, $-C(=0)NR_C-$, $-S(0)_mNH-$, $-S(0)_mNR_C-$, -

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PTO 246888

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

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December 26, 2000

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APPLICATION NUMBER *60/224,036*
FILING DATE *August 09, 2000*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

PART (2) OF (2) PART(S)

E. Bornett

E. BORNETT
Certifying Officer

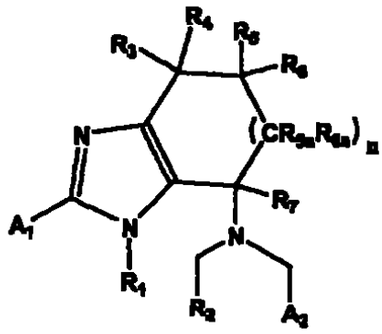
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X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_c-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_c-$, $-C(=O)NH-$, $-C(=O)NR_c-$, $-S(O)_mNH-$, $-S(O)_mNR_c-$, $-NHC(=O)-$, $-NR_cC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_cS(O)_m-$ (where m is 0, 1, or 2), and

R_a and R_c, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from

oxo, hydroxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_x$(alkyl), $-S(O)_x$(alkyl), $-S(O)_xNH$(alkyl), $-S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2)

3 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

n is an integer from 0 to 3, and

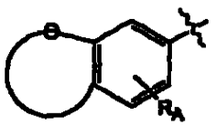
R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_6 alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, and C_1-C_6 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

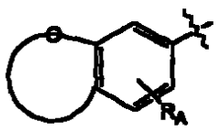
halogen, C_1-C_7 alkyl, C_2-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or

$-XR_8$, wherein X and R_8 are as defined below; or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino, and

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_a$, wherein X and R_a are as defined below, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

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X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_c-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_c-$, $-C(=O)NH-$, $-C(=O)NR_c-$, $-S(O)_mNH-$, $-S(O)_mNR_c-$, $-NHC(=O)-$, $-NR_cC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_cS(O)_m-$ (where m is 0, 1, or 2), and

R_b and R_c, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$(C_1-C_4$ alkyl), $-NHC(O)(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$C(O)(C_1-C_4$ alkyl), $-NHS(O)_x(C_1-C_4$ alkyl), $-S(O)_x(C_1-C_4$ alkyl), $-S(O)_xNH(C_1-C_4$ alkyl), $-S(O)_xN(C_1-C_4$ alkyl)$(C_1-C_4$ alkyl), (where x is 0, 1, or 2)

4 A compound according to Claim 3 wherein

R_3 and R_4 are the same or different and represent hydrogen or methyl,

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl

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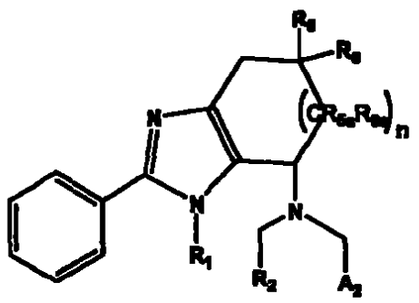
5 A compound according to Claim 3 wherein

R_3 and R_4 are hydrogen;

R_5 and R_6 are the same or different and represent hydrogen or methyl, and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl

6 A compound according to Claim 3 of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_3 and R_6 are the same or different and represent hydrogen or methyl,

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen and methyl, and

R_1, R_2, A_2, and n are as defined for Claim 3

7 A compound according to Claim 6,

or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

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R_2, A_2, and n are as defined for Claim 6

8 A compound according to Claim 6,

or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

A_2, and n are as defined for Claim 6

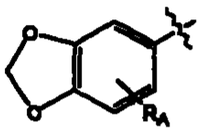
9 A compound according to Claim 6,

or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is phenyl, which may be unsubstituted or substituted with C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 cycloalkyl, (C_3-C_6cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

A_2 is phenyl which is unsubstituted or substituted with up to four groups independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined for Claim 6, and

n is as defined in Claim 6

10 A compound according to Claim 6,

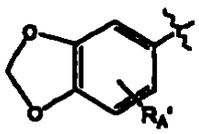
or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R

A_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is as defined for Claim 6, and

n is as defined for Claim 6

11 A compound according to claim 1, which is selected from

4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol,

4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino]methyl}-3-chlorophenol,

4-{[(1-Butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))benzylamino] methyl}phenol,

4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}phenol,

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))amine,

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(1-butyl-2-phenyl(4,5,6-trihydrocyclopenty[3,2-d]imidazol-6-yl))benzylamine,

(2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl)(3-butyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))benzylamine,

4-{[(3-Butyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazoly-4-yl))benzylamino]methyl}-3-chlorophenol,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2H- benzo[3,4-d]1,3-dioxolan-5-ylmethyl)benzylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4-hydroxybenzyl) benzylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2H-benzo[d]1,3-dioxolen-5-ylmethyl,butylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(2-chloro-4- hydroxybenzyl) butylamine;

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(4- hydroxybenzyl)butylamine,

(3-Butyl-6,6-dimethyl-2-phenyl(3,4,5,6,7-pentahydrobenzimidazol-4-yl))(3-hydroxybenzyl)butylamine, and

(1-Butyl-2-phenyl-4,5,6,7,8-pentahydrocyclohepta[3,2-d]imidazol-8-yl)(2H-benzo[d]1,3-dioxolen-5-ylmethyl)butylamine

12 A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient

13 A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 14 in a container and instructions for using the composition to treat a patient in need thereof

14 The packaged pharmaceutical composition of claim 13, wherein said patient is suffering from rheumatoid arthritis, Crohn's disease, irritable bowel syndrome, ARDS, extracorporeal post-dialysis syndrome, systemic lupus erythematosus, psoriasis or bronchial asthma

15 The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory diseases

16 A method of treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory disorders which comprises administering to patient in need of such treatment a C5a receptor-modulatory effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof

17 A method of inhibiting leukocyte chemotaxis, which comprises

contacting a compound of Claim 1 with white blood cells, wherein the compound is contacted at a concentration sufficient to inhibit chemotaxis of white blood cells *in vitro*

18 A method for the treatment of physiological disorders associated with localized excess concentrations of C5a, which method comprises administration to a patient in need of such treatment a compound according Claim 1, wherein the compound is administered in an amount sufficient to yield, at a site of localized excess concentrations of C5a, a concentration of the compound sufficient to inhibit chemotaxis of white blood cells *in vitro*

19 A method for localizing C5a receptors in tissue section samples comprising

contacting with a sample of tissue a detectably-labelled compound of claim 1 under conditions that permit binding of the compound to the sample of tissue,

washing the tissue sample to remove unbound compound, and

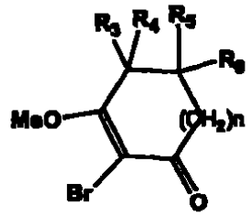
detecting the bound compound

20. A method of inhibiting the binding of C5a to C5a receptors, which method comprises contacting a solution comprising the compound of Claim 1 with C5a receptors, wherein the compound is present in the solution at a concentration sufficient to inhibit C5a binding to C5a receptors *in vitro*

21 A method for altering the activity of cell surface C5a receptors, said method comprising contacting cells expressing such receptors with a solution comprising the compound of Claim 1, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white blood cells in vitro

22 A compound according to claim 1 wherein in a standard assay of C5a mediated chemotaxis the compound exhibits an IC_{50} of 1 micromolar or less

23 A compound of the formula



wherein

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n is an integer from 0 to 3,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring, and

R_5 and R_6 are the same or different and represent hydrogen or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring

24 A compound according to Claim 23, wherein

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms, and

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

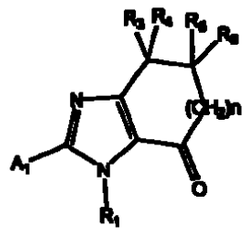
R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms

25 A compound according to Claim 23, wherein

R_3 and R_4 are hydrogen, and

R_5 and R_6 are the same or different and represent hydrogen or methyl

26 A compound of the formula



wherein

n is an integer from 0 to 3,

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl (i e cyclopentylmethyl), or haloalkyl, each of which may be substituted or unsubstituted,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring, and

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having

from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

27 A compound according to Claim 26 in which

R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms, and

R_5 and R_6 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or

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$-XR_B$, wherein X and R_B are as defined below, or

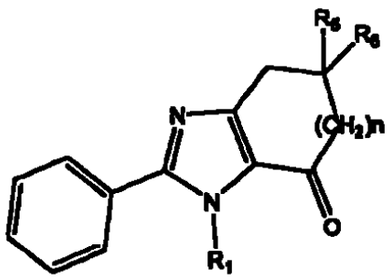
A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1$-C_4 alkyl), $-NH(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)(C_1-C_4 alkyl), $-NHC(O)(C_1$-C_4 alkyl), $-N(C_1$-C_4 alkyl)$C(O)(C_1$-C_4 alkyl), $-NHS(O)_x(C_1$-C_4 alkyl), $-S(O)_x(C_1$-C_4 alkyl), $-S(O)_xNH(C_1$-C_4 alkyl), $-S(O)_xN(C_1$-C_4 alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

28 A compound according to Claim 26 of the formula

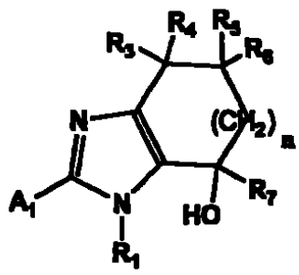


wherein

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

R_5 and R_6 are the same or different and represent hydrogen or methyl

29 A compound of the formula



wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

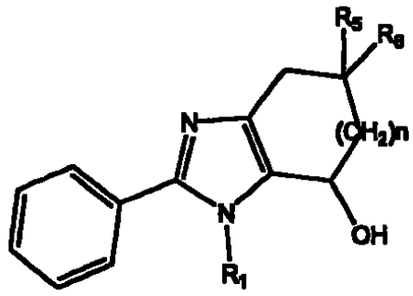
R_5 and R_6 are the same or different and represent hydrogen or alkyl, or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_7 represents hydrogen or alkyl, and

A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

30 A compound according to Claim 30, of the formula



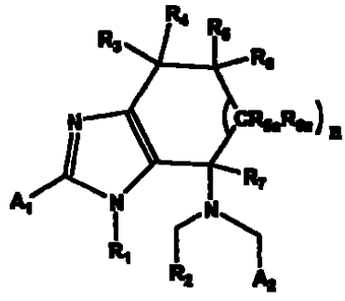
wherein

n is an integer from 0 to 3,

R_1 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl, and

R_5 and R_6 are the same or different and represent hydrogen or methyl

31 A process for preparing a compound of the formula



wherein

n is an integer from 0 to 3, and

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted, or

R_2 is substituted or unsubstituted carbocyclic aryl, substituted or unsubstituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_4 are the same or different and represent hydrogen or alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy, or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, or alkoxy,

R_7 represents hydrogen or alkyl,

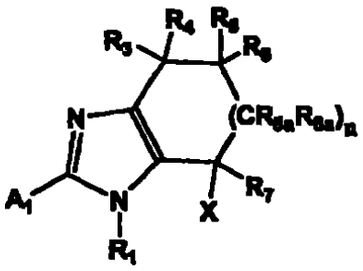
A_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having

from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

A_2 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted araalkyl, or a substituted or unsubstituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

the process comprising

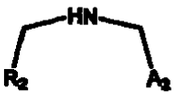
reacting a compound of the formula



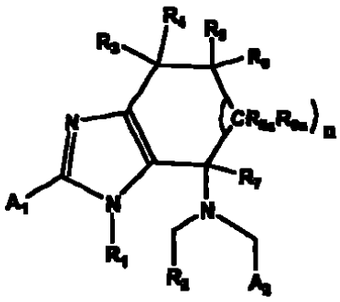
wherein X halogen or sulfonate ester,

in a suitable solvent in the presence of a suitable base,

with a secondary amine of the formula



32 A process according to Claim 31, of preparing a compound of the formula



wherein

n is an integer from 0 to 3, and

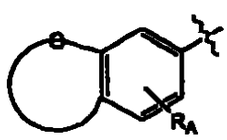
R_1 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 (cycloalkyl)alkyl, or C_1-C_8 haloalkyl,

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl C_1-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_6 alkyl, C_1-C_8 haloalkyl, or

R_2 is phenyl, naphthalene, thiophene or pyridine each of which may be unsubstituted or substituted with.

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

R_3 and R_4 are the same or different and represent hydrogen or C_1-C_7 alkyl, or

R_3 and R_4, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms,

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms,

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_7 alkyl, or C_1-C_7 alkoxy,

R_7 represents hydrogen or C_1-C_7 alkyl,

A_1 is phenyl which is unsubstituted or substituted with up to four substituents independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, hydroxy, acetoxy, aminoalkyloxy, mono or dialkylaminoalkyloxy, morpholino, nitro, carboxylic

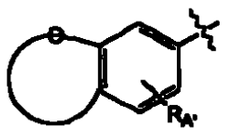
acid or esters thereof, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1- trifluoromethyl or trifluoromethoxy, or $-XR_8$, wherein X and R_8 are as defined below, or

A_1 is thiophene or pyridine each of which is unsubstituted or substituted with C_1-C_7 alkyl, halogen, C_1-C_7 alkoxy, amino or mono or di(C_1-C_6)alkylamino, and

A_2 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which is unsubstituted or substituted with up to four groups independently selected from

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, 3,4-methylenedioxy, trifluoromethyl, and trifluoromethoxy or $-XR_8$, wherein X and R_8 are as defined below, or

R_2 is a bicyclic oxygen containing group of the formula



wherein R_A' is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_6 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino,

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2), and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which is unsubstituted or substituted with one or more substituents selected from

oxo, hydroxy, $-O(C_1-C_4$ alkyl), $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)(C_1-C_4 alkyl), $-NHC(O)(C_1-C_4$ alkyl), $-N(C_1-C_4$ alkyl)$C(O)(C_1-C_4$ alkyl), $-NHS(O)_x(C_1-C_4$ alkyl), $-S(O)_x(C_1-C_4$ alkyl), $-S(O)_xNH(C_1-C_4$ alkyl), $-S(O)_xN(C_1-C_4$ alkyl)(C_1-C_4 alkyl), (where x is 0, 1, or 2)

Title 2-PHENYL-4-AMINOMETHYLPYRIDINES

BACKGROUND

Field of the Invention

This invention relates to certain 2-Phenyl-4-aminomethyl pyridines which when appropriately substituted, are modulators of human complement C5a receptors This invention also relates to pharmaceutical compositions comprising such compounds It further relates to the use of such compounds in treating a variety of inflammatory and immune system disorders Additionally, this invention relates to the use such compounds as probes for the localization of C5a receptors

Background of the Invention

Inflammation is the normal physiological response to cellular injury - microbial infection, physical or chemical trauma, or invasion of cancerous cells While necessary to remove infectious particles and damaged tissue, inflammation can also cause pain and further tissue damage Pathogenic inflammation is associated with various diseases, and is a hallmark of autoimmune disease

Proteins of the complement cascade play a key role in the mediation of inflammation This system of more than 20 interacting soluble and membrane-bound proteins undergoes a series of proteolytic reactions that set in motion a number of important immune functions including the recruitment of leukocytic cells to sites of injury and/or infection Additionally, proteins of the complement system mediate changes in vascular permeability and blood flow, target cells for opsonization, and effect formation of the membrane attack complex, which mediates the immune lysis of foreign cells

C5a, a 74 amino acid peptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement enzyme C5 convertase The anaphylatoxic effects of the C5a peptide are mediated through its interation with the C5a receptor, a 52 kD membrane bound G-protein coupled receptor C5a is a potent chemoattractant for polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to sites of inflammation and/or cellular injury Additionally, C5a stimulates the release of inflammatory mediators (e g , histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes, C5a also promotes the production of activated oxygen radicals and the contraction of smooth muscle

Considerable experimental evidence implicates increased levels of C5a in a number of autoimmune diseases and inflammatory and related disorders Such autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus (and associated glomerulonephritis), psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, and immunovasculitis Such inflammatory and related conditions include neutropenia, sepsis, septic shock, Alzheimer's disease, stroke, inflammation associated with severe burns, lung injury, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, artherosclerosis and ischemic heart disease, as well as acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), tissue graft rejection, hyperacute rejection of transplanted organs, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), myasthenia gravis, pathologic sequellae associated with insulin-dependent diabetes mellitus (including diabetic retinopathy), Heyman nephritis (and other forms of glomerulonephritis), inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (e g , during

hemodialysis or via a heart-lung machine, for example, in association with heart surgery such as coronary artery bypass grafting or heart valve replacement) such as extracorporeal post-dialysis syndrome or in association with contact with other artificial vessel or container surfaces (e g , ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, and the like) Antagonists that block the binding of C5a to its receptor or which modulate signal transduction associated with C5a-receptor interactions can inhibit the pathogenic chemotaxis associated with such inflammatory and autoimmune conditions Indeed, certain modified C5a peptides have been identified as C5a antagonists and have been shown to block a number of C5a mediated actions including neutrophil chemotaxis, neutropenia and superoxide formation

Despite many attempts, no one has previously been able to provide any small molecule (less than 500 Daltons MW) non-peptide, amino acid free, C5a antagonist that is free of agonist activity at the C5a receptor and that exhibits a K_i at the C5a receptor of less than 1 micromolar

SUMMARY OF THE INVENTION

The present invention provides novel compounds that are small molecule C5a receptor antagonists that are non-peptide, amino acid free, and free of C5a receptor agonist activity, which

compounds exhibit a K_i at the C5a receptor of less than 1 micromolar Preferred C5a receptors are mammalian receptors, including human C5a receptors and may either be cloned, recombinantly expressed receptors or naturally expressed receptors

In certain embodiments these compounds also possess one or more, and preferably two or more, three or more, four or more, five or more, or all of the following properties in that they are 1) multi-aryl in structure (having a plurality of un-fused or fused aryl groups), 2) heteroaryl in structure, 3) orally available in vivo (such that a sub-lethal or pharmaceutically acceptable oral dose can provide a detectable in vitro effect such as a reduction of C5a-induced neutropenia), 4) without amide bonds, and 5) capable of inhibiting leukocyte chemotaxis at nanomolar concentrations or 6) is capable of inhibiting leukocyte chemotaxis at sub-nanomolar concentrations

In one of its aspects, the invention provides substituted 2-phenyl-4-methylaminopyridines The invention also provides novel compounds of Formula I, shown below, that bind specifically, and preferably with high affinity, to C5a receptors

Novel intermediates useful for synthesizing compounds of the invention are also provided

The invention also provides pharmaceutical compositions comprising compounds of Formula I The compounds are

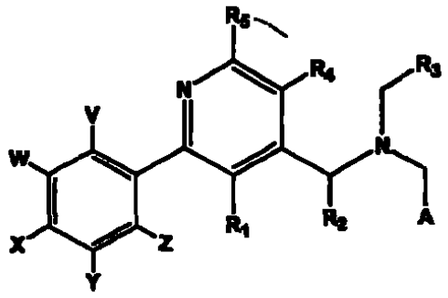
particularly useful in the treatment of C5a-mediated inflammation, e g , inflammation associated with various inflammatory and immune system disorders The invention further comprises a method of treating a patient in need of such anti-inflammatory treatment with a sufficient concentration of a compound of the invention A preferred concentration is one sufficient to inhibit white blood cell chemotaxis in vitro Treatment of humans, domesticated companion animals (pets) or livestock animals suffering such conditions with an effective amount of a compound of the invention is contemplated by the invention

In a separate aspect, the invention provides methods of using compounds of this invention as positive controls in assays for receptor activity and using appropriately labeled compounds of the invention as probes for the localization of receptors, particularly C5a receptors, in tissue sections

The invention provides compounds and compositions that are useful as inhibitors of C5a-mediated chemotaxis (e g , they may be used as standards in assays of such chemotaxis) The invention additionally comprises methods of inhibiting C5a-mediated chemotaxis, preferably leukocyte chemotaxis, the methods comprising contacting white blood cells with a chemotaxis-inhibitory concentration of a compound of the invention Preferably the concentration is sufficient to inhibit chemotaxis

of white blood cells in an *in vitro* chemotaxis assay, so that the levels of chemotaxis observed in a control assay (e g , one to which a compound of the invention has not been added) are significantly higher (significantly here measured as $p \leq 0.05$ using a conventional parametric statistical analysis method) than the levels observed in an assay to which one or more compounds of the invention have been added

Accordingly, a broad embodiment of the invention is directed to compounds of Formula I



Formula I

and the pharmaceutically acceptable salts thereof, wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3

rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

A represents optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

DETAILED DESCRIPTION OF THE INVENTION

In addition to the compounds of general Formula I, described above, the invention provides compounds of the same general Formula I, and the pharmaceutically acceptable salts thereof, wherein the variables R_1, R_2, R_3, R_4, R_5, A, V, W, X, Y, and Z are defined as follows

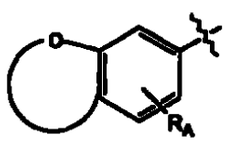
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, or

R_3 is a phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl or indolyl group, each of which is optionally ausbstituted with up to four groups independently selected from halogen, nitro, trifluorotheyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

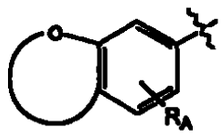
R_4 is hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl or alkoxy, or

R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono or dialkyl sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cyclolalkyl)alkyl or haloalkyl, each of which may be substituted or unsubstituted,

A is a phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, or indolyl group, each of which is optionally substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or dialkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl or

A is a bicyclic oxygen containing group of the formula



wherein R_A, represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or dialkylamino, alkyl, alkoxy, akenyl,. alkynyl, cycloalkyl, (cycloalkyl)alkyl, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of General Formula IA

Alternatively, the invention includes compounds of general Formula I, described above, and the pharmaceutically acceptable salts thereof, wherein the variables R_1, R_2, R_3, R_4, R_5, A, V, W, X, Y, and Z are defined as follows

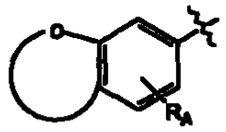
R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_6cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

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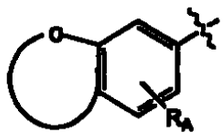
R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkyl]amino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

A is a bicyclic oxygen containing group of the formula

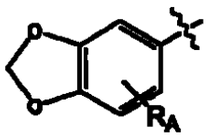
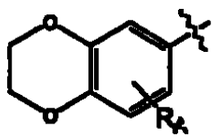
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wherein R_A, represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

Such compounds will be referred to as compounds of General Formula IB Preferred bicyclic oxygen containing groups for formula IB include

 or 

for the variable R_3 or the same groups substituted by R_A for the variable A

Preferred compounds of General Formula IB are those compounds wherein

R_1 is C_3-C_8 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of Formula IC

Other preferred compounds of General Formula IB are those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of Formula ID

More preferred compounds of General Formula IB are those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

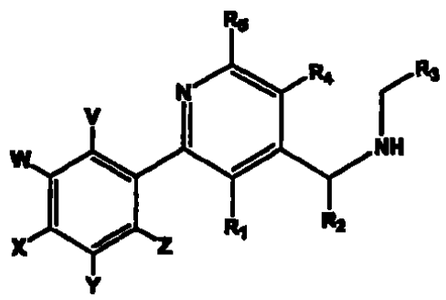
V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to as compounds of Formula IE

For all preferred compounds of the invention the pharmaceutically acceptable salts thereof are included as part of the invention

Also provided are novel intermediates useful for synthesizing compounds of the invention and methods of synthesizing compounds of the invention using such intermediates

Specifically provided, as intermediates, are compounds of Formula II



Formula II

wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

Preferred intermediates of Formula II, are those compounds wherein

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl; and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy Such compounds are referred to as compounds of Formula IIA

A more preferred class of compounds of Formula II, includes those compounds wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy Such compounds are referred to as compounds of Formula IIB

Preferred compounds of Formula II also include those compounds wherein

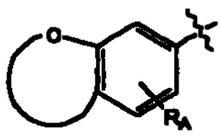
R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, carboxylic acid esters, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

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R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8

alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

Such compounds are referred to as compounds of Formula IIC

Especially preferred compounds of Formula IIC includes those compounds wherein

R_1 is C_3-C_8 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds are referred to as compounds of Formula IIC

In certain situations, the compounds of Formula I may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms These compounds can be, for example, racemates or optically active forms In these situations, the single enantiomers, i e , optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds of Table 1 and their pharmaceutically acceptable salts Pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0 - 4, and the like Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts

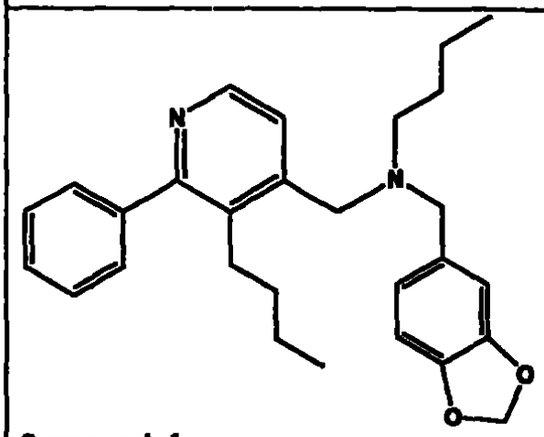
The present invention also encompasses the acylated prodrugs of the compounds of Formula I Those skilled in the art will recognize various synthetic methodologies which may be employed

to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I

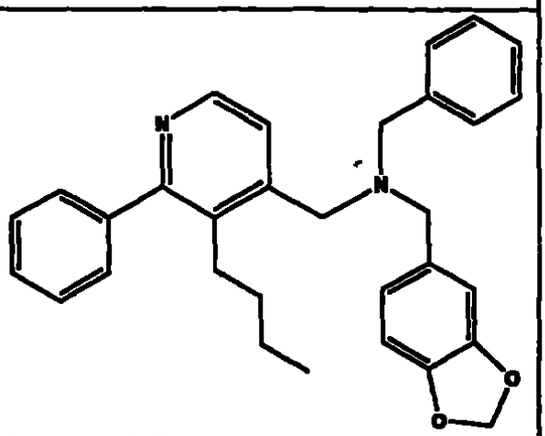
Representative compounds of the invention are shown in Table 1

TABLE 1

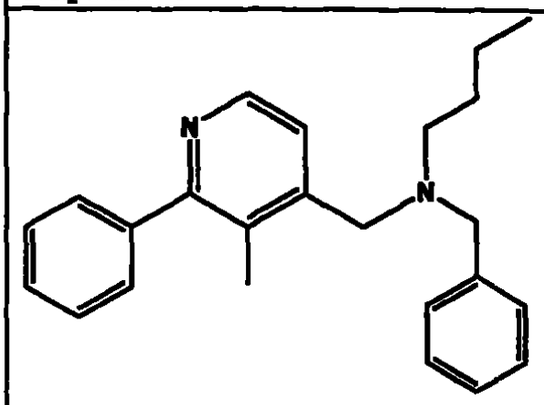
Representative 2-Phenyl-4-aminomethylpyridines



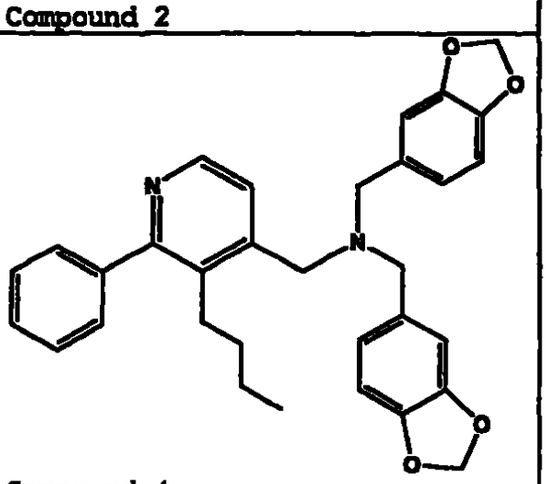
Compound 1



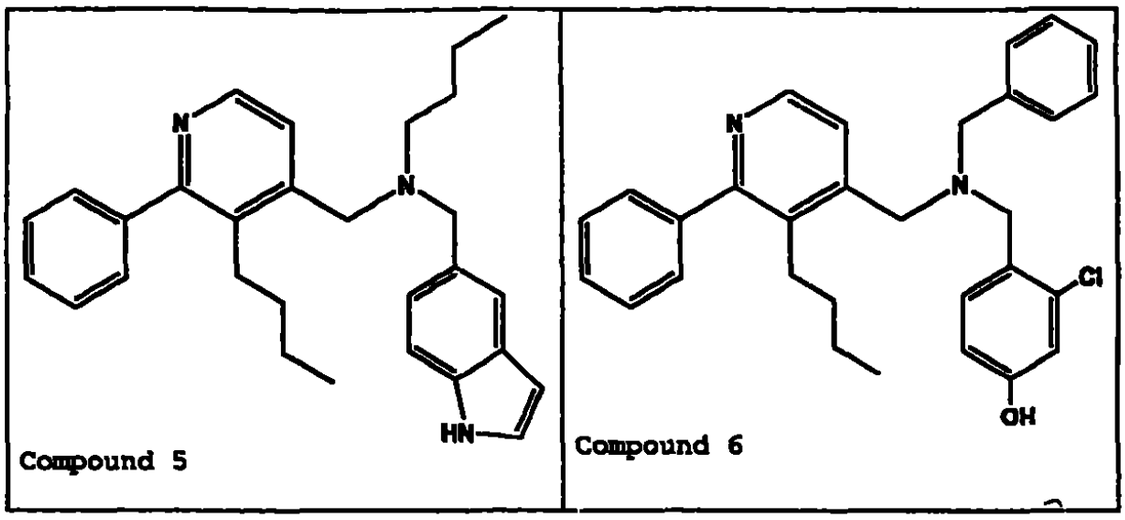
Compound 2



Compound 3



Compound 4



This invention provides 2-phenyl-4-aminomethylpyridine compounds that bind with high affinity to C5a receptors, particularly human C5a receptors This invention also comprises such compounds that bind with high selectivity to C5a receptors, particularly human C5a receptors The interaction of compounds of the invention with C5a receptors is shown by the inhibition of C5a-mediated chemotaxis e g , as described in Example 3. While not wishing to be bound by any particular theory of operation, it is believed that this interaction results in the pharmacological activity of these compounds This invention includes compounds that inhibit C5a mediated chemotaxis Preferred compounds exhibit EC_{50} values of less than 1 μM in an assay of C5a mediated chemotaxis, more preferred compounds exhibit EC_{50} values of less than 500 nM, and most preferred compounds exhibit EC_{50} values of less than 250 nM

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The invention includes methods for the treatment or prevention of disorders responsive to C5a receptor modulation, including but not limited to all of the inflammatory or autoimmune disorders involving pathogenic C5a activity discussed above in the "background of the invention" section, which comprise administering to a patient in need of such treatment an effective amount of compound of the invention

The present invention furthermore provides pharmaceutical compositions comprising a compound or compounds of the invention together with at least one pharmaceutically acceptable carrier or excipient The invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to C5a receptor modulation, e g , any of the inflammatory or autoimmune disorders discussed above as the "background of the invention" including but not limited to arthritis, ARDS, and Alzheimer's Disease The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one C5a receptor modulator as described supra and instructions for its use for the treatment of a disorder responsive to C5a receptor modulation

This invention also includes compounds that act as selective modulators of G-coupled protein receptors, especially the C5a receptor Preferably, compounds of this invention do not bind to dopamine receptors Most preferably compounds of this invention do not exhibit binding constants less than 1 μM at dopamine

receptors in a standard radioligand binding assay for dopamine binding activity (US patent no 5,159,083 is hereby incorporated by reference for its teachings in regard to such assays at col 8)

The present invention also pertains to methods of inhibiting the binding of C5a to C5a receptors which methods involve contacting a compound of the invention with cells expressing C5a receptors, wherein the compound is present at a concentration sufficient to inhibit C5a binding to C5a receptors *in vitro* This method includes inhibiting the binding of C5a to C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I sufficient to produce a body fluid concentration capable of altering the chemotactic responses to C5a of white blood cells *in vitro* In one embodiment, such methods are useful in treating physiological disorders associated with excess concentrations of C5a The amount of a compound that would be sufficient to inhibit the binding of a C5a to the C5a receptor may be readily determined via a C5a receptor binding assay, or from the EC_{50} obtained via a C5a receptor functional assay, such as the standard assay of C5a receptor mediated chemotaxis described in Example 3 The C5a receptors used to determine in vitro binding may be obtained from a variety of sources, for example from preparations of leukocytes or from cells expressing cloned human C5a receptors, e g human promonocytic U937 cells

The present invention also pertains to methods for altering

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the activity of C5a receptors, said method comprising exposing cells expressing such receptors to a solution comprising an effective amount of a compound of the invention, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white blood cells *in vitro* This method includes altering the activity of C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I sufficient to produce a body fluid concentration capable of altering the chemotactic responses to C5a of white blood cells *in vitro* The amount of a compound that would be sufficient to alter the chemotactic activity of C5a receptors may be determined via an assay of C5a receptor mediated chemotaxis, such as the standard assay described in Example 5

The C5a receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a compound to interact with the C5a receptor

Labeled derivatives the C5a receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT)

Definitions

As indicated above, various substituents of the various formulae may be "substituted or unsubstituted" or "optionally substituted" including A, R_1, R_2, R_3, R_4, R_5, V, W, X, Y, and Z or

Formula I, and such substituents as recited in the sub-formulae such as Formulae II and the like When substituted, those substituents (A, R_1, R_2, R_3, R_4, R_5, V, W, X, Y, and Z) may be substituted by other than hydrogen at one or more available positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein Suitable groups that may be present on a "substituted" A, R_1, R_2, R_3, R_4, R_5, V, W, X, Y, and Z group or other substituent include e g halogen such as fluoro, chloro, bromo and iodo, cyano, hydroxyl, nitro, azido, alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like, carboxamido, alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, aryloxy such as phenoxy, alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms,

aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl (e g an Ar group being a substituted or unsubstituted biphenyl moiety), aralkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group, aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group, or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e g coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl

When "araalkyl" is specified in the present invention the point of attachment is the alkyl group

By the term "C_1-C_x alkyl" in the present invention is meant straight or branched chain alkyl groups having 1 to x carbon atoms, generally up to 6 or 7 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl Preferred C_1-C_6 alkyl groups are methyl, ethyl, propyl, butyl, pentyl and cyclopentyl

The term "C_1-C_x alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy

The term "alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl

The term "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl

The term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl

In the term "(C_{3-x} cycloalkyl)C_{1-y} alkyl the point of attachment is on the alkyl group This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl, cyclohexylmethyl

The term "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more

halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1) Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl

By the term "halogen" is meant fluorine, chlorine, bromine or iodine

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7-to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3 3 0]bicyclooctane, [4 3 0]bicyclononane, [4 4 0]bicyclodecane, [2 2 2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl

As used herein, the term "heterocycle" or "heterocycloalkyl" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, 0 and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring The nitrogen and sulfur heteroatoms may optionally be oxidized

The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable A nitrogen in the heterocycle may optionally be quaternized It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another It is preferred that the total number of S and O atoms in the heterocycle is not more than 1 As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1

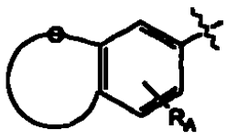
Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benoztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl,

imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,- 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl

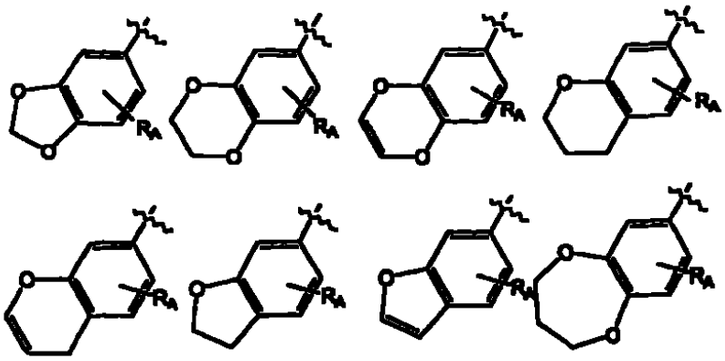
Preferred heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, piperonyl, furanyl, thienyl, pyrrolyl, pyrazolyl,

pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles

Examples of bicyclic oxygen containing groups of the formula



(R_A may also be indicated R_A') include the following



Pharmaceutical Preparations

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles Oral administration in the form of a pill, capsule,

elixir, syrup, lozenge, troche, or the like is particularly preferred The term parenteral as used herein includes injections and the like, such as subcutaneous, intradermal, intravascular (e g , intravenous), intramuscular, intrasternal, spinal, intrathecal, and like injection or infusion techniques, with subcutaneous, intramuscular and intravascular injections or infusions being preferred In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations Tablets contain the active ingredient in admixture

with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, corn starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate,

polyvinylpyrrolidone, gum tragacanth and gum acacia, dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above Additional excipients, for example sweetening, flavoring and coloring agents, may also be present

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents The pharmaceutical

compositions may be in the form of a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides In addition, fatty acids such as oleic acid find use in the preparation of injectables

The compounds of general Formula I may also be administered in the form of suppositories e g , for rectal administration of the drug These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug Such materials are cocoa butter and polyethylene glycols

Compounds of general Formula I may be administered parenterally, preferably in a sterile non-toxic, pyrogen-free medium The drug, depending on the vehicle and concentration

used, can either be suspended or dissolved in the vehicle Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle

Dosage levels of the order of from about 0 1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment or preventions of conditions involving pathogenic C5a activity, particularly those disorders list in the "background of the invention" section (about 0 5 mg to about 7 g per patient per day) The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient

Frequency of dosage may also vary depending on the compound used and the particular disease treated However, for treatment of most disorders, a dosage regimen of 4 times daily, three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion,

drug combination (i e , other drugs being administered to the patient), the severity of the particular disease undergoing therapy, and other factors, including the judgment of the prescribing medical practitioner

Preferred compounds of the invention will have favorable pharmacological properties Such properties include, but are not limited to bioavailability (e g , oral bioavailibilty, preferably high enough to permit oral administration), low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lifes Distribution in the body to sites of complement activity is also desirable, e g , compounds to treat compounds used to treat CNS disorders will preferably penetrate the blood brain barrier, while low brain levels of compounds used to treat periphereal disorders are often preferred

Assays may be used to predict these desirable pharmacological properties Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers Toxicity to cultured hepatocyctes may be used to predict compound toxicity Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously

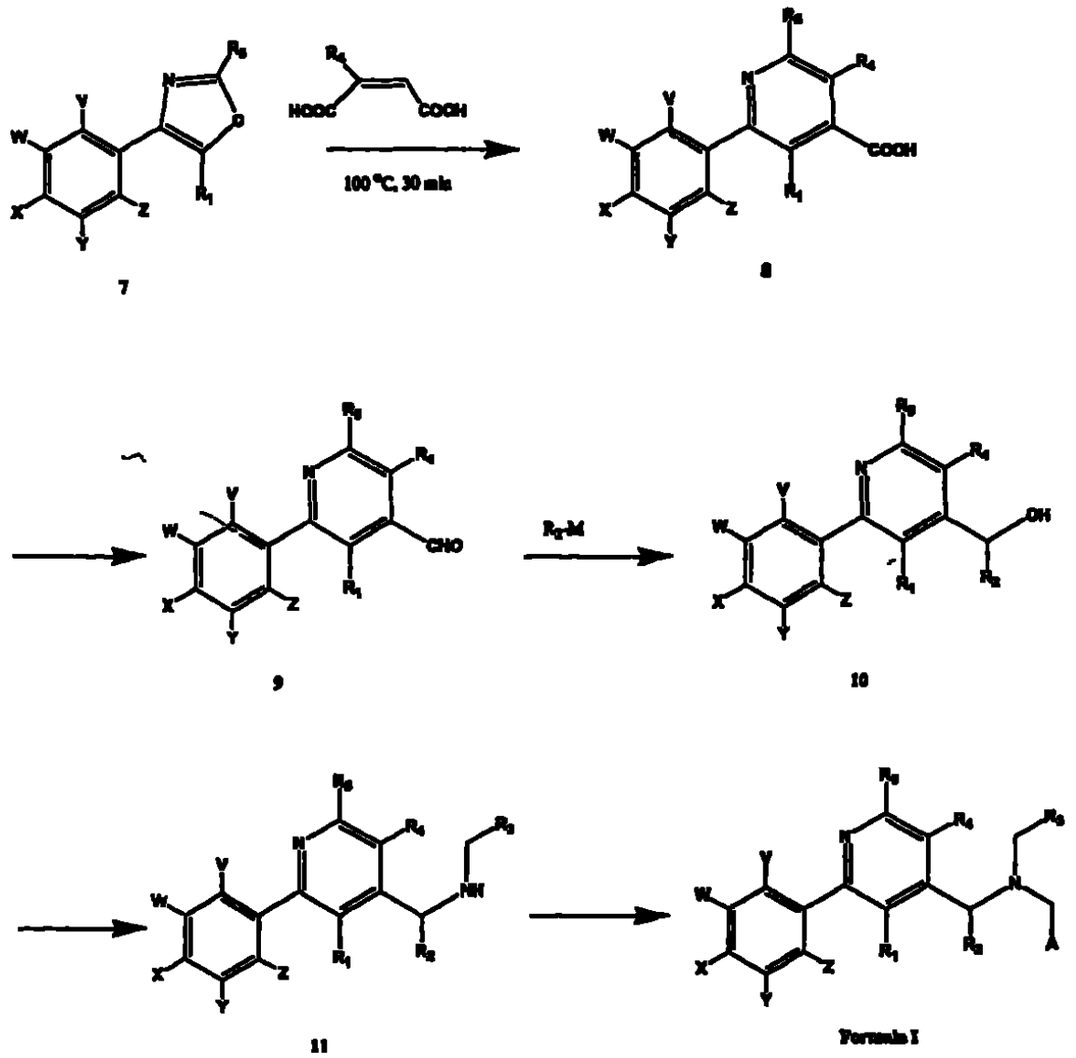
Serum protein binding may be predicted from albumin binding assays Such assays are described in a review by Oravcová, et al (Journal of Chromatography B (1996) volume 677, pages 1-27)

Compound half-life is inversely proportional to the frequency of dosage required for the effective administration of a compound *In vitro* half-lifes of compounds may be predicted, e g , from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127)

Preparation of Compounds

An illustration of the preparation of compounds of the present invention is given in Scheme 1 Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention Within Scheme 1 the variables A, R_1, R_2, R_3, R_4 R_5, V, W, X, Y and Z are defined as previously described

Scheme 1. Preparation of compounds of Formula I



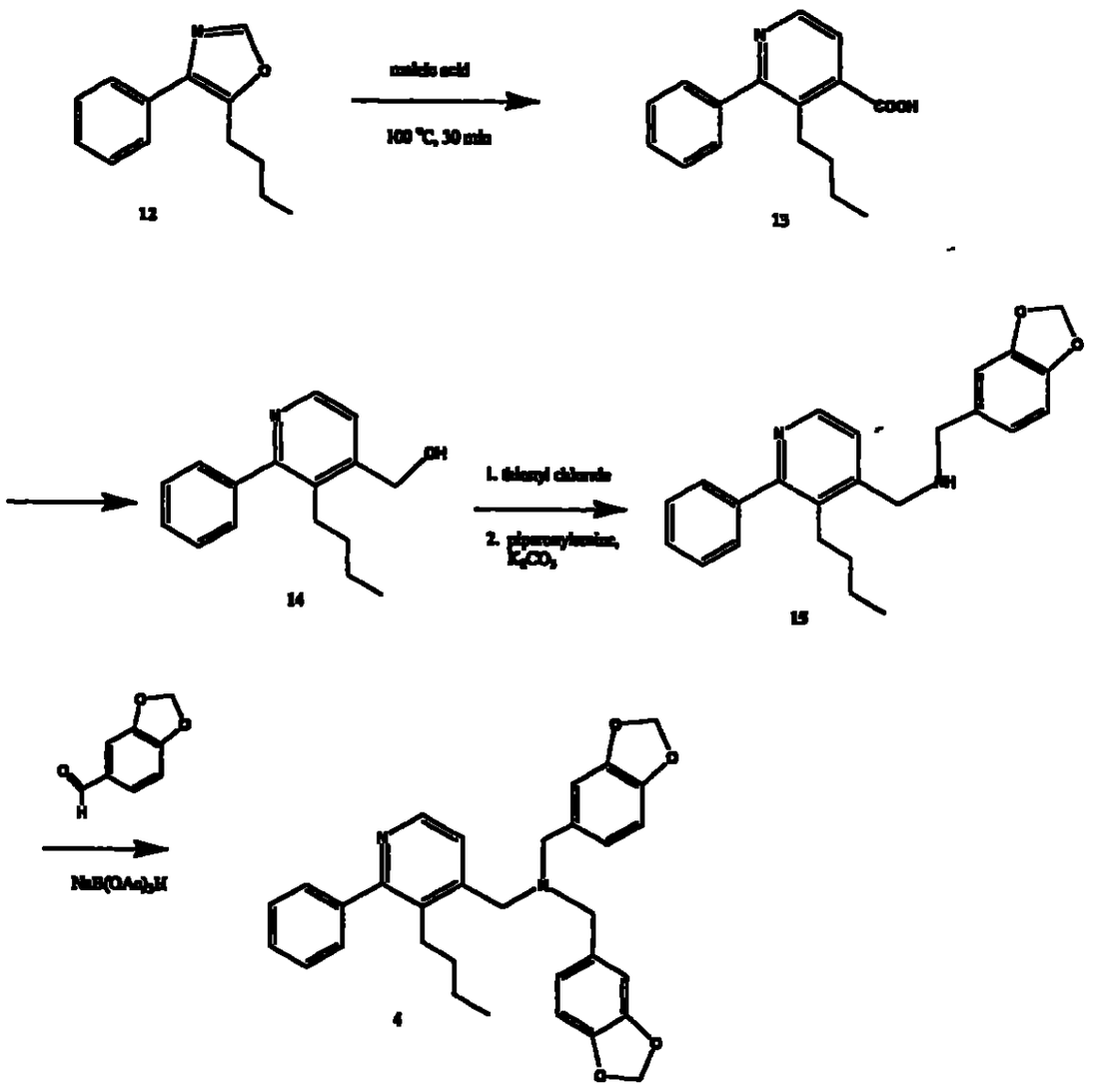
As shown in Scheme 1, an appropriately substituted 4-phenyloxazole 7 is condensed with an appropriately substituted maleic acid to provide a 2-phenylisonicotinic acid 8 The carboxylic acid functionality of 8 can reduced directly to the primary alcohol (10, R_2 = H) or converted by methods known to the

art to an intermediate aldehyde 9 and subsequently treated with the appropriate the appropriate organometallic (for cases where R_2 is alkyl) to give a secondary alcohol 10 Compounds of general formula 11 can be prepared from 10 by one of several methods described in the chemical literature, for instance, by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a primary amine Compounds of formula 11 can then be transformed into compounds of general Formula I by direct treatment with the appropriate alkylating agent or, alternatively, by reductive alkylation Alternatively, the tertiary amine functionality of Formula I may be realized directly from compounds of formula 10 by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a secondary amine

Scheme 2 is a graphical representation of the preparation of a specific compound of this invention (Compound 4) according to the general route described graphically in Scheme 1 The preparation of Compound 4 and the subsequent demonstration of its ability to inhibit C5a mediated chemotaxis represents a reduction to practice of the described invention

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1153

Scheme 2. Preparation of compound 4



12 13 14 15 4

000080 98 11:2203

The invention is further illustrated by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them

EXAMPLE I Preparation of 2-phenyl-4-(N,N-di{2H-Benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}amino)methyl-3-butylpyridine (Compound 4, Table 1)

4-Phenyl-5-butyloxazole (12) A mixture of α-bromohexanophenone (25 5 g, 0 1 mole), ammonium formate (22 g, 0 35 mole) and formic acid (110 mL) was refluxed with stirring for 3 h The reaction mixture was poured onto ice and made basic with 10 N NaOH and extracted with ether The organic layer was washed with water, dried over sodium sulfate and concentrated The crude product was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane To provide the desired compound as an oil (8 3 g, 41 %), ^{1}H NMR (δ, $CDCl_3$, 400 MHz) 7 55 (m, 2H), 7 40 (s, 1H), 7 34 (dd, J = 7,7 Hz, 2H), 7 22 (dd, J = 7, 7 Hz, 1H), 2 74 (m, 2H), 1 6 (m, 2H), 1 30 (m, 2H), 0 84 (t, J = 7 Hz, 3H) ppm

2-Phenyl-3-butylisonicotinic acid (13) A mixture of 4-phenyl-5-butyloxazole (12, 5 g, 25 mmol) and maleic acid (3 5 g, 30 mmol) was heated at 100 °C for 30 min After cooling, the semisolid mass was triturated with ether and the solid collected by filtration ^{1}H NMR (δ, $CDCl_3$, 400 MHz) 11 68 (brs, 1H), 8 72 (d, J = 6 0 Hz, 1H), 7 73 (d, J = 5 6 Hz, 1H), 7 48-7 51 (m, 2H), 7 42-7 44 (m, 2H), 6 25 (s, 1H), 2 86 (d, J = 7 6 Hz, 2H), 1 36 (m, 2H), 1 11 (dt, J = 7 6, 7 2 Hz, 2H), 0 68 (t, J = 7 6 Hz, 3H) MS (M+1) 256, (M - 1) 254

2-Phenyl-4-hydroxymethyl-3-butylpyridine (14) To a solution of 2-phenyl-3-butylisonicotinic acid (13, 510 mg, 2 mmol) in tetrahydrofuran (20 mL) was added 4 mL of a 1M solution of lithium aluminum hydride in tetrahydrofuran The reaction was stirred overnight and then quenched with 5 mL of 15% aqueous NaOH The resulting mixture was extracted with ether, dried (Na_2SO_4) and concentrated to provide the desired hydroxymethylpyridine as an oil (470 mg) LC-MS (M+1) 242, ^{1}H NMR (□, $CDCL_3$) 8 35 (1H, d, J = 5 2 Hz), 7 30-7 39 (6H, m), 4 59 (2H, s), 2 43 (2H, t, J = 8 0 Hz), 1 23 (2H, m), 1 13 (2H, m), 0 70 (3H, t, J = 7 2 Hz)

2-Phenyl-4-{N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}}aminomethyl-3-butylpyridine (15) To a solution of 2-phenyl-4-hydroxymethyl-3-butylpyridine (400 mg, 1 66 mmol) in pentene stabilized chloroform (8 mL) was added thionyl chloride

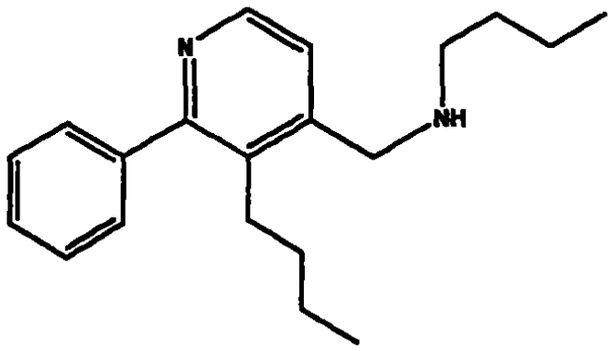
(200 mg, 1 67 mmol) and the mixture heated to 50 °C for 2 h The resulting mixture was cooled, washed with saturated sodium bicarbonate solution , dried (Na_2SO_4) and concentrated The resulting crude chloride was taken up in dimethylformamide (10 mL) and added dropwise to a refluxing solution of piperonylamine (1 0 g, 4 equiv) in dimethylformamide (30 mL) containing 3 g of powdered potassium carbonate After the addition was complete, the resulting mixture was refluxed for an additional 3 h, cooled and partitioned between water (200 mL) and ether (100 mL) The ethereal layer was washed 2 times with water, dried (Na_2SO_4) and concentrated The resulting material was purified by chromatography on silica eluting with 10% $CH_3OH/CHCl_3$ to give the desired secondary amine 15 LC-MS (M+1) 375 3, ^{1}H-NMR (δ, $CDCl_3$) 0 73 (3H, t, J = 7 2 Hz), 1 15 (2H, m J = 7 2 Hz), 1 30 (2H, m), 2 58 (2H, t, J = 8 0 Hz), 3 79 (2H, s), 3 83 (2H, s), 5 93 (2H, s), 6 75-6 82 (2H, m), 6 89 (1H, d, J = 1 2 Hz), 7 36-7 42 (6H, m), 8 45 (1H, d, J = 4 8 Hz) ppm

2-Phenyl-4-(*N*,*N*-di{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl})aminomethyl-3-butylpyridine (4) To a solution of 14 (38 mg) in dichloroethane (5 mL) was added piperonal (30 mg) The resulting mixture was stirred for 3 h after which time sodium triacetoxyborohydride (150 mg) was added in one portion and the resulting mixture was stirred overnight The reaction mixture

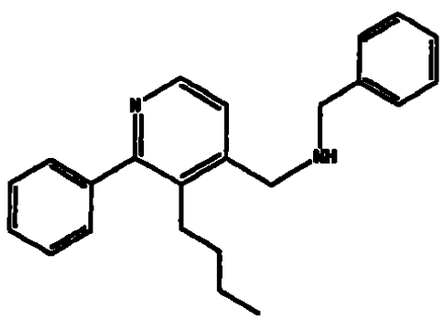
was quenched with 10% ammonium hydroxide solution (5 ml) The organic layer was washed with water and extracted with 1N HCl solution The acidic extract was made basic with 1N NaOH solution and extracted with chloroform The organic extract was dried (Na_2SO_4) and concentrated The resulting oil was purified on preparative thin layer chromatography eluting with 10% $CH_3OH/CHCl_3$ to give the desired tertiary amine 4 as an oil (18 mg) LC-MS (M+1) 509 4, ^{1}H-NMR (δ, $CDCl_3$) 0 71 (3H, t, J = 7 2 Hz), 1 10 (2H, m, J = 7 2 Hz), 2 60 (2H, t, J = 8 0 Hz), 3 48 (4H, s), 3 58 (2H, s), 5 94 (4H, s), 6 75 (1H, d, J = 8 0 Hz),6 80 (1H, dd, J = 0 8, 8 0 Hz), 6 91 (1H, d, J = 0 8 Hz), 7 36-7 43 (5H, m), 7 56 (1H, d, J = 5 2 Hz), 8 47 (1H, d, J = 5 2 Hz) ppm

Example 2

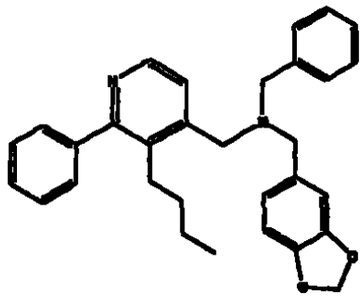
The following compounds were prepared using methods similar to those described in Example 1 Those skilled in the art will recognized where reagents or reaction conditions may be modified to provide the described final products



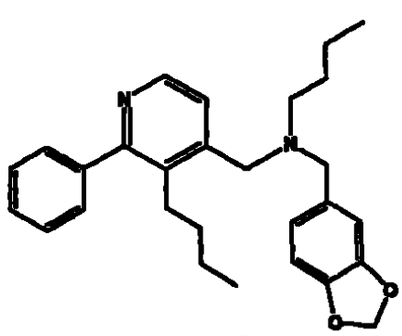
2-Phenyl-4-(*N*-{n-butyl})aminomehyl-3-butylpyridine LC-MS (M+1) 297 3, ^{1}H-NMR (δ, $CDCl_3$) 8 43 (1H, d, J = 5 2 Hz), 7 34 - 7 42 (5H, m), 7 32 (1H, d, J = 4 8 Hz), 3 85 (2H, s), 2 68 (2H, t, J = 7 2 Hz), 2 61 (2H, m), 1 53 (2H, m), 1 30 - 1 44 (4H, m), 1 19 (2H, m, J = 7 6 Hz), 0 92 (3H, t, J = 7 2 Hz,), 0 74 (3H, t, J = 7 2 Hz)



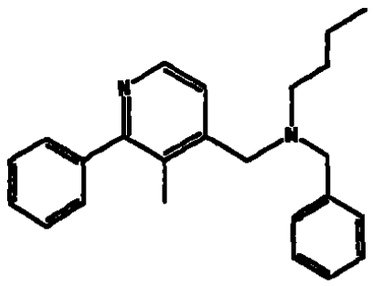
2-Phenyl-4-(*N*-benzyl)aminomethyl-3-butylpyridine LC-MS (M+1) 331 3, ^{1}H-NMR (δ, $CDCl_3$) 8 40 (1H, d, J = 5 Hz), 7 35 - 7 45 (10H, m), 7 30 (1H, d, J = 5 Hz), 3 90 (2H, s), 3 75 (2H, s), 2 58 (2H, M), 1 30 (2H, m), 1 14 (2H, m, J = 7 2 Hz), 0 74 (3H, t, J = 7 2 Hz)



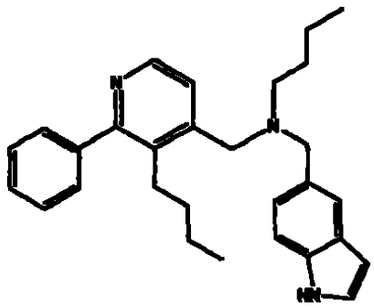
2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-benzyl)aminomethyl-3-butylpyridine (Compound 2, Table 1) LC-MS (M+1) 465 3, ^{1}H-NMR (δ, $CDCl_3$,. 0 70 (3H, t, J = 7 2 Hz), 1 09 (2H, m, J = 7 2 Hz), 1 22 (2H, m), 2 59 (2H, t, J = 8 0 Hz), 3 49 (2H, s), 3 58 (2H, s), 3 60 (2H, s), 5 94 (2H, s), 6 75 (1H, d, J = 8 0 Hz), 6 81 (1H, dd, J = 1 6, 8 0 Hz), 6 88 (1H, d, J = 1 6 Hz), 7 22-7 44 (10H, m), 7 60 (1H, d, J = 5 2 Hz), 8 47 (1H, d, J = 5 2 Hz) ppm



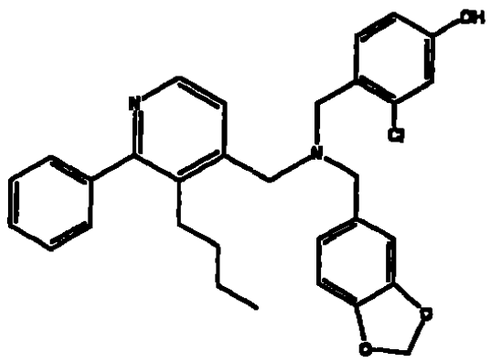
2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-butyl)aminomethyl-3-butylpyridine (Compound 1, Table 1)



2-Phenyl-4-(*N*-benzyl-*N*-{n-butyl})aminomethyl-3-methylpyridine (Compound 3, Table 1)

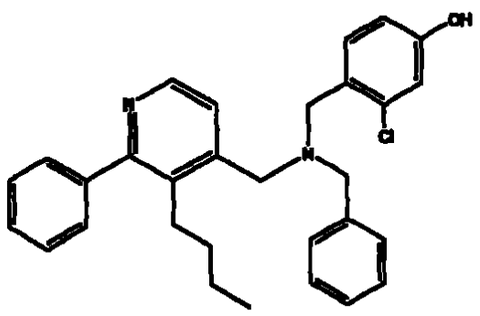


2-Phenyl-4-(*N*-indol-5-ylmethyl-*N*-{n-butyl})aminomethyl-3-butylpyridine (Compound 5, Table 1)

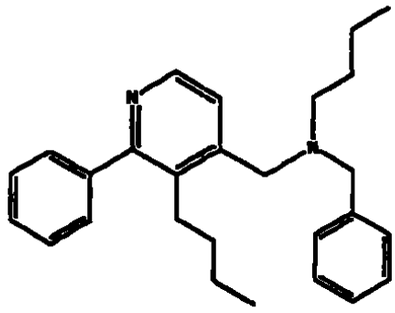


2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-{2-chloro-4-hydroxybenzyl})aminomethyl-3-butylpyridine LC-MS (M+1)

515 3, ^{1}H-NMR (δ, $CDCl_3$) 0 69 (3H, t, J = 7 2 Hz), 1.08 (2H, m, J = 7 2 Hz), 1 20 (2H, m), 2 57 (2H, t, J = 8 0 Hz), 3 50 (2H, s), 3 58 (2H, s), 3 60 (2H, s), 5 92 (2H, s), 6 52 (1H, dd, J = 2 8, 8 4 Hz), 6 61 (1H, d, J = 2.8 Hz), 6 73 (1H, d, J = 8 4 Hz), 6 79 (1H, dd, J = 1 2, 8 0 Hz), 6 89 (1H, d, J = 1 2 Hz), 7 23 (1H, d, J = 8 0 Hz), 7 30-7 43 (5H, m), 7 58 (1H, d, J = 5 2 Hz), 8 37 (1H, d, J = 5 2 Hz) ppm

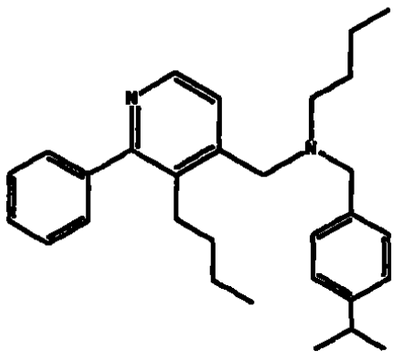


2-Phenyl-4-{*N*-(2-chloro-4-hydroxybenzyl}-*N*-benzyl)aminomethyl-3-butylpyridine (Compound 6, Table 1) LC-MS (M+1) 471 3; ^{1}H-NMR (δ, $CDCl_3$) 0 69 (3H, t, J = 7 2 Hz), 1 08 (2H, m, J = 7 2 Hz), 1 20 (2H, m), 2 57 (2H, t, J = 8 0 Hz), 3 60 (2H, s), 3 61 (2H, s), 3 63 (2H, s), 6 53 (1H, dd, J = 2 8, 8 4 Hz), 6 62 (1H, d, J = 2 8 Hz), 7 23-7 41 (11H, m), 7 63 (1H, d, J = 5 2 Hz), 8 38 (1H, d, J = 5 2 Hz) ppm



2-Phenyl-4-(*N*-benzyl-*N*-(n-butyl))aminomethyl-3-butylpyridine LC-MS (M+1) 437 4, ^{1}H-NMR (δ, $CDCl_3$) 0 72 (3H, t, J = 7 2 Hz), 0 86 (3H, t, J = 7 2 Hz), 1 13 (2H, m, J = 7 2 Hz), 1 21-1 36 (4H, m), 1 53 (2H, m), 2 45 (2H, t, J = 7 2 Hz), 2 58 (2H, t, J = 8 0 Hz), 3 59 (4H, s), 6 49 (1H, dd, J = 2 8, 8 4 Hz), 6 59 (1H, d, J = 2 8 Hz), 7 19 (1H, d, J = 8 4 Hz), 7 30-7 40 (5H, m), 7 56 (1H, d, J = 5 2 Hz), 8 36 (1H, d, J = 5 2 Hz) ppm

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2-Phenyl-4-(N-{4-[2-propyl]benzyl}-N-(n-butyl})aminomethyl-3-butylpyridine LC-MS (M+1) 429 6, ^{1}H-NMR (δ, $CDCl_3$) 0 73 (3H, t, J = 7 2 Hz), 0 87 (3H, t, J = 7 2 Hz), 1 12 (2H, m, J = 7 2 Hz), 1 25 (6H, d, J = 7 2 Hz), 1 21-1 38 (4H, m), 1 54 (2H, m, J = 7 2 Hz), 2.46 (2H, t, J = 7 2 Hz), 2 61 (2H, t, J = 8 0 Hz),

2 90 (1H, m, J = 7 2 Hz), 3 58 (2H, s), 3 59 (2H, s), 7 19 (2H, d, J = 8 0 Hz), 7 30 (2H, d J = 8 0 Hz), 7 35-7 44 (5H, m), 7 55 (1H, d, J = 5 2 Hz), 8 45 (1H, d, J = 5 2 Hz) ppm

Example 3

Assay for C5a Receptor Mediated Chemotaxis

This assay is a standard assay of C5a receptor mediated chemotaxis

Human promonocytic U937 cells are treated with dibutyryl cAMP for 48 hours prior to performing the assay The cells are pelleted and resuspended in culture media containing 0 1% fetal bovine serum (FBS) and 10 ug/ml calcein AM (a fluorescent dye) This suspension is then incubated at 37 °C for 30 minutes such that the cells take up the fluorescent dye The suspension is then centrifuged briefly to pellet the cells, which are then resuspended in culture media containing 0 1% FBS at a concentration of approximately 3 x 10^6 cells/mL Aliquots of this cell suspension are transferred to clean test tubes, which contain vehicle (1% DMSO) or varying concentrations of a compound of interest, and incubated at room temperature for at least 30 minutes The chemotaxis assay is performed in ChemoTx 101-8, 96 well plates The bottom wells of the plate are filled with varying concentrations of human C5a (0-10 nM) The top wells of the plate are filled with cell suspensions (compound or vehicle-

treated) The plate is then placed in a tissue culture incubator for 60 minutes The top surface of the plate is washed with PBS to remove excess cell suspension The number of cells that have migrated into the bottom well is then determined using a fluorescence reader Chemotaxis index (the ratio of migrated cells to total number of cells loaded) is then calculated for each compound concentration to determine an EC_{50} value

As a control to insure that cells retain chemotactic ability in the presence of the compound of interest, the bottom wells of the plate may be filled with varying concentrations chemoattractants that do not mediate chemotaxis via the C5a receptor, e g zymosan-activated serum (ZAS), N-formylmethionyl-leucyl-phenylalanine (FMLP) or leukotriene B4(LTB4)

Compounds of the accompanying Examples exhibit EC_{50} values of less than 1 5 μM in the above assay for C5a mediated chemotaxis Data is shown for several representative compounds of this invention in Table 2

TABLE 2

Compound Number	EC_{50}
2	442 nM
4	488 nM
6	485 nM

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Example 4
Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I) Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds Such suppliers include Amersham Corporation, Arlington Heights, IL, Cambridge Isotope Laboratories, Inc Andover, MA, SRI International, Menlo Park, CA, Wizard Laboratories, West Sacramento, CA, ChemSyn Laboratories, Lexena, KS, American Radiolabeled Chemicals, Inc , St Louis, MO, and Moravek Biochemicals Inc , Brea, CA

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate In addition, certain precursors may be subjected to

tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate

Example 4a

Preparation of a Radiolabeled compounds of the invention

Maleic acid, [1,4-^{14}C], ARC-568, supplied by American Radiolabeled Chemicals, Inc , St Louis MO, may be used in one synthetic method for preparing radiolabeled compounds of the invention In this method, an appropriately substituted 4-phenyloxazole (7) is condensed with ^{14}C labeled maleic acid to provide the labeled 2-phenylisonicotinic acid (8) as shown in Scheme I above

Example 5

Use of compounds of the invention as probes for C5a receptors in cultured cells and tissue samples

Receptor autoradiography (receptor mapping) of C5a receptors in cultured cells or tissue samples is carried out in vitro as described by Kuhar in sections 8 1 1 to 8 1 9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example

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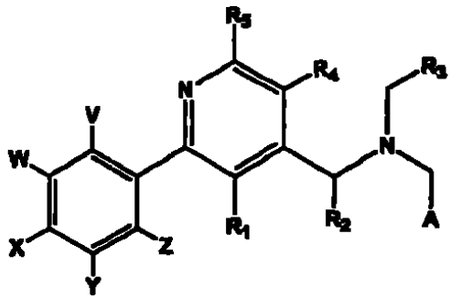
The disclosures in this application of all articles and references, including patents, are incorporated herein by reference

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference

The invention and the manner and process of making and using it are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims To particularly point out and distinctly claim the subject matter regarded as the invention, the following claims conclude the specification

What is claimed is

1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein,

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted aralkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

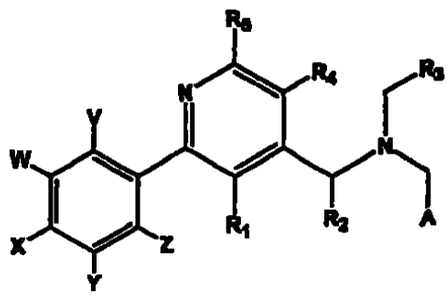
R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

R_3 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

A represents optionally substituted carbocyclic aryl, optionally substituted aralkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

2 A compound according to Claim 1, of the formula



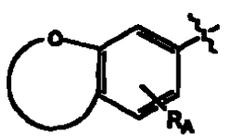
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, or

R_3 is a phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl or indolyl group, each of which is optionally susbstituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

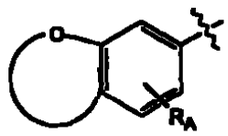
R_4 is hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl or alkoxy, or

R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono or dialkyl sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl or haloalkyl, each of which may be substituted or unsubstituted,

A is phenyl, pyridyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, or indolyl group, each of which is optionally substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or dialkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

A is a bicyclic oxygen containing group of the formula

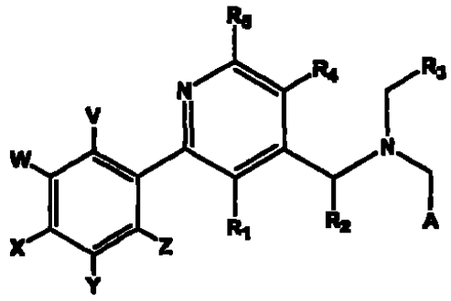


wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl,

haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or dialkylamino, alkyl, alkoxy, akenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, trifluoromethyl, or trifluoromethoxy

3 A compound according to Claim 1, of the formula



R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

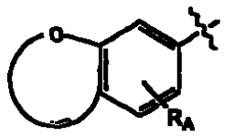
R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl,

C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

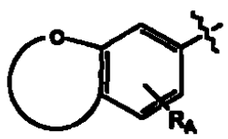
R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

A is a bicyclic oxygen containing group of the formula



wherein R_A, represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or

di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

4 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

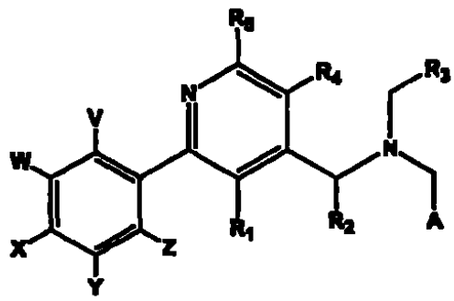
R_2 is hydrogen, methyl or ethyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

4 A compound according to Claim 1, of the formula:



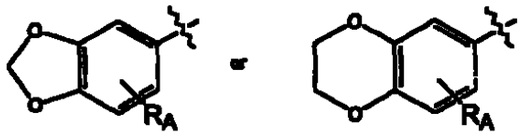
R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

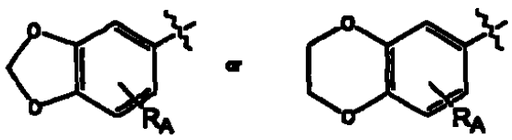
R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, or

A is a bicyclic oxygen containing group of the formula



wherein R_A, represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy.

5 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl;

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

6 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydiogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

7 A compound according to Claim 3, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

8 A compound according to claim 1, which is selected from

2-Phenyl-4-(*N*,*N*-di{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl})aminomethyl-3- butylpyridine,

2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-benzyl)aminomethyl-3- butylpyridine,

2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-butyl)aminomethyl-3-butylpyridine,

2-Phenyl-4-(*N*-benzyl-*N*-{n-butyl})aminomethyl-3-methylpyridine,

2-Phenyl-4-(*N*-indol-5-ylmethyl-*N*-{n-butyl})aminomethyl-3-butylpyridine,

2-Phenyl-4-(*N*-{2H-Benzo[3,4-d]1,3-dioxolan-5-ylmethyl}-*N*-{2-chloro-4- hydroxybenzyl})aminomethyl-3-butylpyridine,

2-Phenyl-4-(*N*-{2-chloro-4-hydroxybenzyl}-*N*-benzyl)aminomethyl-3-butylpyridine, and

2-Phenyl-4-(N-{4-[2-propyl]benzyl}-N-{n-butyl})aminomethyl-3-butylpyridine

9 A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient

10 A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 9 in a container and comprising instructions for using the composition to treat a patient in need of anti-inflammatory treatment

11 The packaged pharmaceutical composition of claim 9, wherein said patient is suffering from rheumatoid arthritis, Crohn's disease, irritable bowel syndrome, ARDS, extracorporeal post-dialysis syndrome, systemic lupus erythematosus, psoriasis or bronchial asthma

12 The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory diseases

13 A method of treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory disorders which comprises administering to patient in need of such

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treatment a C5a receptor-modulatory effective amount of a compound according to Claim 1

14 A method of inhibiting leukocyte chemotaxis, which comprises

contacting a compound of Claim 1 with white blood cells, wherein the compound is present at a concentration sufficient to inhibit chemotaxis of white blood cells *in vitro*

15 A method for the treatment of physiological disorders associated with localized excess concentrations of C5a, which method comprises administration to a patient in need of such treatment a compound according Claim 1, wherein the compound is administered in an amount sufficient to yield, at a site of localized excess concentrations of C5a, a concentration of the compound sufficient to inhibit chemotaxis of white blood cells *in vitro*

16 A method for localizing C5a receptors in tissue section samples comprising

contacting with a sample of tissue a detectably-labelled compound of claim 1 under conditions that permit binding of the compound to the sample of tissue,

washing the tissue sample to remove unbound compound, and

detecting the bound compound

17 A method of inhibiting the binding of C5a to C5a receptors, which method comprises contacting a solution comprising the compound of Claim 1 with C5a receptors, wherein the compound is present in the solution at a concentration sufficient to alter the chemotactic responses to C5a of white blood cells *in vitro*

18 A method for altering the activity of cell surface C5a receptors, said method comprising contacting cells expressing such receptors with a solution comprising the compound of Claim 1, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white blood cells in vitro.

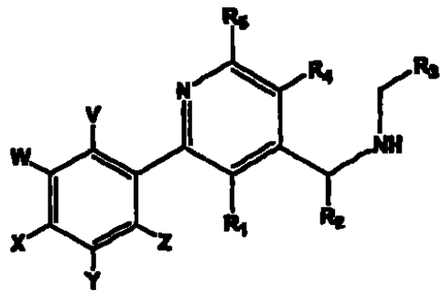
19 A compound according to claim 1 wherein in an assay of C5a mediated chemotaxis the compound exhibits an IC_{50} of 1 micromolar or less

20 A compound according to claim 1 wherein in an assay of C5a mediated chemotaxis the compound exhibits an IC_{50} of 100 nanomolar or less

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21 A compound of the formula



wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted araalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted phenyl,

R_5 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, optionally substituted mono or dialkylamino, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, or optionally substituted haloalkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl, or optionally substituted alkylsulfonyl

22 A compound according to Claim 21, wherein

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-

C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

23 A compound according to Claim 21, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_1-C_8 alkyl,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

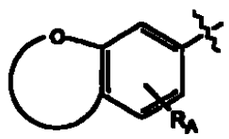
24 A compound according to Claim 21, wherein

R_1 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl,

R_2 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl,

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 3-, or 4-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R_4 is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

R_5 is hydrogen, C_1-C_8 alkyl C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_1-C_6)alkylamino, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, trifluoromethyl or trifluoromethoxy

25 A compound according to Claim 21, wherein

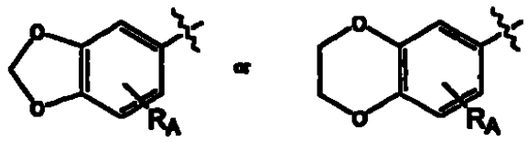
R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-

C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, or

R_3 is a bicyclic oxygen containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, or trifluormethyl,

R_5 is hydrogen, methyl or ethyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, amino, mono or di(C_1-C_3)alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Title 1-Aryl-4-aminomethylpyrazoles

BACKGROUND

Field of the Invention

This invention relates to certain 1-Aryl-4-aminomethylpyrazoles which when appropriately substituted, are modulators of human complement C5a receptors This invention also relates to pharmaceutical compositions comprising such compounds It further relates to the use of such compounds in treating a variety of inflammatory and immune system disorders Additionally, this invention relates to the use such compounds as probes for the localization of C5a receptors

Background of the Invention

Inflammation is the normal physiological response to cellular injury - microbial infection, physical or chemical trauma, or invasion of cancerous cells While necessary to remove infectious particles and damaged tissue, inflammation can also cause pain and further tissue damage Pathogenic inflammation is associated with various diseases, and is a hallmark of autoimmune disease

Proteins of the complement cascade play a key role in the mediation of inflammation This system of more than 20

interacting soluble and membrane-bound proteins undergoes a series of proteolytic reactions that set in motion a number of important immune functions including the recruitment of leukocytic cells to sites of injury and/or infection Additionally, proteins of the complement system mediate changes in vascular permeability and blood flow, target cells for opsonization, and effect formation of the membrane attack complex, which mediates the immune lysis of foreign cells

C5a, a 74 amino acid peptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement C5 convertase enzyme The anaphylatoxic effects of the C5a peptide are mediated through its interation with the C5a receptor, a 52 kD membrane bound G-protein coupled receptor C5a is a potent chemoattractant for polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to sites of inflammation and/or cellular injury Additionally, C5a stimulates the release of inflammatory mediators (e g , histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes, C5a also promotes the production of activated oxygen radicals and the contraction of smooth muscle

Considerable experimental evidence implicates increased levels of C5a in a number of autoimmune diseases and inflammatory

and related disorders Such autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus (and associated glomerulonephritis), psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, and immunovasculitis Such inflammatory and related conditions include neutropenia, sepsis, septic shock, Alzheimer's disease, stroke, inflammation associated with severe burns, lung injury, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, artherosclerosis and ischemic heart disease, as well as acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), tissue graft rejection, hyperacute rejection of transplanted organs, autoimmune hemolytic and thrombocytopenic states, and Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage) Also included are myasthenia gravis, pathologic sequellae associated with insulin-dependent diabetes mellitus (including diabetic retinopathy), Heyman nephritis (and other forms of glomerulonephritis), and inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (e g , during hemodialysis or via a heart-lung machine, for example, in association with heart surgery such

as coronary artery bypass grafting or heart valve replacement) such as extracorporeal post-dialysis syndrome or in association with contact with other artificial vessel or container surfaces (e g , ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, and the like) Antagonists that block the binding of C5a to its receptor or which modulate signal transduction associated with C5a-receptor interactions can inhibit the pathogenic chemotaxis associated with such inflammatory and autoimmune conditions Indeed, certain modified C5a peptides have been identified as partial C5a antagonists and have been shown to block a number of C5a mediated actions including neutrophil chemotaxis, neutropenia and superoxide formation

Despite many attempts, no one has previously been able to provide any small molecule (less than 500 Daltons MW) non-peptide, amino acid free, C5a antagonist that is free of agonist activity at the C5a receptor and that exhibits a K_i at the C5a receptor of less than 1 micromolar

SUMMARY OF THE INVENTION

The present invention provides novel compounds that are small molecule C5a receptor antagonists that are non-peptide, amino acid free, and free of C5a receptor agonist activity, which compounds exhibit a K_i at the C5a receptor of less than 1

micromolar Preferred C5a receptors are mammalian, preferably primate receptors, including human C5a receptors and may either be cloned, recombinantly expressed receptors or naturally expressed receptors

In certain embodiments these compounds also possess one or more, and preferably two or more, three or more, four or more, five or more, or all of the following properties in that they are 1) multi-aryl in structure (having a plurality of un-fused or fused aryl groups), 2) heteroaryl in structure, 3) orally available in vivo (such that a sub-lethal or pharmaceutically acceptable oral dose can provide a detectable in vitro effect such as a reduction of C5a-induced neutropenia), 4) without amide bonds, and 5) capable of inhibiting leukocyte chemotaxis at nanomolar concentrations or 6) capable of inhibiting leukocyte chemotaxis at sub-nanomolar concentrations

In one of its aspects, the invention provides substituted 2-phenyl-4-methylaminopyridines The invention also provides novel compounds of Formula I, shown below, that bind specifically, and preferably with high affinity, to C5a receptors

Novel intermediates useful for synthesizing compounds of the invention are also provided

The invention also provides pharmaceutical compositions comprising compounds of Formula I The compounds are particularly useful in the treatment of C5a-mediated

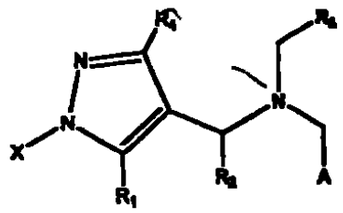
inflammation, e g , inflammation associated with various inflammatory and immune system disorders The invention further comprises a method of treating a patient in need of such anti-inflammatory treatment with a sufficient concentration of a compound of the invention A preferred concentration is one sufficient to inhibit white blood cell chemotaxis in vitro Treatment of humans, domesticated companion animals (pets) or livestock animals suffering such conditions with an effective amount of a compound of the invention is contemplated by the invention

In a separate aspect, the invention provides methods of using compounds of this invention as positive controls in assays for receptor activity and using appropriately labeled compounds of the invention as probes for the localization of receptors, particularly C5a receptors, in tissue sections

The invention provides compounds and compositions that are useful as inhibitors of C5a-mediated chemotaxis (e g , they may be used as standards in assays of such chemotaxis) The invention additionally comprises methods of inhibiting C5a-mediated chemotaxis, preferably leukocyte chemotaxis, the methods comprising contacting white blood cells with a chemotaxis-inhibitory concentration of a compound of the invention Preferably the concentration is sufficient to inhibit chemotaxis of white blood cells in an *in vitro* chemotaxis assay, so that the

levels of chemotaxis observed in a control assay (e g , one to which a compound of the invention has not been added) are significantly higher (significantly here measured as $p \leq 0.05$ using a conventional parametric statistical analysis method) than the levels observed in an assay to which one or more compounds of the invention have been added

Accordingly, a broad embodiment of the invention is directed to compounds of Formula I



and the pharmaceutically acceptable salts thereof, wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl) or haloalkyl, each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heterocyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or

R_4 is optionally substituted aryl or optionally substituted heteroaryl, or

R_2 and R_4 may be joined to form an optionally substituted saturated carbocyclic ring of from 5 to 8 members or an optionally substituted saturated heterocyclic ring of from 5 to 8 members, and

A and X independently represent optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heterocyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

DETAILED DESCRIPTION OF THE INVENTION

In addition to the compounds of general Formula I, described above, the invention provides compounds of the same general formula, and the pharmaceutically acceptable salts thereof, wherein

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or

R_4 is optionally substituted aryl or optionally substituted heteroaryl

Such compounds will be referred to as compounds of Formula Ia

The invention further includes compounds of Formula Ia, and the pharmaceutically acceptable salts thereof, wherein

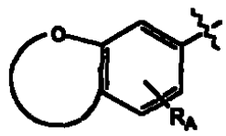
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, or

R_3 is a phenyl, pyridyl, thienyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, benzodioxolanyl, indanyl, or indolyl group, each of which is optionally susbstituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

R_3 is a bicyclic oxygen-containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

R_4 is hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl or alkoxy, or

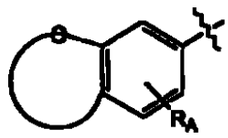
R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono or dialkyl sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy.

A and X are independently chosen from

i) phenyl, pyridyl, thienyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, benzodioxolanyl, indanyl, or indolyl group, each of which is optionally susbstituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-

alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

ii) bicyclic oxygen-containing groups of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino Such compounds will be referred to as compounds of Formula Ib

Preferred compounds of Formula Ib are those compounds wherein, R_1, R_2, R_3, R_4, A and X are defined as

R_1 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl or (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl,

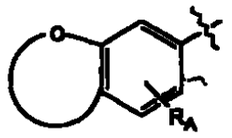
R_2 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl,

R_3 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from

halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

R_3 is a bicyclic oxygen-containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

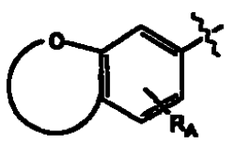
R_4 is hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl, (C_{3-8}cycloalkyl)C_{1-3}alkyl, C_{1-8} alkoxy, or C_{1-8} haloalkyl, or

R_4 is phenyl which may be substituted by up to five substituents independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_{1-6})alkylamino, aminocarbonyl, sulfonamido, mono or di(C_{1-6})alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy, and

A and X are independently chosen from

i) phenyl, 2-, 3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8}alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

ii) a bicyclic oxygen-containing group of the formula

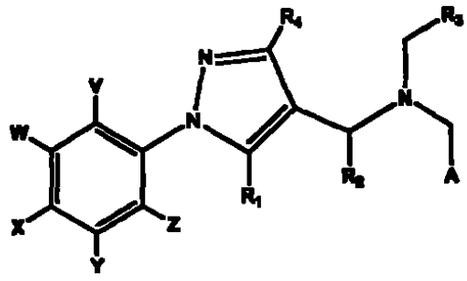


wherein R_A represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino Such compounds will be referred to as compounds of **Formula Ic**

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1203

A particular embodiment of the invention includes compounds of Formula II



Formula II

wherein

R_1 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl or (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl,

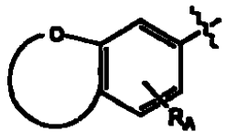
R_2 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8}alkynyl,

R_3 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_{1-3}alkyl, or C_{1-8} haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-}

$_6$)alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

R_3 is a bicyclic oxygen-containing group of the formula



wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

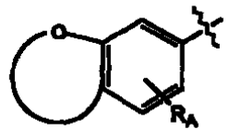
R_4 is hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl, (C_{3-8}cycloalkyl)C_{1-3}alkyl, C_{1-8} alkoxy, or C_{1-8} haloalkyl, or

R_4 is phenyl which may be substituted by up to five substituents independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_{1-6})alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl,

each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

A is a bicyclic oxygen-containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_{1-6})alkylamino, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_1-C_3alkyl, C_{1-8} alkoxy, trifluoromethyl or trifluoromethoxy

Compounds of Formula II include those compounds wherein

R_3 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, or 3-thienyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids,

aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl

Such compounds will be referred to compounds of Formula IIa

Other compounds of Formula II include compounds wherein

R_1 is C_{3-6} alkyl,

R_2 is hydrogen, methyl or ethyl,

R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono or dialkyl sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy, and

V, W, X, Y and Z are the same or different and represent hydrogen, hydroxy, halogen, amino, mono or di(C_{1-3})alkylamino, C_1-C_3 alkyl, C_1-C_3 alkoxy, trifluoromethyl, or trifluoromethoxy

Such compounds will be referred to compounds of Formula IIb

Preferred compounds of Formula II are compounds wherein

R_1 is C_{3-6} alkyl,

R_2 is hydrogen, methyl or ethyl;

R_3 is C_{1-6} alkyl or C_{3-8}cycloalkyl;

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy, or

R_3 is 4-, or 5-benzodioxolanyl, or 1-or 2-indanyl each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, and aminocarbonyl,

R_4 is phenyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, hydroxy, halogen, amino, mono or di(C_{1-3})alkylamino, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, or trifluoromethoxy

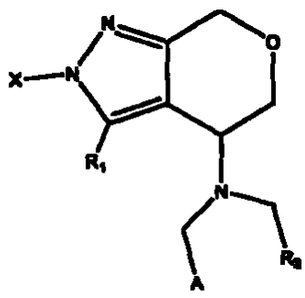
Such compounds will be referred to as compounds of Formula IIc

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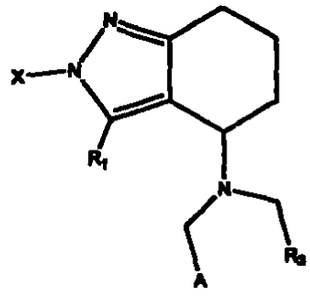
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Preferred compounds of the invention include those compounds where V, W, X, Y, and Z are independently chosen from methyl, halogen, methoxy or hydrogen, and compounds where V, W, X, Y, and Z are all hydrogen Preferred compounds of the invention also include compounds wherein R_1 is C_{1-6} alkyl, R_2 is hydrogen or methyl, and R_4 is substituted or unsubstituted phenyl Preferred R_3 groups include C_{2-6}alkyl, C_{3-8}cycloalkykl, substituted and unsubstituted phenyl, cyclohexyl, indanyl, and bicyclic oxygen-containing groups such as dihydrobenzofuranyl, chromanyl, benzodioxolyl, and benzodioxanyl groups Preferred A groups include bicyclic oxygen-containing groups such as dihydrobenzofuranyl, chromanyl, benzodioxolyl, and benzodioxanyl groups, and substituted and unsubstituted phenyl groups

When R_2 and R_4 are joined to form a form an optionally substituted saturated carbocyclic ring of from 5 to 8 members or and optionally substituted saturated heterocyclic ring of from 5 to 8 members, compounds of the following types are particularly envisioned



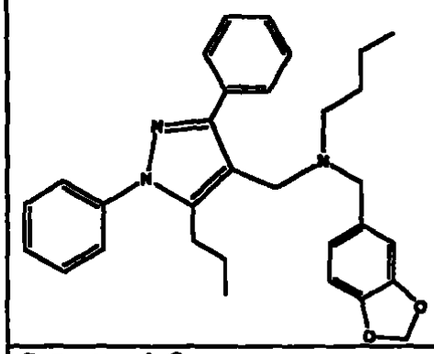
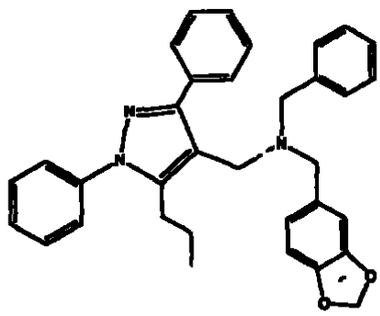
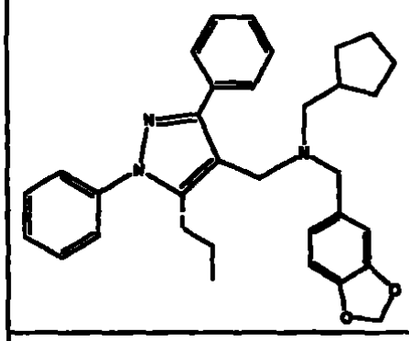
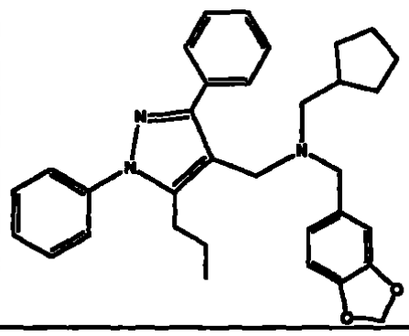
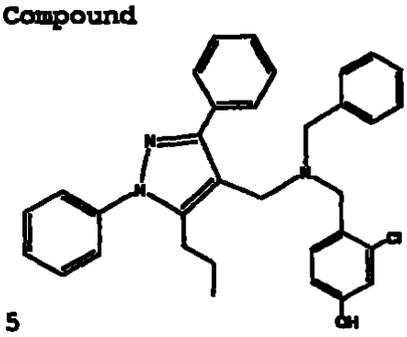
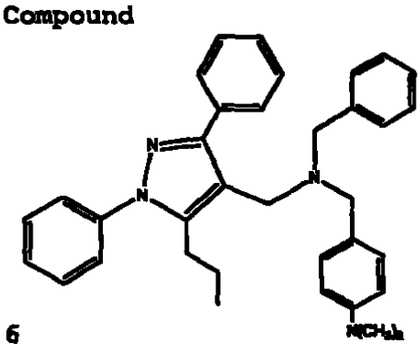
and



Representative compounds of the invention are shown in Table I

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TABLE I

Compound 1 	Compound 2 
Compound 3 	Compound 4 
Compound 5 	Compound 6 

This invention provides 1-aryl-4-aminomethylpyrazole compounds, and especially 1-phenyl-4-aminomethylpyrazole compounds, that bind with high affinity to C5a receptors, particularly human C5a receptors This invention also comprises such compounds that bind with high selectivity to C5a receptors, particularly human C5a receptors The interaction of compounds of the invention with C5a receptors is shown by the inhibition of C5a-mediated chemotaxis e g , as described in Example 3 While not wishing to be bound by any particular theory of operation, it is believed that this interaction results in the pharmacological activity of these compounds This invention includes compounds that inhibit C5a mediated chemotaxis Preferred compounds exhibit EC_{50} values of less than 1 μM in an assay of C5a mediated chemotaxis, more preferred compounds exhibit EC_{50} values of less than 500 nM, and most preferred compounds exhibit EC_{50} values of less than 250 nM

The invention includes methods for the treatment or prevention of disorders responsive to C5a receptor modulation, including but not limited to all of the inflammatory or autoimmune disorders involving pathogenic C5a activity discussed above in the "background of the invention" section, which comprise administering to a patient in need of such treatment an effective amount of compound of the invention

The present invention furthermore provides pharmaceutical compositions comprising a compound or compounds of the invention together with at least one pharmaceutically acceptable carrier or excipient The invention also pertains to packaged pharmaceutical compositions for treating disorders responsive to C5a receptor modulation, e g , any of the inflammatory or autoimmune disorders discussed above as the "background of the invention" including but not limited to arthritis, ARDS, and Alzheimer's Disease The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one C5a receptor modulator as described supra and instructions for its use for the treatment of a disorder responsive to C5a receptor modulation

This invention also includes compounds that act as selective modulators of G-coupled protein receptors, especially the C5a receptor Preferably, compounds of this invention do not bind to dopamine receptors Most preferably compounds of this invention do not exhibit binding constants less than 1 μM at dopamine receptors in a standard radioligand binding assay for dopamine binding activity (US patent no 5,159,083, col 8, and U S patent application no 09/594,040 pages 49-51, which are hereby incorporated herein by reference for their teachings in regard to such assays)

The present invention also pertains to methods of inhibiting the binding of C5a to C5a receptors which methods involve

contacting a compound of the invention with cells expressing C5a receptors, wherein the compound is present at a concentration sufficient to inhibit C5a binding to C5a receptors *in vitro* This method includes inhibiting the binding of C5a to C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I sufficient to produce a body fluid concentration capable of altering the chemotactic responses to C5a of white blood cells *in vitro* In one embodiment, such methods are useful in treating physiological disorders associated with excess concentrations of C5a The amount of a compound that would be sufficient to inhibit the binding of a C5a to the C5a receptor may be readily determined via a C5a receptor binding assay, or from the EC_{50} obtained via a C5a receptor functional assay, such as the standard assay of C5a receptor mediated chemotaxis described in Example 3 The C5a receptors used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of leukocytes, preferably human leukocytes, or from cultured cells expressing human C5a receptors, e g promonocytic U937 cells activated by the method described in Example 3 or cells expressing cloned C5a receptors

The present invention also pertains to methods for altering the activity of C5a receptors, said method comprising exposing cells expressing such receptors to a solution comprising an effective amount of a compound of the invention, wherein the compound is present in the solution at a concentration sufficient to specifically alter the chemotactic responses to C5a of white

blood cells *in vitro* This method includes altering the activity of C5a receptors *in vivo*, e g , in a patient given an amount of a compound of Formula I sufficient to produce a body fluid concentration capable of altering the chemotactic responses to C5a of white blood cells *in vitro* The amount of a compound that would be sufficient to alter the chemotactic activity of C5a receptors may be determined via an assay of C5a receptor mediated chemotaxis, such as the standard assay described in Example 5

The C5a receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a compound to interact with the C5a receptor

Labeled derivatives the C5a receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT)

Definitions

As indicated above, various substituents of the various formulae may be "substituted or unsubstituted" or "optionally substituted" including A, R_1, R_2, R_3, R_4, V, W, X, Y, and Z of Formula I, and such substituents as recited in the sub-formulae such as Formulae II and the like When substituted, those substituents (A, R_1, R_2, R_3, R_4, V, W, X, Y, and Z) may be substituted by other than hydrogen at one or more available

positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein Suitable groups that may be present on a "substituted" A, R_1, R_2, R_3, R_4, V, W, X, Y, and Z group or other substituent include e g halogen such as fluoro, chloro, bromo and iodo, cyano, hydroxyl, nitro, azido, alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like, carboxamido, alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms, alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, aryloxy such as phenoxy, alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms, aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms, carbocyclic aryl having 6 or more carbons, particularly phenyl (e g an "A"group being a substituted or unsubstituted

biphenyl moiety), aralkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group, aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group, or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e g coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl

When "arylalkyl" is specified in the present invention the point of attachment is the alkyl group

By the terms "alkyl" and "C_{y-z} alkyl" in the present invention is meant straight or branched chain alkyl groups of generally up to 6 or 8 carbon atoms, or for C_{y-z} alkyl the number of carbon atoms specified, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl Preferred C_{1-8} alkyl groups are methyl, ethyl, propyl, butyl, pentyl and cyclopentyl

The terms "alkoxy" and "C_{1-z} alkoxy" represent an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge Examples of alkoxy include,

but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy

The term "alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl

The term "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl

The term "carbocylic aryl" is used to indicate aromatic groups that contain only carbon atoms in the ring structure Such groups are optionally substituted

The term "cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl

In the term "(C_{3-x} cycloalkyl)C_{1-y} alkyl the point of attachment is on the alkyl group This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl, cyclohexylmethyl

The term "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having

the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1) Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl

By the term "halogen" is meant fluorine, chlorine, bromine or iodine

As used herein, the terms "heterocyclic group" or "heterocycloalkyl" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, 0 and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring The nitrogen and sulfur heteroatoms may optionally be oxidized The term "heteroaryl" is used to specifically indicate aromatic heterocyclic groups.

The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable A nitrogen in the heterocycle may optionally be quaternized It is preferred that when the total number of S

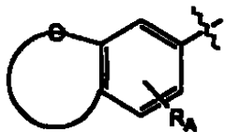
and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another It is preferred that the total number of S and O atoms in the heterocycle is not more than 1 As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from N, O and S It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benoztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,- 1,2,5-

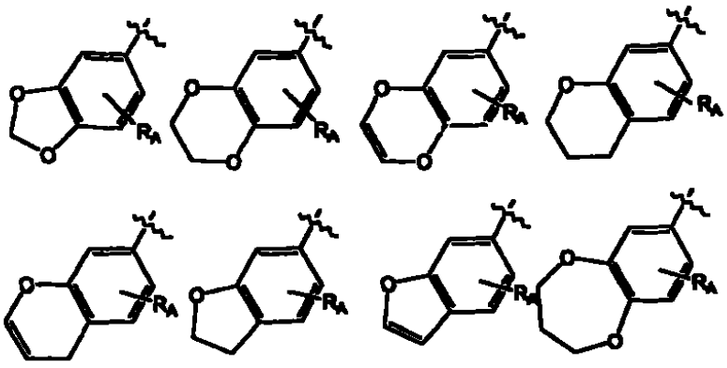
oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl

Preferred heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, benzodioxolanyl, piperonyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl Also included are fused ring and spiro compounds containing, for example, the above heterocycles

Examples of bicyclic oxygen-containing groups of the formula



include the following (R_A may also be indicated by R_A')



Pharmaceutical Preparations

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred The term parenteral as used herein includes injections and the like, such as subcutaneous, intradermal, intravascular (e g , intravenous), intramuscular, intrasternal, spinal, intrathecal, and like injection or infusion techniques,

with subcutaneous, intramuscular and intravascular injections or infusions being preferred In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, corn starch,

or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic

alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives Suitable dispersing or wetting agents and suspending agents are

exemplified by those already mentioned above Additional excipients, for example sweetening, flavoring and coloring agents, may also be present

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate The emulsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above The sterile injectable preparation may also be sterile

injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables

The compounds of general Formula I may also be administered in the form of suppositories e g , for rectal administration of the drug These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug Such materials are cocoa butter and polyethylene glycols

Compounds of general Formula I may be administered parenterally, preferably in a sterile non-toxic, pyrogen-free medium The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle

Dosage levels of the order of from about 0 1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment or preventions of conditions involving pathogenic C5a activity, particularly those disorders list in the "background of the invention" section (about 0 5 mg to about 7 g, and preferably 0 5 to 1 g, per human patient per day) The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient

Frequency of dosage may also vary depending on the compound used and the particular disease treated However, for treatment of most disorders, a dosage regimen of 4 times daily, three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i e , other drugs being administered to the patient), the severity of the particular disease undergoing

therapy, and other factors, including the judgment of the prescribing medical practitioner

Preferred compounds of the invention will have favorable pharmacological properties Such properties include, but are not limited to bioavailability (e g., oral bioavailibilty, preferably high enough to permit oral administration), low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lifes Distribution in the body to sites of complement activity is also desirable, e g , compounds to treat compounds used to treat CNS disorders will preferably penetrate the blood brain barrier, while low brain levels of compounds used to treat periphereal disorders are often preferred

Assays may be used to predict these desirable pharmacological properties Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers Toxicity to cultured hepatocyctes may be used to predict compound toxicity Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously

Serum protein binding may be predicted from albumin binding assays Such assays are described in a review by Oravcová, et al (Journal of Chromatography B (1996) volume 677, pages 1-27)

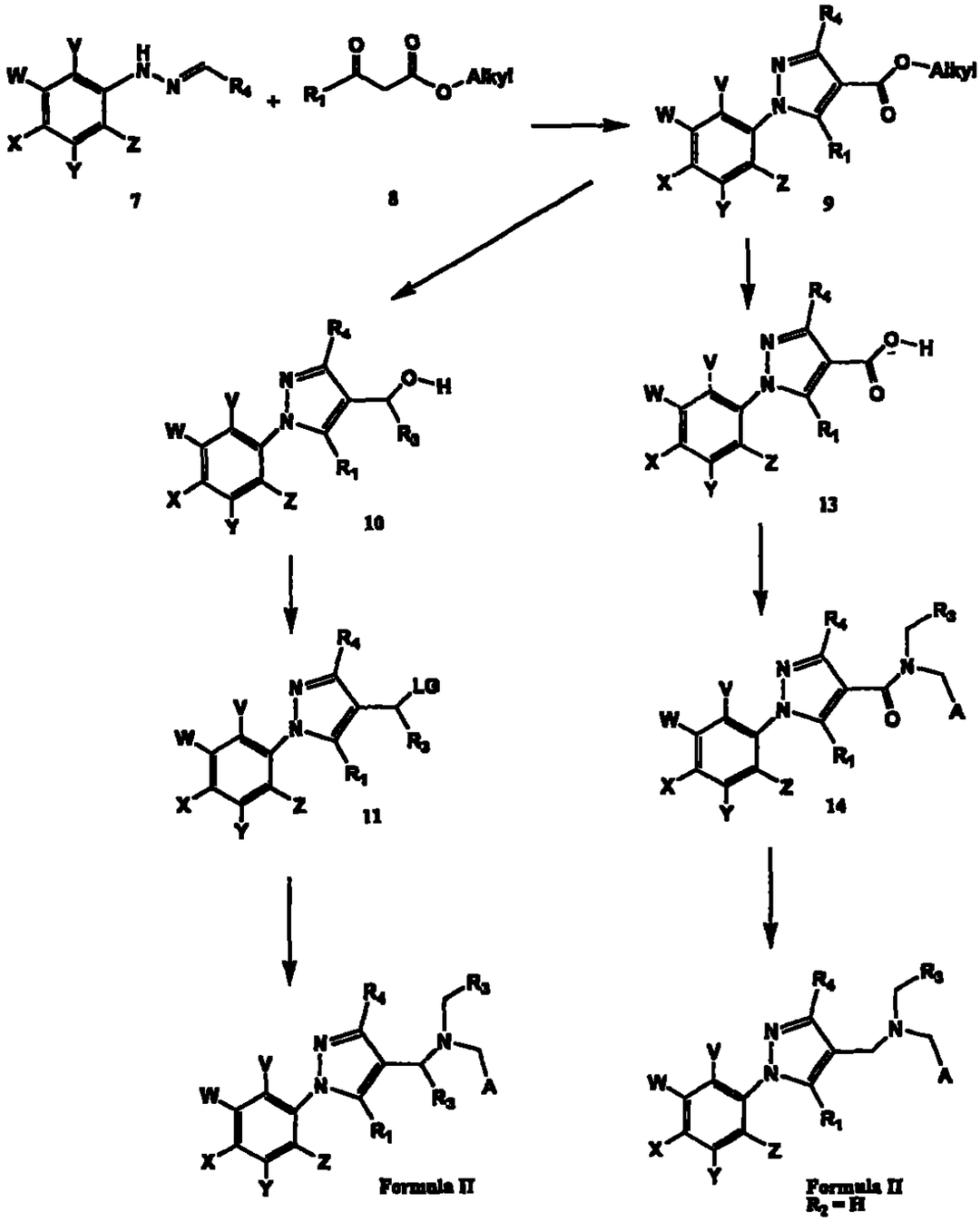
Compound half-life is inversely proportional to the frequency of dosage required for the effective administration of a compound *In vitro* half-lifes of compounds may be predicted, e g , from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127)

Preparation of Compounds

An illustration of the preparation of compounds of the present invention is given in Scheme 1 Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention Within Scheme 1 the variables A, R_1, R_2, R_3, R_4, V, W, X, Y, and Z are defined as previously described

1235
1230

Scheme 1. Preparation of Compounds of Formula II.



As shown in Scheme 1, an appropriately substituted phenylhydrazine adduct 7 is condensed with an appropriately substituted β-ketoester acid 8, in the presence of a Louis acid, preferably $ZnCl_2$, with heating at 50 - 200 °C, preferably at 125 °C to provide a 1-phenylpyrazole ester 9 The carboxylic acid functionality of 9 can be reduced directly to the primary alcohol (10, R_2 = H) or converted by methods known to the art to an intermediate aldehyde and subsequently treated with the appropriate the appropriate organometallic (for cases where R_2 is alkyl) to give a secondary alcohol 10 Compounds of general formula 11, where LG represents a leaving group, can be prepared from 10 by one of several methods described in the chemical literature, for instance, by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a primary amine Compounds of formula 11 can then be transformed into compounds of general Formula II by sequential treatment with the appropriate primary amine followed by direct alkylation or reductive alkylation of the intermediate secondary amine Alternatively, the tertiary amine functionality of Formula II may be realized directly from compounds of formula 10 by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a secondary amine

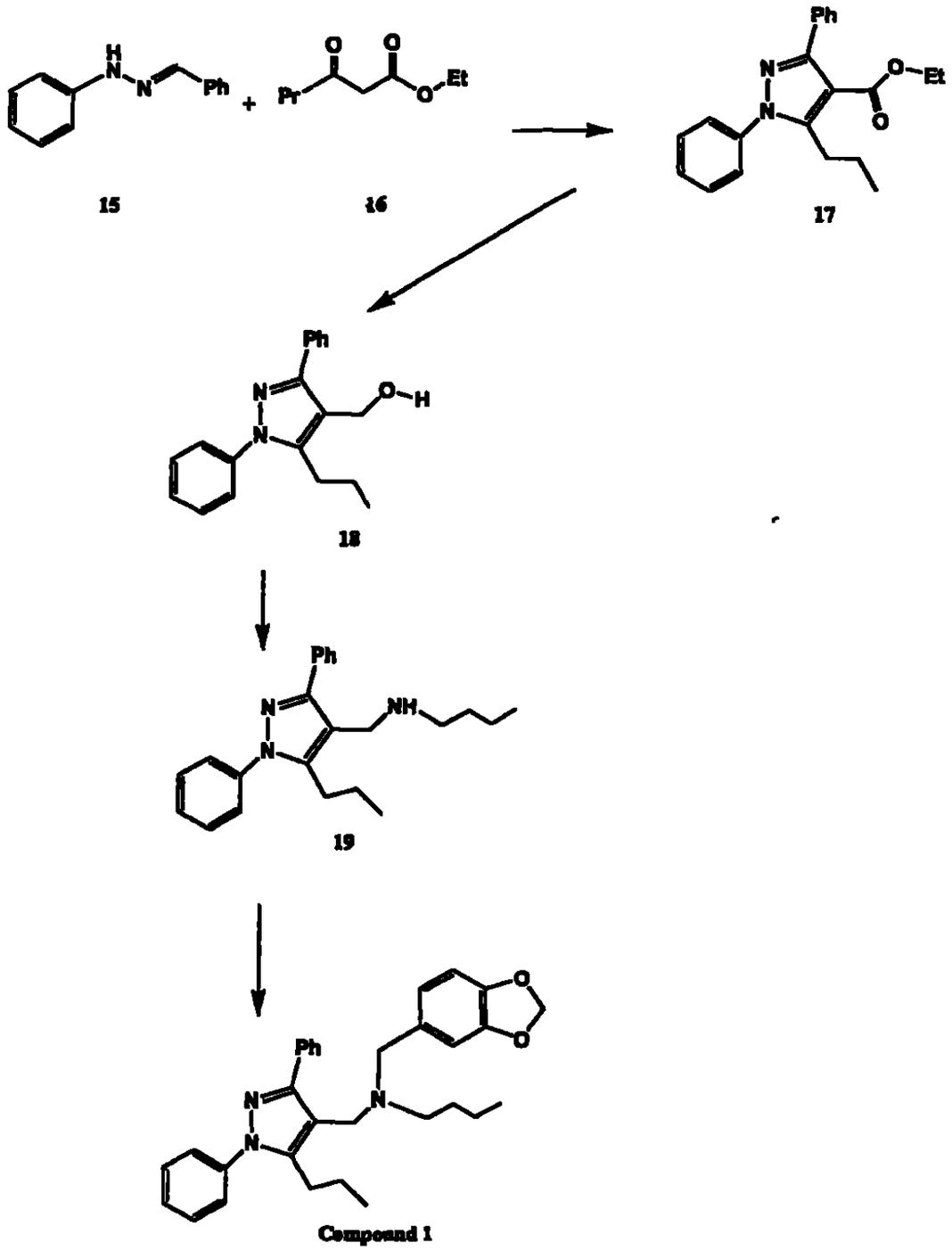
An alternative route to the preparation of compounds of Formula II from the 1-phenylpyrazole ester 9 may be realized by hydrolysis of 9 to a carboxylic acid of general structure 13, followed by amide formation to provide 14 and, finally, reduction of the amide functionality to the tertiary amine of Formula II

Scheme 2 is a graphical representation of the preparation of a specific compound of this invention (Compound 1, Table 1) according to the general route described graphically in Scheme 1

000080-9E0i.2203

1239
1233

Scheme 2. Preparation of Compound 1.



15 16 17 18 19

Compound 1

The invention is further illustrated by the following examples, which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them

EXAMPLE I Preparation of 1,3-diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-butylamino)methyl-5-propylpyrazole (Compound 1, Table 1)

N'-Phenyl-N-phenylhydrazone (15) Benzaldehyde (9 81 g, 9 25 mmol) is added at 0-5 °C to a solution of phenyl hydrazine (10 g, 9 25 mmol) in ethanol (100 mL) A cream colored solid forms and the reaction mixture is allowed to stand for 2h The solid is collected by filtration, washed with ice-cold ethanol and dried under vacuum to provide the desired compound, compound 15 (14 92 g),LC-MS m/z 197 2, ^{1}H NMR (δ, $CDCl_3$, 400 MHz) ppm

Ethyl 1,3-diphenyl-5-propylpyrazole-4-carboxylate (17) A mixture of 15 (5 g, 25.5 mmol) and ethyl butyrylacetate (20 2 g, 128 mmol) and a catalytic amount of zinc chloride is heated at 125 °C under an air atmosphere for 3h The reaction vessel is fitted with a short path distillation head and excess ethyl butyrylacetate iss distilled away under vacuum The resulting material is purified by column chromatography on silica eluting with 10% ethyl acetate in hexanes to provide the desired ester 17 as a yellow oil (6 39 g) which crystallizes upon standing

Recrystallization from diisopropyl ether provides a white solid ^1H NMR (δ, $CDCl_3$, 400 MHz) MS (M+1) 335 2

1,3-Diphenyl-4-hydroxymethyl-5-propylpyrazole (18) To a solution of ester 17 (670 mg, 2 mmol) in tetrahydrofuran (20 mL) is added 4 mL of a 1M solution of lithium aluminum hydride in tetrahydrofuran The reaction is stirred overnight and then quenched with 5 mL of 15% aqueous NaOH The resulting mixture is extracted with ether, dried (Na_2SO_4) and concentrated to provide the desired hydroxymethylpyrazole as an oil (505 mg) LC-MS (M+1) 293 3, ^1H NMR (δ, $CDCL_3$) 7 86 (dd, J = 8 4 Hz, 2H), 7 34-7 52 (m, 8H), 4 65 (s, 2H), 2 72 (t, J = 8 0 Hz, 2H), 1 52 (m, 2H), 0 87 (t, J = 7 6 Hz, 3H)

[(1,3-Diphenyl-5-propylpyrazol-4-yl)methyl]butylamine (19) To a solution of 18 (289 mg) in pentene stabilized chloroform (8 mL) is added thionyl chloride (1 mL) and the mixture heated to 60 °C for 2 h The resulting mixture is cooled, washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and concentrated The resulting crude chloride is taken up in dimethylformamide (3 mL) and added dropwise to a solution of butylamine (1 0 g) in dimethylformamide (10 mL) containing 2 g of powdered potassium carbonate After the addition is complete, the resulting mixture is stirred for an additional 3 h and partitioned between water (20 mL) and ether (10 mL) The ethereal layer is washed 2 times with water, dried (Na_2SO_4) and

concentrated The resulting material is purified by chromatography on silica eluting with 10% $CH_3OH/CHCl_3$ to give the desired secondary amine 19 (190 mg) LC-MS (M+1) 348 3, ^1H-NMR (δ, $CDCl_3$) 7 87 (dd, J = 8 0, 1 6 Hz, 2H), 7 32-7 48 (m, 8H), 3 77 (s, 2H), 2 70 (m, 4H), 1 48 (m, 4H), 1 34 (m, 2H), 0 91 (t, J = 7 6 Hz, 3H), 0 87 (t, J = 7 6 Hz, 3H) ppm

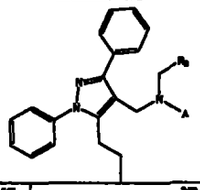
1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-butylamino)methyl-5-propylpyrazole (Compound 1, Table 1) To a solution of 19 (35 mg) in dichloroethane (5 mL) is added piperonal (30 mg) The resulting mixture is stirred for 3 h after which time sodium triacetoxyborohydride (150 mg) is added in one portion and the resulting mixture is stirred overnight The reaction mixture is quenched with 10% ammonium hydroxide solution (5 ml) The organic layer is washed with water and extracted with 1N HCl solution The acidic extract is made basic with 1N NaOH solution and extracted with chloroform The organic extract is dried (Na_2SO_4) and concentrated The resulting oil is purified on preparative thin layer chromatography eluting with 10% $CH_3OH/CHCl_3$ to give the desired tertiary amine (Compound 1) as an oil (24 mg) LC-MS (M+1) 482 5, ^1H-NMR (δ, $CDCl_3$) 7 87 (d, J = 7 2 Hz, 2H), 7 47 (d, J = 4 4 Hz, 4H), 7 33-7 43 (m, 4H), 6 77 (s, 1H), 6 70 (s, 2H), 5 92 (s, 2H), 3 56 (s, 2H), 3 42 (s, 2H), 2 74 (t, J = 8 0 Hz, 2H), 2 37 (t, J = 7 2 Hz, 2H), 1 42 (m,

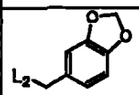
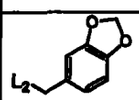
4H), 1 21 (m, 2H), 0 83 (t, J = 7 6 Hz, 3H), 0 81 (t, J = 7 2 Hz, 3H) ppm

Example 2

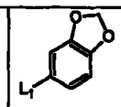
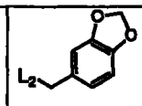
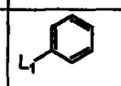
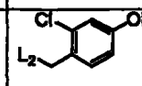
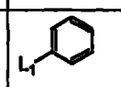
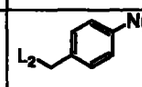
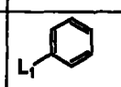
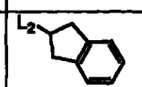
The following compounds are prepared using methods similar to those described in Example 1 Those skilled in the art will recognized where reagents or reaction conditions may be modified to provide the described final products The starting materials and various intermediates may be obtained from commercial sources, or be prepared from commercially available organic and inorganic materials without further purification, using known synthetic methods

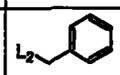
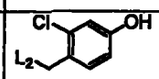
TABLE II

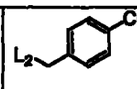
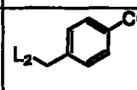
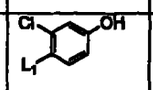
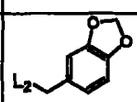


Cmp #	R_3	Ar	LC/MS M +1	NMR ^{1}H-NMR (400 MHz, δ, $CDCl_3$) ppm	Name
2			488 4	2 33 (3H, s), 3 43 (2H, s), 3 52 (2H, s), 3 57 (2H, s), 5 93 (2H, s), 6 71 (2H, s), 6 79 (1H, s), 7 19-7 29 (5H, m), 7 33-7 40 (4H, m), 7 46 (4H, d, J = 4 8 Hz), 7 83 (2H, dd, J = 8 4, 1 6 Hz)	1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-benzylamino)methyl-5-propylpyrazole
3			480 4	1 18 (2H, m), 1 45 (4H, m), 1 69 (2H, m), 2 15 (1H, m, J = 7 6 Hz), 2 28 (2H, d, J = 7 6 Hz), 2 35 (3H, s), 3 44 (2H, s), 3 54 (2H, s), 5 92(2H, s), 6 70 (2H, s), 6 80 (1H, s), 7 32-7 43 (4H, m), 7 45-7 50 (4H, m), 7 92(2H, d, J = 6 8 Hz)	1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-cyclopentylmethylamino)methyl-5-propylpyrazole

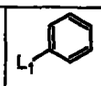
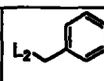
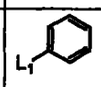
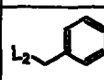
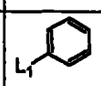
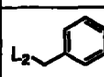
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4			532 3	2 34 (3H, s), 3 41 (4H, s), 3 55 (2H, s), 5 93 (4H, s), 6 71 (4H, s), 6 77 (2H, s), 7 34-7 41 (4H, m), 7 44-7 48 (4H, m), 7 82 (2H, dd, J = 8 4, 1 6 Hz)	1,3-Diphenyl-4-(N,N-bis(2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl)-5-propylpyrazole
5			522 4	0 73 (3H, t, J = 7 6 Hz), 1 29 (2H, m, J = 7 6 Hz), 2 68 (2H, t, J = 8 0 Hz), 3 48 (2H, s), 3 49 (2H, s), 3 57 (2H, s), 6 46 (1H, dd, J = 8 4, 2 4 Hz), 6 63 (1H, d, J = 2 4 Hz), 7 03 (1H, d, J = 8 4 Hz), 7 19-7 25 (5H, m), 7 28-7 35 (4H, m), 7 39 (2H, m), 7 46 (2H, dd, J = 8 0, 1 6 Hz)	1,3-Diphenyl-4-(N-(2-chloro-4-hydroxybenzyl)-N-butylamino)methyl-5-propylpyrazole
6			487 4	2 33 (3H, s), 2 93 (6H, s), 3 46 (2H, s), 3 52 (2H, s), 3 57 (2H, s), 6 69 (2H, d, J = 8 8 Hz), 7 15 (2H, d, J = 8 8 Hz), 7 20-7 28 (5H, m), 7 33-7 39 (4H, m), 7 46 (4H, d, J = 4 8 Hz), 7 85 (2H, dd, J = 8 0, 1 6 Hz)	1,3-Diphenyl-4-(N-(4-dimethylaminobenzyl)-N-benzylamino)methyl-5-propylpyrazole,
20			470 6	2 32 (3H, s), 2 88 (1H, d, J = 8 0 Hz), 2 92 (1H, d, J = 8 0 Hz), 3 03 (1H, d, J = 7 2 Hz), 3 07 (1H, d, J = 7 2 Hz), 3 56 (2H, s), 3 66 (2H, s), 3 79 (1H, pent, J =	1,3-Diphenyl-4-(N-indan-2-yl-N-benzylamino)methyl-5-propylpyrazole

				7 6 Hz), 7 09-7 25 (9H, m), 7 34-7 48 (8H, m), 7 84 (2H, dd, J = 8 0, 1 6 Hz)	
21	L_1-$(CH_2)_2CH_3$		438 4	0 79 (3H, t, J = 7 2 Hz), 0 80 (3H, t, J = 7 2 Hz), 1 20 (2H, m, J = 7 2 Hz), 1 43 (4H, m, J = 7 6 Hz), 2 39 (2H, t, J = 7 2 Hz), 2 73 (2H, t, J = 8 0 Hz), 3 51 (2H, s), 3 58 (2H, s), 7 25 (5H, m), 7 32-7 42 (4H, m), 7 46 (4H, d, J = 4 4 Hz), 7 88 (2H, d, J = 7 2 Hz)	1,3-Diphenyl-4-(N-benzyl-N-butylamino)methyl-5-propylpyrazole,
22	L_1-$(CH_2)_2CH_3$		488 4	0 77 (3H, t, J = 7 2 Hz), 0 79 (3H, t, J = 7 6 Hz), 1 18 (2H, m, J = 7 6 Hz), 1 36 (2H, m, J = 7 6 Hz), 1 44 (2H, m, J = 7 2 Hz), 2 40 (2H, t, J = 7 6 Hz), 2 69 (2H, t, J = 8 0 Hz), 3 53 (2H, s), 3 56 (2H, s), 6 51 (1H, dd, J = 8 4, 2 8 Hz), 6 72 (1H, d, J = 2 8 Hz), 7 09 (1H, d, J = 8 4 Hz), 7 29-7 44 (8H, m), 7 85 (2H, d, J = 7 2 Hz	1,3-Diphenyl-4-(N-(2-chloro-4-hydroxybenzyl)-N-butylamino)methyl-5-propylpyrazole

23	L_1-$(CH_2)_2CH_3$		496 4	0 79 (3H, t, J = 7 6 Hz), 0 82 (3H, t, J = 7 6 Hz), 1 19 (2H, m, J = 7 6 Hz), 1 43 (4H, m, J = 7 6 Hz), 2 38 (2H, t, J = 7 6 Hz), 2 72 (2H, t, J = 9 0 Hz), 3 54 (2H, s), 3 60 (2H, s), 3 89 (3H, s), 7 28 (2H, d, J = 8 0 Hz), 7 33-7 48(8H, m), 7 80 (2H, d, J = 6 8 Hz), 7 92 (2H, d, J = 8 4 Hz)	1,3-Diphenyl-4-(N-(4-methoxycarboxybenzyl)-N-(n-butyl)amino)methyl-5-propylpyrazole,
24	L_1-$(CH_2)_2CH_3$		482 3	0 74 (3H, br s), 0 76 (3H, br s), 1 13 (2H, br), 1 37 (4H, br), 2 31 (2H, br), 2 67 (2H, br), 3 46 (2H, s), 3 54 (2H, s), 7 19 (2H, br), 7 29-7 41 (8H, m), 7 82 (2H, d, J = 6 4 Hz), 7 92 (2H, br s)	1,3-Diphenyl-4-(N-(4-carboxybenzyl)-N-(n-butylamino))methyl-5-propylpyrazole
25			566 3	0 75 (3H, t, J = 7 6 Hz), 1 32 (2H, m, J = 7 6 Hz), 2 69 (2H, t, J = 8 0 Hz), 3 39 (2H, s), 3 48 (2H, s), 3 56 (2H, s), 5 91 (2H, s), 5 94 (1H, s), 6 49 (1H, dd, J = 8 4, 2 4 Hz), 6 65 (1H, d, J =2 4 Hz), 6 67-6 85 (3H, m), 7 02 (1H, d, J = 8 4 Hz), 7 30-7 44 (8H, m), 7 74 (2H, dd, J = 8 0, 2 0 Hz)	1,3-Diphenyl-4-(N-(2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl)-N-(2-chloro-4-hydroxybenzyl)amino)methyl-5-proylpyrazole

000080 90 1.2209

26			502 3	0 77 (3H, t, J = 7 6 Hz), 1 34 (2H, m, J = 7 6 Hz), 2 72 (2H, t, J = 8 0 Hz), 3 48 (4H, s), 3 59 (2H, s), 4 66 (2H, s), 7 21-7 46 (17H, m), 7 76 (2H, dd, J = 8 0, 2 0 Hz)	1,3-Diphenyl-4-(N-{4-hydroxymethylbenzyl}-N-benzylamino)methyl-5-propylpyrazole
27			516 4	0 74 (3H, t, J = 7 6 Hz), 1 32 (2H, m, J = 7 2 Hz), 2 68 (2H, t, J = 7 2 Hz), 3 42 (2H, s), 3 46 (2H, s), 3 56 (2H, s), 7 18-7.27 (7H, m), 7 31-7 46 (8H, m), 7 71 (2H, d, J = 6 8 Hz), 7 95 (2H, s)	1,3-Diphenyl-4-(N-{4-carboxybenzyl}-N-benzyl amino)methyl-5-propyl pyrazole
28			530 4	0 78 (3H, t, J = 7 6 Hz), 1 35 (2H, m, J = 7 6 Hz), 2 71 (2H, t, J = 8 0 Hz), 3 48 (2H, s), 3 52 (2H, s), 3 61 (2H, s), 3 90 (3H, s), 7 22-7 31 (7H, m), 7 35-7 47 (8H, m), 7 74 (2H, dd, J = 7 6, 2 0 Hz), / 94 (2H, d, J = 8 4 Hz)	1,4-Diphenyl-4-(N-{4-methoxycarbonyl benzyl}-N-benzylamino)methyl-5-propylpyrazole

Example 3

Assay for C5a Receptor Mediated Chemotaxis

This assay is a standard assay of C5a receptor mediated chemotaxis

Human promonocytic U937 cells are treated with dibutyryl cAMP for 48 hours prior to performing the assay The cells are pelleted and resuspended in culture media containing 0 1% fetal bovine serum (FBS) and 10 ug/ml calcein AM (a fluorescent dye) This suspension is then incubated at 37 °C for 30 minutes such that the cells take up the fluorescent dye The suspension is then centrifuged briefly to pellet the cells, which are then resuspended in culture media containing 0 1% FBS at a concentration of approximately 3 x 10^6 cells/mL Aliquots of this cell suspension are transferred to clean test tubes, which contain vehicle (1% DMSO) or varying concentrations of a compound of interest, and incubated at room temperature for at least 30 minutes The chemotaxis assay is performed in ChemoTx 101-8, 96 well plates The bottom wells of the plate are filled with varying concentrations of human C5a (0-10 nM) The top wells of the plate are filled with cell suspensions (compound or vehicle-treated) The plate is then placed in a tissue culture incubator for 60 minutes The top surface of the plate is washed with PBS to remove excess cell suspension The number of cells that have

migrated into the bottom well is then determined using a fluorescence reader Chemotaxis index (the ratio of migrated cells to total number of cells loaded) is then calculated for each compound concentration to determine an EC_{50} value

As a control to insure that cells retain chemotactic ability in the presence of the compound of interest, the bottom wells of the plate may be filled with varying concentrations chemoattractants that do not mediate chemotaxis via the C5a receptor, e g zymosan-activated serum (ZAS), N-formylmethionyl-leucyl-phenylalanine (FMLP) or leukotriene B4(LTB4)

Compounds of the accompanying Examples exhibit EC_{50} values of less than 1 5 μM in the above assay for C5a mediated chemotaxis Data is shown for several representative compounds of this invention in Table III

TABLE III

Compound Number	EC_{50}
1	320 nM
4	1127 nM
5	174 nM

Example 4
Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I) Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds Such suppliers include Amersham Corporation, Arlington Heights, IL, Cambridge Isotope Laboratories, Inc Andover, MA, SRI International, Menlo Park, CA, Wizard Laboratories, West Sacramento, CA, ChemSyn Laboratories, Lexena, KS, American Radiolabeled Chemicals, Inc , St Louis, MO, and Moravek Biochemicals Inc , Brea, CA

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction

of unsaturated bonds, or reduction using sodium borotritide, as appropriate

Example 5

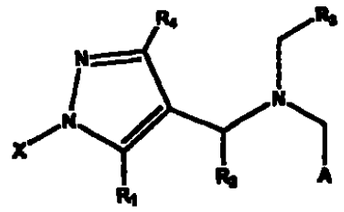
Use of compounds of the invention as probes for C5a receptors in cultured cells and tissue samples

Receptor autoradiography (receptor mapping) of C5a receptors in cultured cells or tissue samples is carried out in vitro as described by Kuhar in sections 8 1 1 to 8 1 9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example

It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims To particularly point out and distinctly claim the subject matter regarded as the invention, the following claims conclude the specification

What is claimed is

1 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl) or haloalkyl each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heterocyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

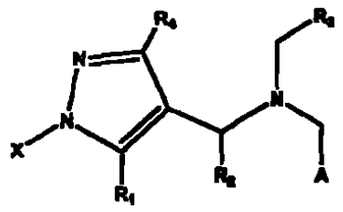
R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or

R_4 is optionally substituted aryl or optionally substituted heteroaryl, or

R_2 and R_4 may be joined to form an optionally substituted saturated carbocyclic ring of from 5 to 8 members or and optionally substituted saturated heterocyclic ring of from 5 to 8 members, and

A and X independently represent optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heterocyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

2 A compound, according to Claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl,

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl(alkyl) or haloalkyl each of which may be susbstituted or unsubstituted, or optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an

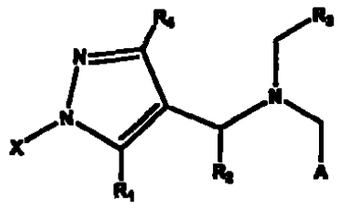
optionally substituted heterocyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_4 is hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be susbstituted or unsubstituted, or

R_4 is optionally substituted aryl or optionally substituted heteroaryl, and

A and X independently represent optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heterocyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms

3 A compound, according to Claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

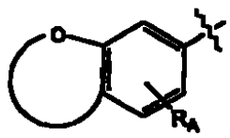
R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl,

R_2 is hydrogen, alkyl, alkenyl, or alkynyl;

R_3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, or

R_3 is a phenyl, pyridyl, thienyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, benzodioxolanyl, indanyl, or indolyl group, each of which is optionally susbstituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

R_3 is a bicyclic oxygen-containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino,

R_4 is hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl or alkoxy, or

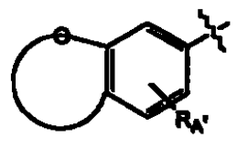
R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy,

halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono or dialkyl sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy,

A and X are independently chosen from

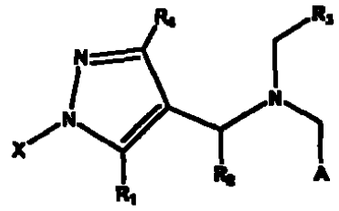
i) phenyl, pyridyl, thienyl, pyrimidinyl, dihydrobenzofuranyl, chromanyl, benzodioxanyl, benzodioxolanyl, indanyl, or indolyl group, each of which is optionally susbstituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, cyano, amino, mono- or alkylamino, haloalkyl, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

ii) bicyclic oxygen-containing groups of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or dialkylamino

4. A compound, according to Claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

R_1 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl or (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl,

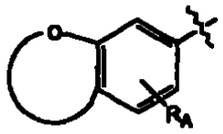
R_2 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl,

R_3 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

R_3 is a bicyclic oxygen-containing group of the formula

1259
1253



wherein R_A represents 0 to 3 qroups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino,

R_4 is hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl, (C_{3-8}cycloalkyl)C_{1-3}alkyl, C_{1-8} alkoxy, or C_{1-8} haloalkyl, or

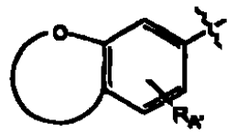
R_4 is phenyl which may be substituted by up to five substituents independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_{1-6})alkylamino, aminocarbonyl, sulfonamido, mono or di(C_{1-6})alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy, and

A and X are independently chosen from

i) phenyl, 2-, 3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1-or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl,

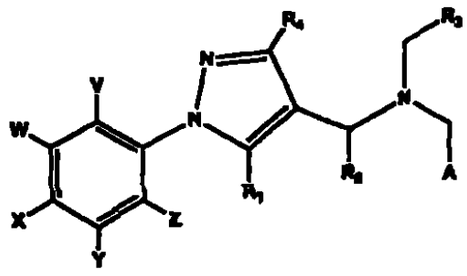
trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

ii) bicyclic oxygen-containing-groups of the formula



wherein $R_{4'}$ represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

A compound according to Claim 1, of the formula



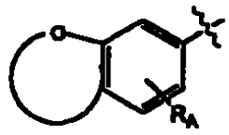
R_1 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl or (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl,

R_2 is hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl,

R_3 is C_{1-8}alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

R_3 is a bicyclic oxygen-containing group of the formula



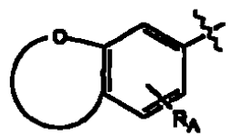
wherein R_A represents 0 to 3 groups selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino

R_4 is hydrogen, halogen, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} cycloalkyl, (C_{3-8}cycloalkyl)C_{1-3}alkyl, C_{1-8} alkoxy, or C_{1-8} haloalkyl, or

R_4 is phenyl which may be substituted by up to five substituents independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_{1-6})alkylamino, aminocarbonyl, sulfonamido, mono or di(C_{1-6})alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy,

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, or 3-thienyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

A is a bicyclic oxygen-containing group of the formula



wherein R_A represents 0 to 3 groups selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, (C_{2-6}cycloalkyl) C_{1-3}alkyl, haloalkyl, C_{1-6}alkoxy, halogen, hydroxy, amino, or mono- or di(C_{1-6}alkyl)amino, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, cyano, nitro, acetoxy, hydroxy, amino, mono or di(C_{1-6})alkylamino, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, (C_{3-8}cycloalkyl)C_{1-3}alkyl, C_{1-8} alkoxy, trifluoromethyl or trifluoromethoxy

6 A compound according to Claim 5, wherein

R_3 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_{1-3}alkyl or C_{1-8} haloalkyl, or

R_3 is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8}alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-}

$_{6}$)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

A is phenyl, 2-, 3-, or 4-pyridyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-dihydrobenzofuranyl, 2-, or 3-thienyl, 2-, 3-, or 4-chromanyl, 2-, 4-, 5-, 6-, or 7-benzodioxanyl, 4-, or 5-benzodioxolanyl, 1- or 2-indanyl, or 1-, 2-, or 3-indolyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl (C_{3-8}cycloalkyl)C_{1-3}alkyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl

7 A compound according to Claim 5, wherein

R_1 is C_{3-6} alkyl,

R_2 is hydrogen, methyl or ethyl,

R_4 is phenyl which may be substituted by up to five substituents independently selected from alkyl, alkenyl, alkynyl, alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or dialkylamino, aminocarbonyl, sulfonamido, mono or dialkyl

sulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl and trifluoromethoxy, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, hydroxy, amino, mono or di(C_{1-3})alkylamino, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, or trifluoromethoxy

8 A compound according to Claim 5, wherein

R_1 is C_{3-6} alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is C_{1-6} alkyl or C_{3-8}cycloalkyl,

R_4 is phenyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, hydroxy, amino, mono or di(C_{1-3})alkylamino, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, or trifluoromethoxy

9 A compound according to Claim 5, wherein

R_1 is C_3-C_6 alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is phenyl which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids,

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aminocarbonyl, mono or di(C_{1-6})alkylaminocarbonyl, N-(C_{1-6})alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, acetoxy, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy,

R_4 is phenyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, hydroxy, amino, mono or di(C_{1-3})alkylamino, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, or trifluoromethoxy

10 A compound according to Claim 5, wherein

R_1 is C_{3-6} alkyl,

R_2 is hydrogen, methyl or ethyl,

R_3 is 4-, or 5-benzodioxolanyl, or 1- or 2-indanyl each of which may be substituted with up to four groups independently selected from halogen, nitro, trifluoromethyl, trifluoromethoxy, hydroxy, acetoxy, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-8} alkoxy, cyano, amino, mono- or di(C_{1-6})alkylamino, carboxylic acid, esters of carboxylic acids, and aminocarbonyl,

R_4 is phenyl, and

V, W, X, Y and Z are the same or different and represent hydrogen, halogen, hydroxy, amino, mono or di(C_{1-}

$_3$)alkylamino, C_{1-3} alkyl, C_{1-3} alkoxy, trifluoromethyl, or trifluoromethoxy

11 A compound according to claim 1, which is

1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-butylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-benzyl)amino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-cyclopentylmethylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N,N-bis{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-5-propylpyrazole,

1,3-Diphenyl-4-(N-{2-chloro-4-hydroxybenzyl}-N-benzylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-{4-dimethylaminobenzyl}-N-benzylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-indan-2-yl-N-benzylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-benzyl-N-butylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-{2-chloro-4-hydroxybenzyl}-N-butylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-{4-methoxycarboxybenzyl}-N-{n-butyl}amino)methyl-5-propylpyrazole,

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1,3-Diphenyl-4-(N-{4-carboxybenzyl}-N-{n-butylamino})methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-{2-chloro-4-hydroxybenzyl}amino)methyl-5-proylpyrazole,

1,3-Diphenyl-4-(N-{4-hydroxymethylbenzyl}-N-benzylamino)methyl-5-propylpyrazole,

1,3-Diphenyl-4-(N-{4-carboxybenzyl}-N-benzylamino)methyl-5-propyl pyrazole, or

1,3-Diphenyl-4-(N-{4-methoxycarbonylbenzyl}-N-benzylamino)methyl-5-propylpyrazole

12 A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier or excipient

13 A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 12 in a container and comprising instructions for using the composition to treat a patient in need of anti-inflammatory treatment

14 The packaged pharmaceutical composition of claim 13, wherein said instructions indicate that said patient is suffering from one or more of rheumatoid arthritis, Crohn's

disease, irritable bowel syndrome, ARDS, extracorporeal post-dialysis syndrome, systemic lupus erythematosus, psoriasis or bronchial asthma

14 The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory diseases

15 A method of treatment of burns, complications of cardiopulmonary bypass, autoimmune or inflammatory disorders which comprises administering to patient in need of such treatment a C5a receptor-modulatory effective amount of a compound according to Claim 1

16 A method of inhibiting leukocyte chemotaxis, which comprises
contacting a compound of Claim 1 with white blood cells, wherein the compound is present at a concentration sufficient to inhibit chemotaxis of white blood cells *in vitro*

17 A method for the treatment of physiological disorders associated with localized excess concentrations of C5a, which method comprises administration to a patient in need of such

treatment a compound according Claim 1, wherein the compound is administered in an amount sufficient to yield, at a site of localized excess concentrations of C5a, a concentration of the compound sufficient to inhibit chemotaxis of white blood cells *in vitro*

18 A method for localizing C5a receptors in tissue section samples comprising

contacting with a sample of tissue a detectably-labelled compound of claim 1 under conditions that permit binding of the

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ABSTRACT

Disclosed are 1-Aryl-4-aminoalkylpyrazole, 1-Aryl-4-aminoalkylimidizole, cycloalkylimidazole, and 2-aryl-4aminoalkylpyridine compounds These compounds are selective modulators of human complement C5a receptors that are, therefore, useful in the treatment of a variety of immune system and inflammatory disorders Methods of treatment of such disorders and well as packaged pharmaceutical compositions are also provided.

Compounds of the invention are also useful as probes for the localization of C5a receptors and as standards in assays for C5a mediated chemotaxis Methods of using the compounds in receptor localization studies are given

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

(Attorney's Docket No. N2000.010)

Applicant or Patentee: Andrew Thurkauf, et. al.

Serial or Patent No. not yet assigned Filed Herewith

Title: Heterocyclic Compounds as Modulators of the C5a Receptor

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 C.F.R. § 1.9(f) AND § 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF SMALL BUSINESS CONCERN	NEUROGEN CORPORATION
ADDRESS OF SMALL BUSINESS CONCERN	35 NORTHEAST INDUSTRIAL ROAD BRANFORD, CT 06405

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 C.F.R. § 121, and referenced in 37 C.F.R. § 1.9(d), for purposes of paying reduced fees to the United States Patent and Trademark Office, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time, or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled Heterocyclic Compounds as Modulators of the C5a Receptor by inventor(s) Andrew Thurkauf, et. al.

described in

☒ the specification filed herewith.
☐ Application Serial No. _____ filed _____
☐ Patent No. _____ issued _____

Patent Department
NEUROGEN CORPORATION
35 Northeast Industrial Road
Branford, CT 06405
203-488-8201

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If the rights held by the above identified small business concern are not exclusive each individual concern or organization having rights in the invention must file verified statements averring to their status as small entities, and no rights to the invention are held by any person, other than the inventor who would not qualify as an independent inventor under 37 CFR § 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR § 1 9(d), or a nonprofit organization under 37 CFR § 1.9(e).

Each person, concern or organization having any rights to the invention is listed below

☒ No such person, concern or organization exists.
☐ Each such person, concern or organization is listed below

FULL NAME _____

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☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

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☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

Separate verified statements are required from each named person, concern or organization having rights in the invention averring to their status as small entities. (37 CFR § 1.27).

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate (37 C.F.R. § 1 28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed

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NAME OF PERSON SIGNING: Stephen R. Davis

TITLE IN ORGANIZATION: Senior VicePresident and Chief Business Officer

ADDRESS OF PERSON SIGNING: 35 Northeast Industrial Road
Branford CT 06405

Signature: Stephen Davis

Date: 8/9/00

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Oficina de Patentes y Marcas de los Estados Unidos

26 de diciembre de 2000

LA PRESENTE ES PARA CERTIFICAR QUE LA ANEXA A ESTA ES UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA MAS ADELANTE QUE SATISFACEN LOS REQUISITOS PARA QUE SE OTORGUE UNA FECHA DE PRIORIDAD BAJO 35 USC 111

SOLICITUD NUMERO 60/224,036

FECHA DE PRESENTACION *9 de agosto de 2000*

Por la Autoridad del
COMISIONADO DE PATENTES Y MARCAS

Firmado por

PARTE (2) DE (2) PARTES

E BORNETT

Funcionario Certificador

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$NHC(=O)-$, $-NR_cC(=O)$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$ y $NR_cS(O)_m-$ (donde m es 0, 1 ó 2),

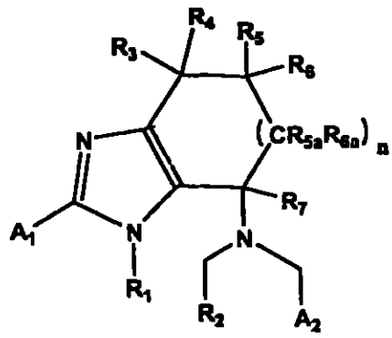
y

R_a y R_c pueden ser iguales o diferentes y están seleccionados independientemente cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada, que pueden contener uno o más dobles o triples enlaces, cada uno de los cuales puede estar no sustituido o puede estar sustituido con uno o más sustituyente(s) seleccionados de

Oxo, hidroxi, -O(alquilo), -NH(alquilo), N-(alquil)(alquilo), -NHC(O)alquilo, -N(alquilo)C(O) (alquilo), -NHS(O)x(alquilo), -S(O)x(alquilo), -S(O)xNH(alquilo), -S(O)xN(alquilo)(alquilo), (donde x es 0, 1 ó 2)

3 Un compuesto de la fórmula



O una sal farmacéuticamente aceptable del mismo, en donde

n es un número entero de 0 a 3, y

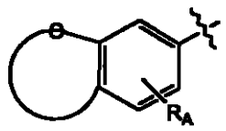
R_1 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 o alquilo C_3-C_8(cicloalquilo) o haloalquilo C_1-C_8,

R_2 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8 cicloalquilo C_1-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8, o

R_2 es fenilo, naftaleno, tiofeno o piridina cada uno de los cuales puede estar o no sustituido con

alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, mono- o dialquil(C_1-C_6)amino, o

R_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo C_3-C_6,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 o alcoxi C_1-C_7, o

R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo C_3-C_6,

R_{5a} y R_{6a} y están independientemente seleccionados cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 y alcoxi C_1-C_7,

R_7 representa hidrógeno o alquilo C_1-C_7,

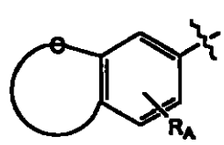
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A_1 es fenilo el cual puede estar o no sustituido con hasta 4 sustituyentes seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, hidroxi, acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo o trifluorometoxi, o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_1 es tiofeno o piridina que puede estar o no sustituido con alquilo C_1-C_7, halógeno, alcoxi C_1-C_7, amino o mono o dialquil(C_1-C_6)amino, y

A_2 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar o no sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo

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C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquil(C_1-C_6)amino,

X está independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_c-$, -O-, $-S(0)_m-$, -NH-, $-NR_c-$, $-C(=0)NH$, $-C(=0)NR_c-$, $-S(0)_mNH-$, $-S(0)_mNR_c-$, $-NHC(=0)-$, $-NR_cC(=0)$, $-NHS(0)_m-$, $-C(=0)NHS(0)_m-$ y $NR_cS(0)_m-$ (donde m es 0, 1 ó 2),

y

R_B y R_C pueden ser iguales o diferentes y están seleccionados independientemente cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada, que pueden contener uno o más dobles o triples enlaces, cada uno de los cuales puede estar no sustituido o puede estar sustituido con uno o más sustituyente(s) seleccionados de

Oxo, hidroxi, -O(alquilo C_1-C_4), -NH(alquilo C_1-C_4), N-(alquil C_1-C_4) (alquilo C_1-C_4), -NHC(O)(alquilo C_1-C_4) -N(alquiloC_1-C_4)C(O)(alquilo C_1-C_4), -NHS(O)x(alquilo C_1-C_4), -S(O)x(alquilo C_1-C_4), -S(O)xNH(alquilo C_1-C_4), -S(O)xN(alquilo C_1-C_4)(alquilo C_1-C_4), (donde x es 0, 1 ó 2)

4 Un compuesto de acuerdo con la reivindicación 3 en donde

R_3 y R_4 son iguales o diferentes y representan hidrógeno o metilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurren de hidrógeno y metilo

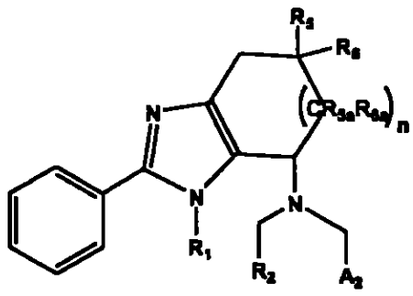
5 Un compuesto de acuerdo con la reivindicación 3, en donde

R_3 y R_4 son hidrógeno,

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurren de hidrógeno y metilo

6 Un compuesto de acuerdo con la reivindicación 3 que tiene la fórmula



O una sal farmacéuticamente aceptable del mismo, en el cual

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo,

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurre de hidrógeno y metilo, y

R_1, R_2 A_2, y n son como se definieron en la reivindicación 3

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7 Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, en el cual

R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8 o alquinilo C_2-C_8, y

R_2 A_2, y n son como se definieron en la reivindicación 6

8 Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, donde

R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8, y

R_2 es alquilo C_1-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8, y

A_2, y n son como se definieron en la reivindicación 6

9 Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, donde

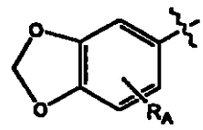
R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8,

R_2 es fenilo, que puede estar no sustituido o puede estar sustituido con

Alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 (cicloalquilo C_3-C_8)alquilo C_1-C_6, haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di alquil(C_1-C_6)amino, o

R_2 es un grupo bicíclico que contiene oxígeno que tiene la fórmula

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Donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 (cicloalquilo C_3-C_8)alquilo C_1-C_6, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquil(C_1-C_6)amino,

A_2 es fenilo que está no sustituido o sustituido con hasta cuatro grupos independientemente seleccionados de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluormetilo, y trifluormetoxi, o $-XR_B$ donde X y R_B son tal como se han definido para la reivindicación 6, y

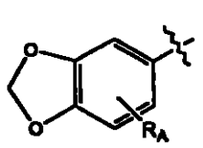
n es tal como se ha definido en la reivindicación 6

Un compuesto de acuerdo con la reivindicación 6, o una sal farmacéuticamente aceptable del mismo, en donde

R_1 es alquilo C_3-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_2 es alquilo C_1-C_8, de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

A_2 es un grupo bicíclico que contiene oxígeno que tiene la fórmula



1237 1297

Donde R_A es como se definió para la reivindicación 6, y n es tal como se ha definido en la reivindicación 6

11 Un compuesto de acuerdo con la reivindicación 1, el cual se selecciona de

4-{[butil(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))amino]metil}-3-clorofenol,

4-{[(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))bencilamino]metil}-3-clorofenol,

4-{[(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))bencilamino]metil}fenol,

4-{[butil(1-butil-2-fenil(4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))amino]metil}fenol,

(2H-benzo[3,4-d]1,3-dioxolan-5-ilmetil)butil(1-butil-2-fenil (4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))amina,

(2H-benzo[3,4-d]1,3-dioxolan-5-ilmetil)(1-butil-2-fenil (4,5,6-trihidrociclopenta[3,2-d]imidazol-6-il))bencilamina,

(2H-benzo[3,4-d]1,3-dioxolan-5-ilmetil)(3-butil-2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il))bencilamina,

4-{[(3-butil-2-fenil(3,4,5,6,7-pentahidrobencimidazol-4-il))bencilamino]metil}-3-clorofenol,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il))(2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil)bencilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (2-cloro-4-hidroxibencil) bencilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (2H-benzo[d]1,3-dioxolan-5-ilmetil) butilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (2-cloro-4-hidroxibencil) butilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (4-hidroxibencil) butilamina,

(3-butil- 6,6-dimetil -2-fenil (3,4,5,6,7-pentahidrobencimidazol-4-il)) (3-hidroxibencil) butilamina, y

(1-butil-2-fenil-4,5,6,7,8-pentahidrociclohepta[3,2-d] imidazol-8-il)(2H-benzo[d]1,3-dioxolen-5-ilmetil) butilamina

12 Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, junto con al menos un adyuvante o excipiente farmacéuticamente aceptable

13 Una composición farmacéutica empacada que comprende la composición farmacéutica de la reivindicación 12 en un envase y que comprende instrucciones para el uso de la composición para tratar un paciente que necesita un tratamiento anti inflamatorio

14 La composición farmacéutica empacada de la reivindicación 13 en donde dicho paciente sufre de artritis reumatoide, enfermedad de Chron, síndrome de intestino irritable, ARDS, síndrome post-diálisis extracorpóreo, lupus sistémico eritematoso, soriasis o asma bronquial

15 El uso de un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en la manufactura de un medicamento para el tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes

16 Un método de tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes, el cual comprende administrar a un paciente que necesita dicho tratamiento una cantidad efectiva C5a receptor-moduladora de un compuesto de acuerdo con la reivindicación 1 o una sal farmacéuticamente aceptable del mismo

17 Un método para inhibir la quimiotaxia de leucocitos, el cual comprende

Poner en contacto un compuesto de la reivindicación 1 con glóbulos blancos, en donde el compuesto está presente en una cantidad suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

18 Un método para el tratamiento de desórdenes fisiológicos asociados con el exceso de concentraciones de C5a localizadas, en donde dicho método comprende la administración a un paciente que necesita dicho tratamiento de un compuesto de acuerdo con la reivindicación 1, en donde el compuesto se administra en cantidad suficiente para producir, en un sitio del exceso de concentraciones de C5a localizadas, una concentración del

1287

compuesto suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

19 Un método para localizar receptores C5a en muestras de secciones de tejido que comprende

Poner en contacto una muestra de tejido con un compuesto de la reivindicación 1, detectable etiquetado, bajo condiciones que permiten el ligamiento del compuesto a la muestra de tejido,

Lavar la muestra de tejido para remover el compuesto no ligado, y

Detectar el compuesto ligado

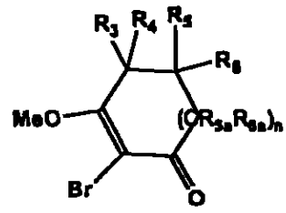
20 Un método para inhibir el ligamiento de C5a a receptores C5a, en donde dicho método comprende poner en contacto una solución que comprende el compuesto de la reivindicación 1 con receptores C5a, en donde el compuesto está presente en la solución a una concentración suficiente para inhibir el ligamiento de C5a a receptores C5a *in vitro*

21 Un método para alterar la actividad de receptores C5a de superficie de célula, en donde dicho método comprende poner en contacto células que expresan dichos receptores con una solución que comprende el compuesto de la reivindicación 1, en donde el compuesto está presente en la solución a una concentración suficiente para alterar específicamente las respuestas quimiotácticas de C5a de glóbulos blancos in vitro

1281 1288

22 Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de quimiotaxia mediada por C5a, el compuesto exhibe un IC_{50} de 1 micromolar o menos

23 Un compuesto de la fórmula



donde

n es un número entero de 0 a 3,

R_3 y R_4 son iguales o diferentes y representan hidrógeno, o alquilo, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo o alcoxi, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo, y

R_{5a} y R_{6a} se seleccionan independientemente en cada ocurrencia de hidrógeno, halógeno, hidroxi, alquilo, o alcoxi

24 Un compuesto de acuerdo con la reivindicación 23, donde

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo de 3 a 6 átomos de carbono,

1282 1284

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo C_1-C_7, o alcoxi C_1-C_7, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo de 3 a 6 átomos de carbono, y

R_{5a} y R_{6A} se seleccionan independientemente en cada ocurrencia de hidrógeno, halógeno, hidroxi, alquilo C_1-C_7, o alcoxi C_1-C_7

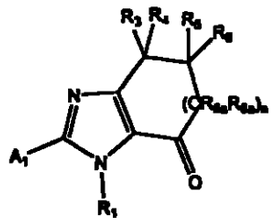
25 Un compuesto de acuerdo con la reivindicación 23, en donde

R_3 y R_4 son hidrógeno, y

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} se seleccionan independientemente en cada ocurrencia de hidrógeno y metilo

26 Un compuesto de la fórmula



en la cual

n es un número entero de 0 a 3,

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo (por ejemplo, ciclopentilmetilo), o

1233 1290

haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo,

R_5 y R_6, son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alcoxi, o alquilo, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo,

R_{5a} y R_{6a} se seleccionan independientemente en cada ocurrencia de hidrógeno, halógeno, hidroxi, alcoxi, o alquilo, y

A_1 es arilo carbobocíclico no sustituido o sustituido, aralquilo no sustituido o sustituido o un grupo heteroaromático o heteroalicíclico no sustituido o sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos

27 Un compuesto de acuerdo con la reivindicación 26 en donde

R_1 es alquilo C_1-C_8 de cadena recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_3-C_8 (cicloalquilo),o haloalquilo C_1-C_8,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo de tres a seis átomos de carbono, y

R_5 y R_6, son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alcoxi C_1-C_7, o alquilo C_1-C_7, o

1284 1291

R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo de tres a seis átomos de carbono,

R_{5a} y R_{6a} se seleccionan independientemente de hidrógeno, halógeno, hidroxi, alcoxi C_1-C_7, o alquilo C_1-C_7, y

A_1 es fenilo el cual está no sustituido o está sustituido con hasta cuatro sustituyentes independientemente seleccionados de

Halógeno, alquilo C_1-C_7 alcoxi C_1-C_7, ciano, amino, mono- o di(C_1-C_6)alquilamino, hidroxi, acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo o trifluorometoxi, o $-XR_B$, donde X y R_B son tal como se definen a continuación, o

A_1 es tiofeno o piridina cada uno de los cuales está o no sustituido con alquilo C_1-C_7 halógeno, alcoxi C_1-C_7, amino, o mono- o dialquil(C_1-C_6)amino,

X es independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C$, $-C(=O)NH-$, $-C(O=)NR_C$ $-S(O)_mNH-$, $S(O)_mNR_C-$, $-NHC(=O)-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, y $-NR_CS(O)_m-$ (donde m es 0, 1, ó 2), y

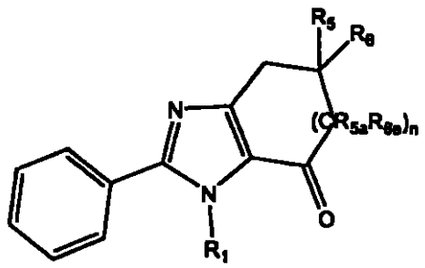
R_B y R_C pueden ser iguales o diferentes y están independientemente seleccionados cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada que pueden contener uno o más dobles o triples enlaces, ceda uno de los cuales puede estar no sustituido o sustituido con uno o más sustituyentes seleccionados de

1285 1291

Oxo, hidroxi, -O(alquilo C_1-C_4), -NH(alquilo C_1-C_4), -N(alquilo C_1-C_4)(alquilo C_1-C_4), -NHC(O)(alquilo C_1-C_4), -N(alquilo C_1-C_4)C(O)(alquilo C_1-C_4), $-NHS(O)_x$(alquilo C_{1-4}), $-S(O)_x$(alquilo C_1-C_4), $-S(O)_xNH$(alquilo C_1-C_4), $-S(O)_xN$(alquilo C_1-C_4) (alquilo C_1-C_4), (donde x es 0, 1, ó 2)

28 Un compuesto de acuerdo con la reivindicación 26 de la fórmula



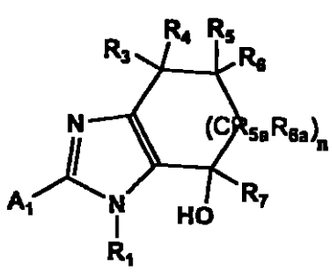
en la cual

R_2 es alquilo C_3-C_8 de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_5 y R_6, son iguales o diferentes y representan hidrógeno o metilo, y

R_{5A} y R_{6A} se seleccionan independientemente en cada ocurrencia de hidrógeno o metilo

29 Un compuesto que tiene la fórmula



1286 1292

en donde

n es un número entero de 0 a 3, y

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o

R_2 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido, o un grupo heteroaromático o heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alcoxi, o alquilo, o

R_5 y R_6 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_{5a} y R_{6b} se seleccionan independientemente cada vez que ocurren de hidrógeno, halógeno, hidroxi, alcoxi, y alquilo,

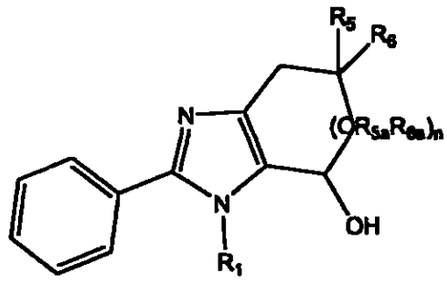
R_7 representa hidrógeno o alquilo, y

A_1 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido o un grupo heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que

1287 1293

tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos

30 Un compuesto de acuerdo con la reivindicación 30, de la fórmula



En donde

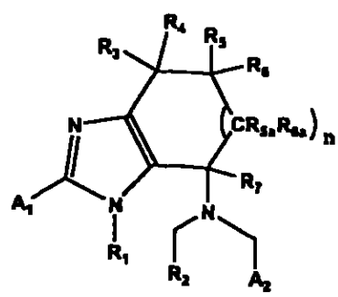
n es un número entero de 0 a 3,

R_1 es alquilo C_3-C_8 de cadena recta o ramificada, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_5 y R_6 son iguales o diferentes y representan hidrógeno o metilo, y

R_{5a} y R_{6a} son iguales o diferentes y representan hidrógeno o metilo

31 Un procedimiento para preparar un compuesto que tiene la fórmula



en la cual

1288 1294

n es un número entero de 0 a 3, y

R_1 alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o

R_2 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido, o un grupo heteroaromático o heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo, o

R_3 y R_4 tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo, o alcoxi, o

R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo,

R_{5a} y R_{6a} están independientemente seleccionados cada vez que ocurren entre hidrógeno, halógeno, hidroxi, alquilo, o alcoxi,

R_7 representa hidrógeno o alquilo,

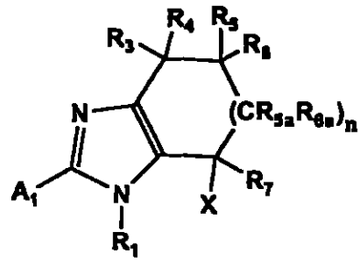
A_1 es arilo carbocíclico sustituido o no sustituido, aralquilo sustituido o no sustituido, o un grupo heteroarilo o heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos, y

1289 1295

A_2 es arilo carbocíclico sustituido o no sustituido, arilalquilo sustituido o no sustituido, o un heteroarilo o un grupo heteroalicíclico sustituido o no sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

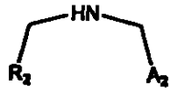
Comprendido dicho procedimiento

Hacer reaccionar un compuesto que tiene la fórmula



en la cual X es halógeno o un éster sulfonato,

en un solvente apropiado en presencia de una base apropiada, con una amina secundaria que tiene la fórmula



32 Un procedimiento para preparar un compuesto de la fórmula de la reivindicación 31, en donde en dicha fórmula

n es un número entero de 0 a 3, y

R_1 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_3-C_8(cicloalquilo) o haloalquilo C_1-C_8,

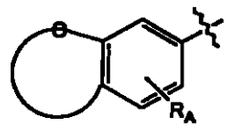
1290 1296

R_2 es una cadena alquilo C_1-C_8 recta o ramificada, alquenilo C_2-C_8, alquinilo C_2-C_8 cicloalquilo C_1-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8, o

R_2 es fenilo, naftaleno, tiofeno o piridina cada uno de los cuales puede estar o no sustituido con

alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8 alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, mono- o dialquil(C_1-C_6)amino, o

R_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_3 y R_4 son iguales o diferentes y representan hidrógeno o alquilo C_1-C_7, o

R_3 y R_4, tomados conjuntamente con el átomo de carbono al cual están unidos, forman un anillo cicloalquilo C_3-C_6,

R_5 y R_6 son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 o alcoxi C_1-C_7, o

R_5 y R_6, tomados conjuntamente con el átomo de carbono al cual están unidos forman un anillo cicloalquilo C_3-C_6,

R_{5a} y R_{6a} son iguales o diferentes, y están independientemente seleccionados cada vez que ocurren de hidrógeno, halógeno, hidroxi, alquilo C_1-C_7 y alcoxi C_1-C_7,

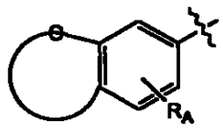
R_7 representa hidrógeno o alquilo C_1-C_7,

A_1 es fenilo el cual puede estar o no sustituido con hasta 4 sustituyentes seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, hidroxi, acetoxi, aminoalquiloxi, mono o dialquilaminoalquiloxi, morfolino, nitro, ácido carboxílico o sus ésteres, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-trifluorometilo o trifluorometoxi, o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_1 es tiofeno o piridina que puede estar o no sustituido con alquilo C_1-C_7, halógeno, alcoxi C_1-C_7, amino o mono o dialquil(C_1-C_6)amino, y

A_2 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar o no sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, alquilo C_1-C_7, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, 1-morfolino, nitro, hidroxi, acetoxi, 3,4-metilendioxi, trifluorometilo, y trifluorometoxi o $-XR_B$, en donde X y R_B son como se definen a continuación, o

A_2 es un grupo bicíclico que contiene oxígeno, de la fórmula



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en donde R_A es hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_6 (cicloalquilo C_3-C_8), haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquil(C_1-C_6)amino,

X está independientemente seleccionado cada vez que ocurre del grupo que consiste en $-CH_2-$, $-CHR_C-$, -O-, $-S(0)_m-$, -NH-, $-NR_C-$, $-C(=0)NH$, $-C(=0)NR_C-$, $-S(0)_mNH-$, $-S(0)_mNR_C-$, $-NHC(=0)-$, $-NR_CC(=0)$, $-NHS(0)_m-$, $-C(=0)NHS(0)_m-$ y $NR_CS(0)_m-$ (donde m es 0, 1 ó 2),

y

R_B y R_C pueden ser iguales o diferentes y están seleccionados independientemente cada vez que ocurren del grupo que consiste en

Hidrógeno, grupos alquilo cíclicos, de cadena recta o ramificada, que pueden contener uno o más dobles o triples enlaces, cada uno de los cuales puede estar no sustituido o puede estar sustituido con uno o más sustituyente(s) seleccionados de

Oxo, hidroxi, -O(alquilo C_1-C_4), -NH(alquilo C_1-C_4), N-(alquilo C_1-C_4) (alquilo C_1-C_4), $-NHC(O)$(alquilo C_1-C_4) - N(alquilo C_1-C_4)$C(O)$(alquilo C_1-C_4), $-NHS(O)_x$(alquilo C_1-C_4), $-S(O)_x$(alquilo C_1-C_4), $-S(O)_xNH$(alquilo C_1-C_4), - $S(O)_xN$(alquilo C_1-C_4)(alquilo C_1-C_4), (donde x es 0, 1 ó 2)

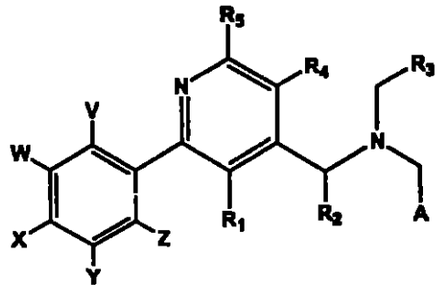
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Lo que se reivindica es

1 Un compuesto de la fórmula



o una sal farmacéuticamente aceptable del mismo, donde

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, o alquinilo,

R_3 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o arilo carbocíclico opcionalmente sustituido, aralquilo opcionalmente sustituido, o un grupo heteroaromático o heteroalicíclico opcionalmente sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

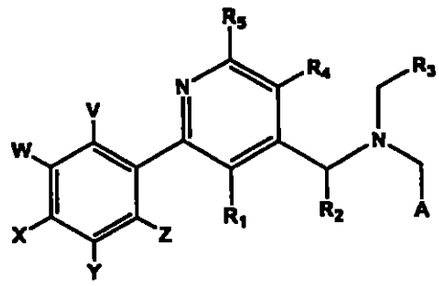
R_4 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o fenilo opcionalmente sustituido,

R_5 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

A representa arilo carbocíclico opcionalmente sustituido, aralquilo opcionalmente sustituido, o un grupo heteroaromático o

heteroalicíclico opcionalmente sustituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos, y V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquilamino opcionalmente sustituido, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, alquenilo opcionalmente sustituido, alquinilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, (cicloalquilo) ' alquilo opcionalmente sustituido, o haloalquilo opcionalmente sustituido, alquiltio opcionalmente sustituido, alquilsulfinilo opcionalmente sustituido, o alquilsulfonilo opcionalmente sustituido

2 Un compuesto de acuerdo con la reivindicación 1, de la fórmula



R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo,

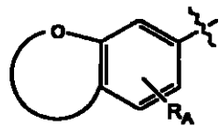
R_2 es hidrógeno, alquilo, alquenilo, o alquinilo,

R_3 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, o

R_3 es un grupo fenilo, piridilo, pirimidinilo, dihidrobenzofuranilo, cromanilo, benzodioxanilo, o indolilo, cada de los cuales puede estar opcionalmente sustituido con hasta 4 grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo,

alquenilo, alquinilo, alcoxi, ciano, amino, mono- o alquilamino, haloalquilo, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

R_4 es hidrógeno, halógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo o alcoxi, o

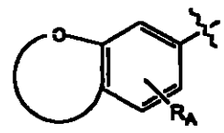
R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo, alquenilo, alquinilo, alcoxi, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquilamino, aminocarbonilo, sulfonamido, mono o dialquilsulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo y trifluorometoxi,

R_5 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

A es un grupo fenilo, piridilo, pirimidinilo, dihidrobenzofuranilo, cromanilo, benzodioxanilo, o indolilo, cada de los cuales puede estar opcionalmente sustituido con hasta 4 grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo,

alquenilo, alquinilo, alcoxi, ciano, amino, mono- o dialquilamino, haloalquilo, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

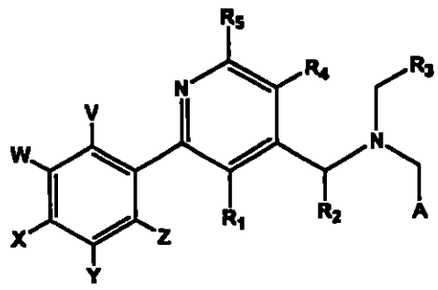
A es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquilamino, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, trifluorometilo o trifluorometoxi

3 Un compuesto de acuerdo con la reivindicación 1, de la fórmula



R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquiloC_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

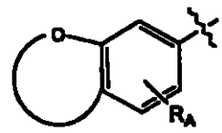
R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8,

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R_3 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8, o

R_3 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

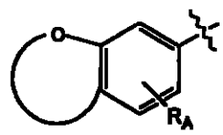
R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8

A es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

A es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_6, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

4 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

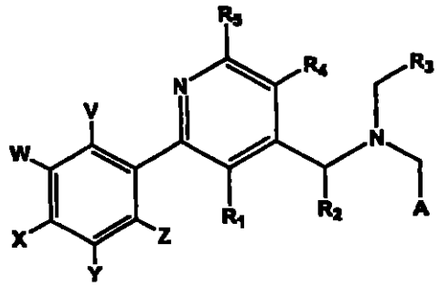
R_2 es hidrógeno, metilo o etilo,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

4 Un compuesto de acuerdo con la reivindicación 1 de la fórmula



R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquiloC_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

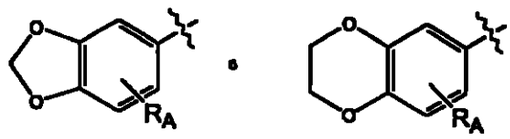
R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_3 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8, o

R_3 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-

C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

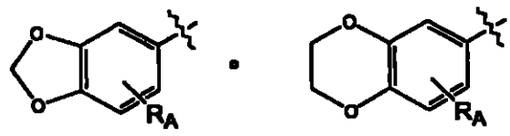
R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(C_3-C_8 cicloalquilo) o haloalquilo C_1-C_8

A es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo,

trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, o

A es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

5 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

6 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es alquilo C_1-C_8,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

7 Un compuesto de acuerdo con la reivindicación 3, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es fenilo el cual puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, 3,4-metilendioxi, y 3,4-(1,2-etilen) dioxi,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

8 Un compuesto de acuerdo con la reivindicación 1, el cual se selecciona de

2-fenil-4-(N,N-di{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil}) aminometil-3-butilpiridina,

2-fenil-4-(N-{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil})-N-bencil) aminometil-3-butilpiridina,

2-fenil-4-(N-{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil})-N-butil) aminometil-3-butilpiridina,

2-fenil-4-(N-bencil-N-{n-butil}) aminometil-3-butilpiridina,

2-fenil-4-(N-{2H-benzo[3,4-d] 1,3-dioxolan-5-ilmetil})-N-{2-cloro-4-hidroxibencil}) aminometil-3-butilpiridina,

2-fenil-4-(N-{2-cloro-4-hidroxibencil}-N-bencil) aminometil-3-butilpiridina, y

2-fenil-4-(N-{4-[2-propil] bencil}-N-{n-butil}) aminometil-3-butilpiridina

9 Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, junto con al menos un adyuvante o excipiente farmacéuticamente aceptable

10 Una composición farmacéutica empacada que comprende la composición farmacéutica de la reivindicación 9 en un envase y que comprende instrucciones para el uso de la composición para tratar un paciente que necesita un tratamiento anti inflamatorio

11 La composición farmacéutica empacada de la reivindicación 9 en donde dicho paciente sufre de artritis reumatoide, enfermedad de Chron, síndrome de intestino irritable, ARDS, síndrome post-diálisis extracorpóreo, lupus sistémico eritematoso, soriasis o asma bronquial

12 El uso de un compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en la manufactura de un medicamento para el tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes

13 Un método de tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades inflamatorias o autoinmunes, el cual comprende administrar a un paciente que necesita dicho tratamiento una cantidad efectiva C5a receptor-moduladora de un compuesto de acuerdo con la reivindicación 1

14 Un método para inhibir la quimiotaxia, el cual comprende

Poner en contacto un compuesto de la reivindicación 1 con glóbulos blancos, en donde el compuesto está presente en una cantidad suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

15 Un método para el tratamiento de desórdenes fisiológicos asociados con el exceso de concentraciones de C5a localizadas, en donde dicho método comprende la administración a un paciente que necesita dicho tratamiento de un compuesto de acuerdo con la reivindicación 1, en donde el compuesto se administra en cantidad suficiente para producir, en un sitio del exceso de concentraciones de C5a localizadas, una concentración del compuesto suficiente para inhibir la quimiotaxia de glóbulos blancos *in vitro*

16 Un método para localizar receptores C5a en muestras de secciones de tejido que comprende

Poner en contacto una muestra de tejido con un compuesto de la reivindicación 1, detectable etiquetado, bajo condiciones que permiten el ligamiento del compuesto a la muestra de tejido,

Lavar la muestra de tejido para remover el compuesto no ligado, y

Detectar el compuesto ligado

17 Un método para inhibir el ligamiento de C5a a receptores C5a, en donde dicho método comprende poner en contacto una solución que comprende el compuesto de la reivindicación 1 con receptores C5a, en donde el compuesto está presente en la solución a una concentración suficiente para alterar las respuestas quimiotácticas a C5a de los glóbulos blancos in vitro

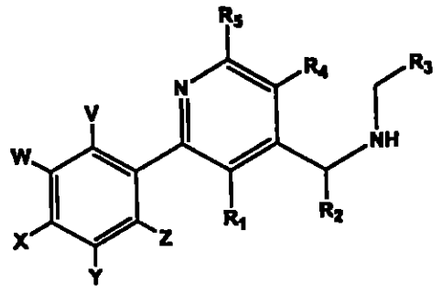
18 Un método para alterar la actividad de receptores C5a de superficie de célula, en donde dicho método comprende poner en

contacto células que expresan dichos receptores con una solución que comprende el compuesto de la reivindicación 1, en donde el compuesto está presente en la solución a una concentración suficiente para alterar específicamente las respuestas quimiotácticas de C5a de glóbulos blancos in vitro

19 Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de quimiotaxia mediada por C5a, el compuesto exhibe un IC_{50} de 1 micromolar o menos

20 Un compuesto de acuerdo con la reivindicación 1 en donde en un ensayo de quimiotaxia mediada por C5a, el compuesto exhibe un IC_{50} de 100 nanomolar o menos

21 Un compuesto de la fórmula



, En donde

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido,

R_2 es hidrógeno, alquilo, alquenilo, o alquinilo,

R_3 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o arilo carbocíclico opcionalmente sustituido, aralquilo opcionalmente sustituido, o un grupo heteroaromático o heteroalicíclico opcionalmente sustituido que

tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos,

R_4 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, o fenilo opcionalmente sustituido,

R_5 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquilo) alquilo, o haloalquilo, cada uno de los cuales puede estar sustituido o no sustituido, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquilamino opcionalmente sustituido, alquilo opcionalmente sustituido, alcoxi opcionalmente sustituido, alquenilo opcionalmente sustituido, alquinilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, (cicloalquilo) alquilo opcionalmente sustituido, o haloalquilo opcionalmente sustituido, alquiltio opcionalmente sustituido, alquilsulfinilo opcionalmente sustituido, o alquilsulfonilo opcionalmente sustituido

22 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8,

R_3 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8 y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

23 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es alquilo C_1-C_8,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

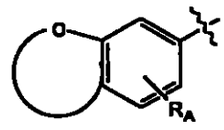
24 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8 o alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8,

R_2 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, o alquinilo C_2-C_8,

R_3 es fenilo, 2-, 3-, o 4-piridilo, 2-, 3-, o 4-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



en donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,

R_4 es hidrógeno, halógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_1-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), haloalquilo C_1-C_8 o alcoxi C_1-C_8, o

R_4 es fenilo el cual puede estar sustituido con hasta 5 sustituyentes independientemente seleccionados de alquilo C_1-C_8,

alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_8, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquil(C_1-C_6)amino, aminocarbonilo, sulfonamido, mono o dialquil(C_1-C_6)sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo o trifluorometoxi,

R_5 es hidrógeno, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8 alquilo C_1-C_3(cicloalquilo C_3-C_8) o haloalquilo C_1-C_8 y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o dialquil(C_1-C_6)amino, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_3-C_8), alcoxi C_1-C_8, trifluorometilo o trifluorometoxi

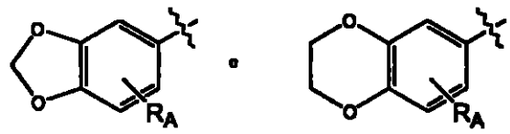
25 Un compuesto de acuerdo con la reivindicación 21, en donde

R_1 es alquilo C_3-C_6,

R_2 es hidrógeno, metilo o etilo,

R_3 es fenilo el cual puede estar sustituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo C_1-C_8, alquenilo C_2-C_8, alquinilo C_2-C_8, alcoxi C_1-C_7, ciano, amino, mono- o dialquil(C_1-C_6)amino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o dialquil(C_1-C_6)aminocarbonilo, N-alquil(C_1-C_6)sulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, 1-piperidilo, acetoxi, o

R_3 es un grupo bicíclico que contiene oxígeno, de la fórmula



En donde R_A representa de 0 a 3 grupos seleccionados de alquilo C_1-C_6, alquenilo C_2-C_6, alquinilo C_2-C_6, cicloalquilo C_3-C_8, alquilo C_1-C_3 (cicloalquilo C_2-C_6), haloalquilo, alcoxi C_1-C_6, halógeno, hidroxi, amino, o mono- o di(alquil C_1-C_6)amino,,

R_4 es hidrógeno, halógeno, metilo, etilo, metoxi, etoxi, o trifluorometilo,

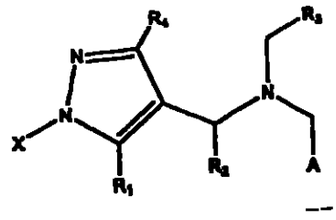
R_5 es hidrógeno, metilo o etilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, amino, mono o dialquil(C_1-C_3)amino, alquilo C_1-C_3, alcoxi C_1-C_3, trifluorometilo o trifluorometoxi

1312 13A

REIVINDICACIONES

1 Un compuesto de fórmula



o una sal farmacéuticamente aceptable de la misma, donde

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, o haloalquilo, cada uno el cual puede ser substituido o no substituido,

R_2 es hidrógeno, alquilo, alquenilo, o alquinilo,

R_3 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil (alquilo) o halo alquilo cada uno de los cuales puede ser substituido o no substituido, o un arilo carbocíclico opcionalmente substituido, un arilalquilo opcionalmente substituido, o un grupo heterocíclico opcionalmente substituido, que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 hetroátomos,

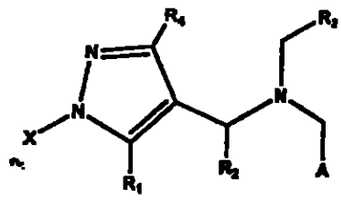
R_4 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo, o haloalquilo, cada uno de los cuales puede ser substituido o no substituido, o

R_4 es un arilo opcionalmente substituido o un heteroarilo opcionalmente substituido, o

R_2 y R_4 se pueden unir para formar un anillo carbocíclico saturado de 5 a 8 miembros opcionalmente substituido o y un anillo heterocíclico saturado opcionalmente substituido de 5 a 8 miembros, y

A y X independientemente representan un arilo carbocíclico opcionalmente substituido, un arilaquilo opcionalmente substituido, o un grupo heterocíclico opcionalmente substituido que tiene de 1 a 3 anillos, de 3 a 8 miembros en cada anillo y de 1 hasta 3 heteroátomos

2 Un compuesto, de acuerdo a la reivindicación 1 de fórmula



o una sal farmacéuticamente aceptable de la misma , donde

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo, o haloalquilo, cada uno de los cuales puede ser substituido o no substituido,

R_2 es hidrógeno, alquilo, alquenilo o alquinilo,

R_3 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil (alquilo) o haloalquilo cada uno de los cuales puede ser substituido o no substituido, o un arilo carbocíclico opcionalmente substituido, o un arilalquilo opcionalmente substituido, o un grupo heterocíclico opcionalmente substituido que tiene de 1 a 3 anillos , 3 a 8 miembros en cada anillo y de 1 hasta 3 heteroátomos,

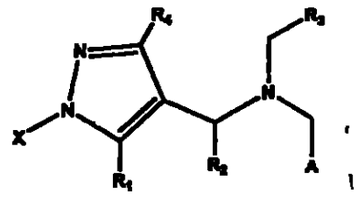
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R_4 es hidrógeno, halógeno, alquilo, alcoxi, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo, o haloalquilo, cada uno de los cuales puede estar substituido o no substituido, o

R_4 es un arilo opcionalmente substituido o un heteroarilo opcionalmente substituido, y

A y X independientemente representan un arilo carbocíclico opcionalmente substituido, un arilalaquilo opcionalmente substituido, o un grupo heterocíclico opcionalmente substituido que tiene de 1 a 3 anillos, 3 a 8 miembros en cada anillo y de 1 a 3 heteroátomos

3 Un compuesto, de acuerdo a la reivindicación 1 de fórmula



o una sal farmacéuticamente aceptable de la misma, donde

R_1 es alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo, o haloalquilo,

R_2 es hidrógeno, alquilo, alquenilo o alquinilo,

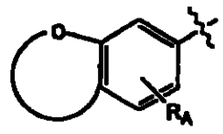
R_3 es hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo, o haloalquilo, o

R_3 es un fenilo, piridilo, tienilo, pirimidinilo, dihidrobenzofuranilo, cromanilo, benzodioxanilo, benzodioxolanilo, indanilo, o un grupo indolilo, cada uno de los cuales es opcionalmente

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substituido con hasta cuatro grupos independientemente seleccionados de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo, alquenilo, alquinilo, alcoxi, ciano, amino, mono- o alquilamino, haloalquilo, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo y 1-piperidilo o

R_3 es un grupo que contiene un oxígeno bicíclico de fórmula



Donde R_A representa 0 a 3 átomos seleccionados de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino, o mono- o dialquilamino,

R_4 es hidrógeno, halógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil)alquilo, haloalquilo o alcoxi, o

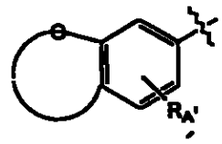
R_4 es fenilo el cual puede ser substituido por hasta cinco substituyentes seleccionados de alquilo, alquenilo, alquinilo, alcoxi, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquilamino, aminocarbonilo, sulfonamido, mono o dialquil sulfonamido, 3,4-metilendioxi, 3,4-(1,2-etilen)dioxi, trifluorometilo, y trifluorometoxi,

A y X se seleccionan independientemente de

1) fenilo, piridilo, tienilo, pirimidinilo, dihidrobenzofuranilo, cromanilo, benzodioxanilo, benzodioxolanilo, indanilo, o un grupo indolilo, cada uno

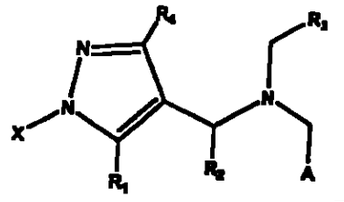
de los cuales es opcionalmente substituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, alquilo, alquenilo, alquinilo, alcoxi, ciano, amino, mono- o alquilamino, haloalquilo, ácido carboxílico, ésteres de ácidos carboxílico, aminocarbonilo, mono o dialquilaminocarbonilo, N-alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, y 1- piperidilo y

ii) grupos que contienen oxígeno bicíclico de fórmula



donde R_A representa 0 a 3 grupos seleccionados de hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, (cicloalquil) alquilo, haloalquilo, alcoxi, halógeno, hidroxi, amino o mono- o dialquilamino

4 Un compuesto, de acuerdo a la reivindicación 1 de fórmula



O una sal farmacéuticamente aceptable de la misma, donde

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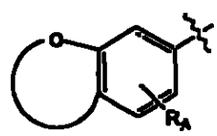
R_1 es C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} cicloalquilo o (C_{3-8} cicloalquil)C_{1-3} alquilo o C_{1-8} haloalquilo,

R_2 es hidrógeno, C_{1-8} alquilo, C_{2-8} alquenilo, o C_{2-8} alquinilo,

R_3 es C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{3-8} cicloalquilo, (C_{3-8} cocloalquil)C_{1-3} alquilo o C_{1-8} haloalquilo o

R_3 es fenilo, 2-,3-, o 4-piridilo, 2-,4-, o 5-pirimidinilo, 2-, o 3-dihidrobenzofuranilo, 2-,3-, o 4 chromanilo, 2-, 4-,5-,6-, o 7-benzodioxanilo, 4-, o 5-benzodioxolanilo, 1- o 2-indanilo, o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar substituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometil, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8}) alquinilo, C_{1-8} alcoxi, ciano, amino, mono o di (C_{1-6})alquilamino, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o di(C_{1-6})alquilaminocarbonil, N- (C_{1-6})alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo, y 1-piperidilo, o

R_3 es un grupo conteniendo oxígeno bicíclico de la fórmula



Donde R_A representa 0 a 3 grupos seleccionados de C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{3-8} cicloalquilo, (C_{2-6} cicloalquil) C_{1-3} alquilo, haloalquilo, C_{1-6} alcoxi, halógeno, hidroxi, amino, o mono- o di (C_{1-6} alquil) amino,

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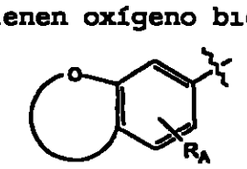
R_4 es hidrógeno, halógeno, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} cicloalquilo, (C_{3-8} cicloalquil)C_{1-3} alquilo, C_{1-8} alcoxi, o C_{1-8} haloalquilo, o

R_4 es fenilo el cual puede estar sustituido por hasta cinco substituyentes independientemente escogidos de C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} alcoxi, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o di (C1-6) alquilamino, aminocarbonilo, sulfonamido, mono o di (C1-6) alquilsulfonamido, 3,4-metilendioxi, 3,4-(1,2 etilen) dioxi, trifluorometil y trifluorometoxi, y

A y X se escogen independientemente de

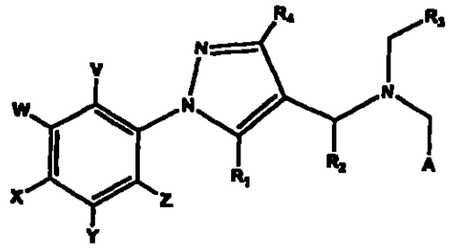
i) fenilo, 2-,3-, o 4-piridilo, 2-,o 3-tienilo, 2-, 4-, o 5-pirimidinilo, 2- o 3-dihidrobenzofuranilo, 2-3-, o 4-cromanilo, 2-, 4-,5-,6-, o 7-benzodioxanilo, 4- o 5-benzodioxolanilo, 1-o 2-indinilo, o 1-,2-, o 3-indolilo, cada uno de los cuales puede estar substituido con hasta cuatro grupos independientemente seleccionados de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} alcoxi, ciano, amino, mono-o di (C_{1-6}) alquilamino, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o di (C_{1-6}) alquilaminocarbonilo, N-(C_{1-6}) alquilsulfonilaminocarbonilo, 1-acetidinilo, 1-pirrolidinilo, y 1-piperidilo, y

ii) grupos que contienen oxígeno bicíclico de fórmula



Donde R_A representa de 0 hasta 3 grupos seleccionados de hidrógeno, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{3-8} cicloalquilo, (C_{2-6} cicloalquil) C^{1-3} alquilo, haloalquilo, C_{1-6} alcoxi, halógeno, hidroxi, amino, o mono- o di (C_{1-6} alquil) amino

5 Un compuesto de acuerdo a la reivindicación 1, de fórmula



R_1 es C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} cicloalquilo o (C_{3-8} cicloalquil) C_{1-3} alquilo o C_{1-8} haloalquilo,

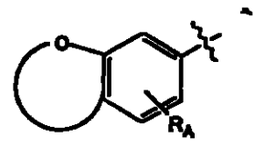
R_2 es hidrógeno, C_{1-8} alquilo, C_{2-8} alquenilo, o C_{2-8} alquinilo,

R_3 es C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{3-8} cicloalquilo, (C_{3-8} cicloalquil)C_{1-3} alquilo o C_{1-8} haloalquilo, o

R_3 es fenilo, 2-,3-, o 4-piridilo, 2-,4-, o 5-pirimidinilo, 2-o3-dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-,4-,5-, 6-, o 7-benzodioxanilo, 4- o 5-benzodioxanilo, 1- o 2-indanilo, o 1-, 2--, o 3-indolilo, cada uno de los cuales puede estar sustituido con hasta cuatro grupos independientemente seleccionados de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-7} alcoxi, ciano, amino, mono-o di (C_{1-6})alquilamino, ácido carboxílico, ésteres de ácidos carboxílico, aminocarbonilo, mono

o di(C_{1-6})alquilaminocarbonilo, N-(C_{1-6}) alquilsulfonilaminocarbonilo, 1-acetidinilo, 1-pirrolidinilo, y 1-piperidilo, o

R_3 es un grupo que contiene un oxígeno bicíclico de fórmula



Donde R_A representa de 0 a 3 grupos seleccionados de C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{3-8} cicloalquilo, (C_{2-6} cicloalquil) C_{1-3} alquilo, haloalquilo, C_{1-6} alcoxi, halógeno, hidroxi, amino, o mono-o di (C_{1-6} alquil) amino

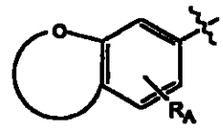
R_4 es hidrógeno, halógeno, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} cicloalquilo, (C_{3-8} cicloalquil) C_{1-3} alquilo, C_{1-8} alcoxi, o C_{1-8} haloalquilo, o

R_4 es fenilo el cual puede ser sustituido hasta por cinco substituyentes independientemente escogodos de C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} alcoxi, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o di (C_{1-6}) alquilamino, aminocarbonilo, sulfonamido, mono o di (C_{1-6}) alquilsulfonamido, 3,4-metilendioxi, 3,4-(1,2 etilen)dioxi, trifluorometilo y trifluorometoxi,

A es fenilo, 2-, 3-, o 4-piridinilo, 2-, o 3-tienilo, 2-, 4-, o 5 pirimidinilo, 2- o 3- dihidrobenzofuranilo, 2-, 3-, o 4-cromanilo, 2-, 4-, 5-, 6-, o 7-benzodioxanilo, 4-, o 5-benzodioxolanilo, 1- o 2-indanilo, o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar substituido hasta por cuatro

grupos seleccionados independientemente de halógeno, nitro, trifluorometil, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} alcoxi, ciano, amino, mono-o di (C_{1-6})alquilamino, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o di (C_{1-6})alquilaminocarbonilo, N-(C_{1-6}) alquilsulfonilaminocarbonilo, 1-acetidinilo, 1-pirrolidinilo, y 1-piperidinilo, o

A es un grupo que contiene un oxígeno bicíclico de fórmula



Donde R_A representa de 0 a 3 grupos seleccionados de hidrógeno, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, C_{3-8} cicloalquilo, $(C_{2-6}$ cicloalquil) C_{1-3} alquilo, haloalquilo, C_{1-6} alcoxi, halógeno, hidroxi, amino, o mono-o di $(C_{1-6}$ alquil) amino, y

V, W, X, Y y Z son iguales o diferentes y representa hidrógeno, halógeno, ciano, nitro, acetoxi, hidroxi, amino, mono o di (C_{1-6}) alquilamino, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{3-8} cíloalquilo, $(C_{3-8}$ cicloalquil) C_{1-3} alquilo, C_{1-8} alcoxi, trifluorometil o trifluorometoxi

6 Un compuesto de acuerdo a la reivindicación 5, donde

R_3 es C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{3-8} cicloalquilo $(C_{3-8}$ cicloalquil)C_{1-3} alquilo o C_{1-8} haloalquilo o

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R_3 es fenilo, 2-, 3-, 4-piridilo, 2-, 4-,o 5-pirimidinilo, 2-o 3-dihidrobenzofuranilo, 2-, 3-,o 4-cromanilo, 2-, 4-,5-,6-,o 7-benzodioxanilo, 4-, o 5-benzodioxolanilo, 1- o 2-indanilo, o 1-, 2- o 3-indolilo, cada uno de los cuales puede ser substituido con hasta cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} alcoxi, ciano, amino, mono o di (C_{1-6})alquilamino, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o di (C_{1-6})alquilaminocarbonilo, N-(C_{1-6}) alquilsulfonilaminocarbonilo, 1-azetidinilo, 1-pirrolidinilo y 1-piperidinilo,

A es fenil, 2-,3-, o 4-piridilo, 2-4-, o 5-pirimidinilo, 2-o 3-dihidrobenzofuranilo, 2-, o 3-tienilo, 2-, 3-, o 4- cromanilo, 2-,4-,5-,6-, o 7-benzo dioxanilo, 4-o 5-benzodioxolanilo, 1-o 2-indanilo, o 1-, 2-, o 3-indolilo, cada uno de los cuales puede estar substituido hasta con cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{3-8} cicloalquilo, $(C_{3-8}$ cicloalquil$)C_{1-3}$ alquilo, C_{1-8} alcoxi, ciano, amino, mono-o di (C_{1-6})alquilamino, ácido carboxílico, ésteres de ácidos carboxílicos, aminocarbonilo, mono o di (C_{1-6}) alquilaminocarbonilo, N-(C_{1-6}) alquilsulfonilaminocarbonilo, 1-acetidinilo, 1-pirolidinilo y 1-piperidilo

7 Un compuesto de acuerdo a la reivindicación 5, donde

R_1 es C_{3-6} alquilo,

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R_2 es hidrógeno, metilo, o etilo,

R_4 es fenilo el cual puede estar substituido hasta por cinco substituyentes seleccionados independientemente de alquilo, alquenilo, alquinilo, alcoxi, halógeno, ciano, ácido carboxílico, hidroxi, acetoxi, nitro, amino, mono o dialquilamino, aminocarbonilo, sulfonamido, mono o dialquilsulfonamido, 3,4 metilendioxi, 3,4-(1,2 etilen)dioxi, trifluorometilo y trifluorometoxi, y

V, W, X, Y, y Z son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, amino, mono o di(C_{1-3})alquilamino, C_{1-3} alquilo, C_{1-3} alcoxi, trifluorometilo, otrifluorometoxi

8 Un compuesto de acuerdo a la reivindicación 5, donde

R_1 es C_{3-6} alquilo,

R_2 es hidrógeno, metilo, o etilo,

R_3 es C_{1-6} alquilo o C_{3-8} cicloalquilo,

R_4 es fenilo, y

V, W, X, Y, y Z son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, amino, mono o di (C_{1-3})alquilamino, C_{1-3} alquilo, C_{1-3} alcoxi, trifluorometilo o trifluorometoxi

9 Un compuesto de acuerdo a la reivindicación 5, donde

R_1 es C_3-C_6 alquilo,

R_2 es hidrógeno, metilo, o etilo,

R_3 es fenilo el cual puede ser substituido hasta con cuatro grupos seleccionados independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo,

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C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} alcoxi, ciano, amino, mono- o di(C_{1-6}) alquilamino, ácido carboxílico, ésteres de ácido carboxílico, aminocarbonilo, mono o di (C_{1-6})alquilaminocarbonilo, N-(C_{1-6})alquilsulfonilaminocarbonilo, 1-acetidinilo, 1-pirolidinilo, 1-piperidilo, acetoxi, 3,4-metilendioxi y 3,4-(1,2-etilen)dioxi,

R_4 es fenilo, y

V, W, X, Y y Z son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, amino, mono o di (C_{1-3})alquilamino, C_{1-3} alquilo, C_{1-3} alcoxi, trifluorometilo, o trifluorometoxi

10 El compuesto de acuerdo a la reivindicación 5, donde

R_1 es C_{3-6} alquilo,

R_2 es hidrógeno, metilo o etilo,

R_3 es 4-, o 5-benzodioxolanilo, o 1-o 2-indanilo cada uno de los cuales puede estar substituido hasta con cuatro grupos seleccionado independientemente de halógeno, nitro, trifluorometilo, trifluorometoxi, hidroxi, acetoxi, C_{1-8} alquilo, C_{2-8} alquenilo, C_{2-8} alquinilo, C_{1-8} alcoxi, ciano, amino, mono- o di (C_{1-6})alquilamino, ácido carboxílico, ésteres de ácidos carboxílicos, y aminocarbonilo,

R_4 es fenilo, y

V,W,X,Y y Z son iguales o diferentes y representan hidrógeno, halógeno, hidroxi, amino, mono o di(C_{1-3})alquilamino, C_{1-3} alquilo, C_{1-3} alcoxi, trifluorometilo, o trifluorometoxi

11 El compuesto de acuerdo a la reivindicación 1 el cual es

1,3-Difenıl-4-(N-{2H-benzo[3,4-d]-1,3-dıoxolan-5-ilmetıl}-N-butilamıno) metıl-5-propilpirazol,

1,3-Difenıl-4-(N-{2H-benzo[3,4-d]-1,3-dıoxolan-5-ılmetil}-N-bencılamino) metil-5-propilpirazol,

1,3-Difenil-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ilmetıl}-N-ciclopentilmetilamıno)metil-5-propılpirazol,

1,3-Dıfenıl-4-(N,N-bıs{2H-benzo[3,4-d]-1,3-dioxolan-5-ilmetıl}-5-propılpirazol,

1,3-Difenıl-4-(N-{2-cloro-4-hidroxıbencılo}-N-bencılamino)metıl-5-propilpirazol,

1,3-Dıfenil-4-(N-{4-dimetilaminobencıl}-N-bencılamino)metıl-5-propilpırazol,

1,3-Difenil-4-(N-ından-2-il-N-bencılamino)metil-5-propılpirazol,

1,3-Difenil-4-(N-benzyl-N-butilamino)metil-5-propılpirazol,

1,3-Dıfenil-4-(N-{2-cloro-4-hıdroxibencil}-N-butilamıno)metil-5-propılpırazol,

1,3-Dıfenil-4-(N-{4-metoxicarboxibencil}-N-{n-butil}aminometil-5-propilpirazol,

1,3-Difenil-4-(N-{4—carboxıbencil}-N-{n-butilamino})metil-5-propılpırazol,

1,3-Difenil-4-(N-{2H-benzo[3,4-d]-1,3-dıoxolan-5-ilmetil}-N-{2-cloro-4-hıdroxibencıl}amino)metil-5-proilpirazol,

1,3-Dıfenil-4-(N-{4-hidroxımetilbencil}-N-bencilamıno)metil-5-propılpirazol,

1,3-Difenil-4-(N-{4-carboxibencil}-N-bencilamino)metil-5-propil pirazol,

o

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1,3-Difenil-4-(N-{4-metoxicarbonilbencil}-N-bencilamino)metil-5-propilpirazol

12 Una composición farmacéutica que comprende el compuesto de acuerdo a la reivindicación 1, o una sal farmacéuticamente aceptable del mismo Juntos con al menos un portador o excipiente farmacéuticamente aceptable

13 Una composición farmacéutica empacada que comprende la composición de la reivindicación 12 en un recipiente y que comprende instrucciones para el uso de la composición para tratar a un paciente que necesita un tratamiento anti-inflamatorio

14 La composición farmacéutica empacada de la reivindicación 13 donde dichas instrucciones indican que dicho paciente está sufriendo de una o más artritis reumatoideasla enfermedad de Crohn, el síndrome de intestino irritable, ARDS, Síndrome de post diálisis extracorporal, lupus sistémico eritematoso, psoriasis o asma bronquial

14 El uso del compuesto de acuerdo a la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en la manufactura de un medicamento para el tratamiento de quemaduras, complicaciones de bypass cardiopulmonar, enfermedades autoinmunes o inflamatorias

15 El método de tratamiento de quemaduras, complicaciones de bypass cardiopulmonares, desórdenes autoinmunes o inflamatorios el cual comprende la administración a un paciente que necesite dicho tratamiento

una cantidad efectiva de receptor-modulador de C5a de un compuesto de acuerdo a la reivindicación 1

16 Un método para inhibir la quimiotaxis del leucocito, el cual comprende

contactar el compuesto de la reivindicación 1 con células sanguíneas blancas, donde el compuesto está presente en una concentración suficiente par inhibir la quimiotaxis de las células sanguíneas blancas *in vitro*

17 Un método para el tratamiento de desórdenes fisiológicos asociados con concentraciones en exceso localizables de C5a, en el cual el método comprende la administración a un paciente que necesite ese tratamiento del compuesto de la reivindicación 1, donde el compuesto es administrado en una cantidad suficiente para disminuir, en el sitio de concentraciones en exceso localizables de C5a, una concentración del compuesto suficiente para inhibir la quimiotaxis de células sanguíneas blancas *in vitro*

18 El método para localizar los receptores C5a en muestras de tejidos el cual comprende

Contactar con una muestra de tejido el compuesto etiquetado de la reivindicación 1 bajo condiciones que permitan la unión del

COLO 10611-801-006-0

JJC-ID-49

Industria y Comercio
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2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 1333

Radicación no __00-85303____

Concepto Técnico no 1393 Clasificación Internacional de Patentes A 61 K 31/495// 31/4164

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 [X] NO [ ] La prioridad coincide con la materia reivindicada.

SI [✓] NO [ ] CUMPLE LOS REQUISITOS TÉCNICOS

OBSERVACIONES Y OTROS. SI [X] NO [ ] ver hoja(s) anexa(s)

1 Anexa copia y traducción, de la cual reclama prioridad excepto la prioridad 60 221 787 del 31 julio del 2000

2 Anexa extracto para publicación, modificación del título, arte final, tarjeta de archivo temático y de propietarios.

EXAMINADOR TÉCNICO
202050

Bogotá D C , Septiembre 17 de 2002

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Conmutador 334 12 21-2-3-4
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SUPERINTENDENCIA

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Folio 1334

2020
Bogotá DC

Doctor
EMILIO FERRERO
Apoderado

REFERENCIA.	Radicación No	00-85303
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No	1825
	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

No obstante lo anterior, no se tendrá en cuenta la prioridad invocada 60.221 787 de 31 de julio de 2000 ya que no se presento de conformidad con lo solicitado en el folio 602

Cúmplase
Dado en Bogotá DC, a los 09 NOV. 2002

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

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