

**JOSE LLOREDA CAMACHO & CO.
ABOGADOS**

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COM
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-054466- -00002-0000

Fecha: 2008-05-13 16:34:40 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Re: P1.-**INCYTE CORPORATION**.-Solicitud de Patente de Invención
en Fase Nacional PCT para "**COMPUESTOS DE LACTAMA Y SU**
USO COMO FARMACEUTICOS".-Clase **C07D 487/04.-**
Expediente número **07-054.466.-**

1. Me refiero a mi memorial de 21 de Agosto de 2007.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **582** de 30 de Noviembre de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo I.
4. Anexo me permito acompañar recibo número 08-37.141, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 809176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-054466- -00002-0000

Fecha: 2008-05-13 16:34:40 Dep. 2020 NUECREACIONE
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RECIBO OFICIAL DE CAJA : 08 - 37,141
FECHA : MAYO 12 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LLORADA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	2756073	12/08/2008	9,293,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-54466

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **582** DE
FECHA **30 DE NOVIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA
LEY EXPIRA EL **27 DE FEBRERO DE 2008**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

469/469

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

202012
Bogotá, D.C., 29 de octubre de 2010

Apoderado: Alicia Lloreda Ricaurte

ASUNTO	Radicación	07-54466
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	14403

Patente de Invención	☒		
Vía PCT fase nacional	☒	Cap. I ☒	Cap. II ☐

No. Sol. Internacional PCT/US2005/040550

Fecha de Presentación Internal. 09/nov/2005

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

1. Documentos estudiados

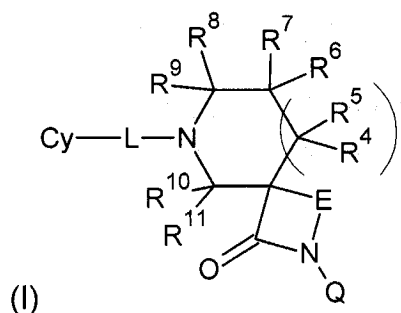
- Descripción: Folios: 216 a 322 Como se radicó inicialmente
- Reivindicaciones: Folios: 323 a 384 Como se radicó inicialmente
- Prioridad: Folio 1: 60/626.617; 10/nov/2004
60/715.020; 08/sep/2005

2. Objeto de la invención

Título de la solicitud: COMPUESTOS DE LACTAMA Y SU USO COMO FARMACEUTICOS.

El objeto de la presente solicitud consiste en derivados de la fórmula Markush (I):

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- Reivindicaciones 1-61,64: Compuesto de fórmula (I).
- Reivindicación 62: compuesto de fórmula (II).
- Reivindicación 63: compuesto de fórmula (IV).
- Reivindicación 65: composiciones que comprenden los compuestos de fórmula (I).
- Reivindicaciones 66, 67: método para modular la actividad.
- Reivindicaciones 68, 69: Método para tratar.

El objeto de la solicitud se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC) : A61K31/52, A61K31/496, A61K31/4747 ,C07D473/02, C07D487/04.

3. De la solicitud de Patente

- Reivindicaciones (artículo 30 D 486 de la C.A.N.)

-Las reivindicaciones 1-62 y 63 son muy amplias y especulativas, toda vez que la formula Markush está construida con base en un modelismo molecular obtenido mediante ordenador, sin ninguna porción fija identificable, con una multiplicidad de sustituyentes mutables, si definir plenamente sino con denominaciones genericas y todo eso sumado a todas sus posibles permutaciones. No son extrapolaciones estrechamente relacionadas con lo que se describió, las reivindicaciones deberían presentar una generalización razonable de los ejemplos dados en la parte descriptiva con las características técnicas establecidas en la descripción-ejemplos como características esenciales de la invención. El motivo de ello es que el problema a resolver debería ser resuelto por todo el alcance de la materia reivindicada (cada compuesto que cae dentro de su alcance) y no sólo por compuestos individuales sometidos a ensayo- especialmente **dado que el problema puede considerarse en la provisión de compuestos que actúan sobre un mismo sistema biológico** (es decir, sobre un sistema que depende de parámetros de ser viviente). Si este no fuera el caso, una invención podría ser arbitrariamente ampliada en cualquier medida, sin ninguna consideración de si los compuestos realmente resuelven el problema, en el que se basa la invención.

4. Excepción a la patentabilidad (artículo 20 D486 literal d))

-Las reivindicaciones 6 y 7 reclaman un método de tratamiento para el cuerpo humano o animal, por lo tanto están comprendida por las disposiciones del artículo 20 D486 literal -d).

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5. Determinación del Estado de la Técnica

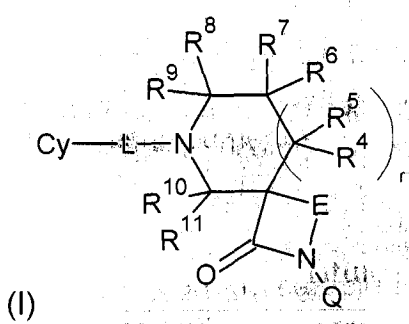
Considerando la fecha de prioridad reclamada de la presente solicitud de patente 10/nov/2004, se realizo la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud. Encontrándose los siguientes documentos relevantes:

N°	Documento	Título	Fecha de Publicación*
D1	US20040009998	Spiro-hydantoin compounds useful as anti-inflammatory agents	15/ene/2004

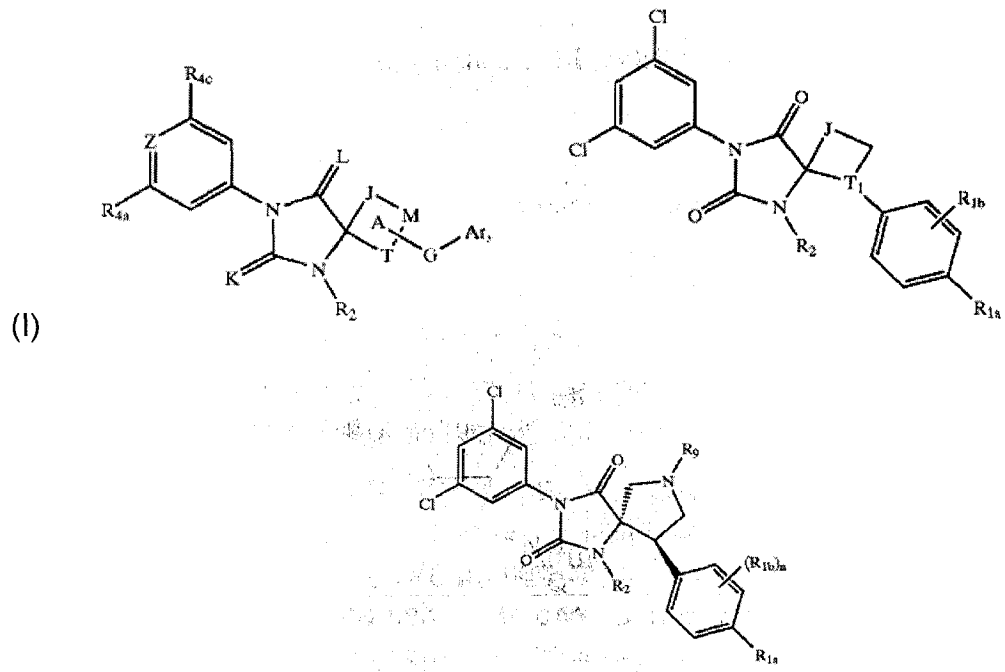
6. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

Novedad (artículo 16 D486 la C.A.N.)

La presente solicitud reclama los derivados de la fórmula Markush (I):



-D1 derivados de la fórmula Markush (I):



Son compuestos con efecto inhibidor de LFA-1/ICAM y como agente

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antiinflamatorio, los significados de los sustituyentes es como aparece en la descripción, véase todo el documento D1, que anticipa a describir los compuestos que en la solicitud se reclaman como nuevo e inventivos.

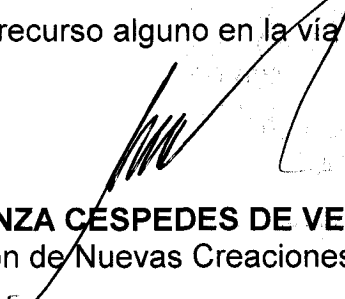
7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	US20040009998	1-65	Novedad.

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

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
_____ 05 NOV. 2010

CONCEPTO TECNICO No. 3893	EXAMINADOR TECNICO Cód N°202012
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US 2004/0009998A1

US 2004/0009998 A1

Jan. 15, 2004

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0009998 A1
(43) Pub. Date: Jan. 15, 2004

(54) SPIRO-HYDANTOIN COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS (52) U.S. CL. 514/278; 514/387; 548/300.7; 546/15

(76) Inventors: T. G. Murali Dhar, Newtown, PA (US); Dominique Potin, Epone (FR); Magali Jeannine Blandine Maillet, Suresnes (FR); Michele Launay, Rueil Malmaison (FR); Eric Antoine Nicolai, Rueil Malmaison (FR); Edwin J. Iwanowicz, Cranbury, NJ (US)

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(21) Appl. No.: 10/262,182

(22) Filed: Oct. 1, 2002

Related U.S. Application Data

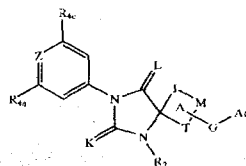
(60) Provisional application No. 60/326,361, filed on Oct. 1, 2001. Provisional application No. 60/354,113, filed on Feb. 4, 2002. Provisional application No. 60/400,259, filed on Aug. 1, 2002.

Publication Classification

(51) Int. Cl.⁷ A61K 31/4747; A61K 31/4172; C07D 487/12

(57) ABSTRACT

Compounds having the formula (I), and pharmaceutically acceptable salts, hydrates, enantiomers, and diastereomers, and prodrugs thereof,

are useful as inhibitors of LFA-1/ICAM and as anti-inflammatory agents, wherein L and K are O or S; Z is N or CR_{4a}; Ar is an optionally-substituted aryl or heteroaryl; G is a linker attached to T or M or is absent; J, M and T are selected to define a three to six membered saturated or partially unsaturated non-aromatic ring; and R₂, R_{4a}, R_{4b} and R_{4c} are as defined in the specification.

SPIRO-HYDANTOIN COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/326,361, filed Oct. 1, 2001, U.S. Provisional Application No. 60/354,113, filed Feb. 4, 2002, and U.S. Provisional Application No. 60/400,259, filed Aug. 1, 2002, each of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to spiro-hydantoin compounds, pharmaceutical compositions containing them, and methods of using such compounds in treating inflammatory or immune disease.

BACKGROUND OF THE INVENTION

[0003] Cells adhere to other cells and to substrates through specific, regulated processes that are critical to various biological functions. The proper functioning of the immune system is dependent upon adhesive interactions and cell migration. A key event in an immune response involves the migration of leukocytes to a disease site. During an inflammatory response, leukocytes are recruited to the site of injury and extravasated by a series of cellular interactions involving cell-cell and cell-substrate adhesion.

[0004] One family of molecules that serves an important adhesive function is integrins. Integrins are expressed on cell surfaces and function in cell-cell and cell-substrate adhesion. Integrins are alpha-beta heterodimers: each integrin has an alpha (α) subunit non-covalently bound to a beta (β) subunit. When activated, integrins bind to extracellular ligands and induce adhesion (the expression of integrins on a cell surface alone is inadequate for adhesion - they must be activated to become adhesive). The integrin activation state is transient, such that there is a rapid flux between adhesive and non-adhesive states which is important for cell movement, e.g., a cell is endowed with the ability to rapidly adhere to various cell surfaces and matrices and to migrate among cells and tissue.

[0005] There are four known integrins having a β₂ or CD18 subunit which comprise the CD11/CD18 integrin sub-family, namely, Lymphocyte Function-associated Antigen 1 (LFA-1) (CD11a/CD18 or α_Lβ₂); Macrophage Antigen 1 (Mac-1) (CD11b/CD18 or α_Mβ₂); p150,95 (CD11c/CD18 or α_Xβ₂); and α_{IIb}β₃. The CD11/CD18 family of integrins is also referred to as Leukointegrins as they are expressed on the surface of various leukocyte cells, and they mediate a number of inflammation-related cellular interactions. See Diamond et al., "The Dynamic Regulation of Integrin Adhesiveness," *Current Biology*, Vol. 4 (1994) at pp. 506-532.

[0006] Ligands to LFA-1 and Mac-1 comprise the intercellular adhesion molecule (ICAM) ICAM-1. The primary CD11/CD18 integrin is LFA-1, which also binds with ICAM-2 and ICAM-3. ICAMs are found on endothelium cells, leukocytes, and other cell types, and their interaction with CD11/CD18 integrins is critical to immune system function. The interaction between the CD18 integrins, particularly LFA-1, and ICAMs mediates antigen presentation, T-cell proliferation, and adhesion between the endothelium

and activated leukocytes which is necessary for leukocytes to migrate from the circulatory system into tissue. A condition termed "Leukocyte Adhesion Deficiency" has been identified in patients having a deficiency in CD18 integrins. These patients are unable to mount a normal inflammatory or immune response; they suffer from disorders such as recurrent infections, poor wound healing, granulocytosis, progressive periodontitis, and umbilical cord separation. See Anderson et al., "Leukocyte LFA-1, OKM1, p150,95 Deficiency Syndrome: Functional and Biosynthesis Studies of Three Kinetics," *Fed. Proc.*, Vol. 44 (1985), at pp. 2671-2677.[0007] While sufficient levels of CD18 integrins interacting with ICAMs are needed to mount a normal immune response, significant cellular and tissue injury can result in chronic inflammatory states where there is an inappropriate influx of leukocytes to the disease site. Continuous recruitment of leukocytes from blood vessels into inflamed tissue, as in chronic inflammatory states, can perpetuate tissue injury and lead to excessive fibrous repair and autoimmune disease. Thus, inhibition of the interaction between LFA-1 and/or Mac-1 and their ICAMs can be advantageous in treating inflammatory or immune disease. For example, monoclonal antibody blockade of either ICAM or LFA-1 has been shown to prevent the migration of leukocytes into tissue and the subsequent development of inflammatory disease in animal models of rheumatoid arthritis, inflammatory bowel disease, and pulmonary inflammation (e.g., asthma). Knockout mice deficient in ICAMs have reduced susceptibility to induced arthritis, ischemia injury, impaired lung inflammatory responses, and increased tolerance to transplantations (e.g. heart grafts). See Anderson, supra. Antibodies blocking the ICAM-LFA-1 interaction reportedly suppress cardiac allograft rejection and islet cell xenograft rejection in animal models. See Gorski, "The Role of Cell Adhesion Molecules in Immunopathology," *Immunology Today*, Vol. 15 (1994), at pp. 251-255.[0008] Compounds inhibiting CD18 integrins, ICAMs, and/or the LFA-1/ICAM interaction could potentially demonstrate a wide range of utilities in treating inflammatory or immune diseases. Blocking LFA-1 reportedly inhibits the influx of leukocytes in almost every system, including the skin, peritoneum, synovium, lung, kidney, and heart, and blocking ICAM-1 would be expected to have similar effects. Also, present therapies for many inflammatory and immune diseases have drawbacks. For example, current treatments for asthma include β₂-agonists, inhaled corticosteroids, and LTD₄ antagonists. However, β₂-agonists have limited efficacy and inhaled corticosteroids raise safety concerns. To treat psoriasis, current therapies include PUVA, methotrexate, cyclosporin A, and topical treatments. The first three of these therapies raise toxicity issues over long-term (e.g., 6-9 month) use, whereas topical treatments have limited efficacy. Additionally, these treatments typically are applied only in response to flares and not as a prophylaxis measure.

[0009] Compounds that reportedly inhibit LFA-1/ICAM (or use as anti-inflammatory agents include thiazole-based compounds (see Intern. Pub. No. WO 99/20,618, "Thiazole Amides Useful as Anti-Inflammatory Agents" filed by Pharmacia & Upjohn Co.; and WO 99/20,617, also to Pharmacia and Upjohn); and thiazole compounds linked to phenyl and pyrazole rings (Sanfilippo et al., "Novel Thiazole Based Heterocycles as Inhibitors of LFA-1/ICAM-1

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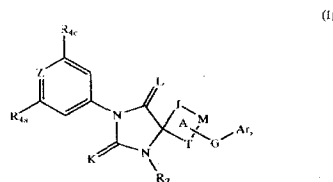
Mediated Cell Adhesion, J. Med. Chem., Vol. 38 (1995) at pp.1057-1059). Small molecules that reportedly are antagonists to the binding of ICAMs with CD18 integrins include various benzylamines and 2-bromobenzoyltryptophan compounds (see Intern. Pub. No. WO99/49,856, "Antagonists for Treatment of CD11/CD18 Adhesion Receptor Mediated Disorders," filed by Genentech, Inc.), and 1-(3,5-dichlorophenyl) imidazolidines (see Intern. Pub. No. WO98/39303, "Small Molecules Useful in the Treatment of Inflammatory Disease," filed by Boehringer Ingelheim Pharmaceuticals, Inc. See also Boehringer patent applications WO 01/07052, WO 01/07048, WO 01/07044, WO 01/06984, and WO 01/07440). Hydantoin compounds are disclosed in Intern. Pub. No's WO 00/59880, WO 00/39081, WO 02/02522, WO 02/02539 (all to Abbott Laboratories). LFA-1 antagonist compounds are also claimed in WO 02/059114 (to Genentech), WO 02/42294 (to Celtech), WO 01/51508 (to Science and Technology corporation), WO 00/21920 and WO 01/58853 (both to Hoffmann-La Roche), WO 99/11258, WO 00/48989 and WO 02/28832 (all to Novartis). Hydantoin compounds are disclosed in Intern. Pub. No. WO 01/30781 A2 (published May 3, 2001) to Tanabe Seiyaku Co. Ltd., "Inhibitors of $\alpha_1\beta_1$ Mediated Cell Adhesion," and in Intern. Pub. No. WO 02/44181 (published Jun. 6, 2002) to "Hydantoin Compounds Useful as Anti-Inflammatory Agents", to the present assignee and having common inventors herewith.

[0010] As may be appreciated, those in the field of pharmaceutical research continue to develop new compounds and compositions for treating inflammatory and immune disease such as inhibitors of Leukointegrins and/or ICAMs. Particularly in the area of immune response, many individuals respond differently to different drugs. Thus, there is an interest in providing consumers not only with pharmaceutical compositions demonstrating increased effectiveness and reduced side-effects but also different structures or mechanisms of action to provide consumers with a choice of options. The instant invention is directed to aryl or heteroaryl substituted spiro-hydantoin compounds that are effective as antagonists of Leukointegrins and/or ICAMs. Diazaspiroheptane compounds are disclosed in Park et al., "Preparation of a 990 Member Chemical Compound Library of Hydantoin and Isoxazoline-Containing Heterocycles Using Multipin Technology," J. Comb. Chem., Vol. 3(2) (2001), at pp. 171-76. Spiro heterocycles are also disclosed in Couture et al., "Chemistry of Cyclic Aminoacylcarbenes," Can. J. Chem., Vol. 75(9) (1997) at pp. 1281-1294; Brandstetter et al., "Glucosylated Analogs of Hydantoin," Tetrahedron, Vol. 52(32) (1996), at pp. 10721-10736; Brandstetter et al., "Spirohydantoin Analogs of Glucosylated Analogs of Hydantoin," Tetrahedron Lett., Vol. 36(12) (1995) at pp. 2149-52; in U.S. Pat. Nos. 6,022,875, 4,241,208, 4,066,615, and 3,941,744, and International patent application WO 01/45704. WO 01/94346 discloses 1,3,8-triazaspiro-4,5 decan-4-one derivatives as neurokinin receptor antagonists.

[0011] Each of the patents, patent applications and publications referenced above and hereinafter is incorporated herein by reference.

SUMMARY OF THE INVENTION

[0012] The present invention provides compounds useful in treating inflammatory or immune disease having the formula (I):



[0013] their enantiomers, diastereomers, and pharmaceutically-acceptable salts, hydrates, solvates, and prodrugs thereof, in which:

[0014] I and K, taken independently, are O or S;

[0015] Z is N or CR₄;

[0016] Ar is aryl or heteroaryl;

[0017] G is attached to ring A at T or M; and (i) when attached to a carbon atom of ring A, G is selected from a bond, —O—, —N—, —S—, C₁₋₃alkylene, C₁₋₃substituted alkylene, or bivalent alkoxy, alkylthio, aminoalkyl, sulfonyl, sulfonamido, acyl, and, alkoxy-carbonyl; or (ii) when attached to a nitrogen atom of ring A, G is selected from a bond, C₁₋₃alkylene, C₁₋₃substituted alkylene, and bivalent acyl or alkoxy-carbonyl, or bivalent alkoxy, alkylthio, aminoalkyl, sulfonyl, or sulfonamido wherein in (ii), each of said G groups have at least one carbon atom directly attached to ring A;

[0018] J is —O—, —S—, —NR₁—, —N—, —S(=O)—, —SO₂—, —NH(SO₂)—, a substituted or unsubstituted C₁₋₃alkylene, a substituted or unsubstituted C₂₋₃alkenylene, an unsubstituted C₁₋₂heteroalkylene, a substituted heteroalkylene having from one to two carbon atoms in the heteroalkylene straight chain, or J is absent so that ring A is a three-membered ring;

[0019] T is T₁ when G-Ar is attached to T, and T₂ when G-Ar is attached to M;

[0020] M is M₁ when G-Ar is attached to M, and M₂ when G-Ar is attached to T;

[0021] T₁ and M₁ are selected from —N— and —C(R₃)—;

[0022] T₂ and M₂ are selected from —O—, —S—, —N(R₃)—, —N—, —S(=O)—, —SO₂—, —NH(SO₂)—, and —C(R₃)—, provided that J, M, and T are selected so that ring A defines a three to six membered saturated or partially unsaturated cycloalkyl or heterocyclic ring having 1 to 4 heteroatoms, wherein no two adjacent heteroatoms of said heterocyclic ring A are simultaneously selected from —O— and —S—;

[0023] R₂ is selected from hydrogen, alkyl, substituted alkyl, OR₁₂, NR₁₂R₁₃, C(=O)R₁₂, CO₂R₁₂, C(=O)NR₁₂R₁₃, NR₁₂C(=O)R₁₃, NR₁₂C(=O)OR₁₃, S(O)₁₃R₁₃, NR₁₂SO₂R₁₃, SO₂NR₁₂R₁₃, cycloalkyl, heterocyclo, aryl, and heteroaryl;

[0024] R₄, R₆, and R₈ are independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, nitro, cyano, SR₁₄, OR₁₄, NR₁₄R₁₅, NR₁₄C(=O)R₁₅, CO₂R₁₄, C(=O)R₁₄, —C(=O)NR₁₄R₁₅, aryl, heterocyclo, cycloalkyl, and heteroaryl;

[0025] R₃ and R₅ are independently selected from hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, alkenyl, substituted alkenyl, aminoalkyl, alkylthio, C(=O)H, acyl, amide, alkoxy-carbonyl, sulfonyl, sulfonamido, cycloalkyl, heterocyclo, aryl, and heteroaryl;

[0026] R₅, R₇, and R₈ are (i) independently selected from hydrogen, alkyl, substituted alkyl, halogen, nitro, cyano, hydroxy, alkoxy, alkenyl, substituted alkenyl, aminoalkyl, alkylthio, C(=O)H, acyl, CO₂H, amide, alkoxy-carbonyl, sulfonyl, sulfonamido, cycloalkyl, heterocyclo, aryl, and heteroaryl; or (ii) R₅ with R₆ may form a cycloalkyl or heterocyclic ring or a double bond to an oxygen atom to define a keto (C=O) group; or (iii) one of R₅ or R₆ may be a bond so that there is a double bond between T and M, or between M and J, respectively; so that ring A is partially unsaturated;

[0027] R₁₂, R₁₃, R₁₄ and R₁₅ (i) are selected independently of each other from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclo; or (ii) R₁₂ is taken together with R₁₃, and/or R₁₄ is taken together with R₁₅, to form a heteroaryl or heterocyclo ring;

[0028] R₁₃ is selected from alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclo; and

[0029] p is 1 or 2.

[0030] The present invention is also directed to pharmaceutical compositions useful in treating immune or inflammatory diseases comprising compounds of formula (I), or pharmaceutically-acceptable salts thereof, and pharmaceutically-acceptable carriers or diluents. The invention further relates to methods of treating immune or inflammatory diseases comprising administering to a patient in need of such treatment a therapeutically-effective amount of a compound according to formula (I).

DETAILED DESCRIPTION OF THE INVENTION

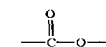
[0031] The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

[0032] The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred.

When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, "C₁ alkyl" refers to straight and branched chain alkyl groups with one to six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, and so forth. The subscript "0" refers to a bond. Thus, the term hydroxy(C₀₋₂)alkyl or (C₀₋₂)hydroxyalkyl includes hydroxy, hydroxymethyl and hydroxyethyl.

[0033] The term "substituted alkyl" refers to an alkyl group as defined above having one, two, or three substituents selected from the group consisting of halo (e.g., trifluoromethyl), alkenyl, substituted alkenyl, alkynyl, nitro, cyano, oxo (C=O), OR₁₆, SR₁₆, (=S), —NR₁₆, —N(alkyl)₂, —NR₁₆SO₂, —NR₁₆SO₂R₁₇, —SO₂R₁₆—SO₂NR₁₆R₁₇, —SO₂NR₁₆C(=O)R₁₇, SO₂H, —PO(OH)₂, —C(=O)R₁₆, —CO₂R₁₆, —C(=O)NR₁₆R₁₇, —C(=O)(C₁₋₃alkylene)NR₁₆R₁₇, —C(=O)NR₁₆(SO₂)R₁₇, —CO₂(C₁₋₃alkylene)NR₁₆R₁₇, —NR₁₆C(=O)R₁₇, —NR₁₆CO₂R₁₇, —NR₁₆(C₁₋₃alkylene)CO₂R₁₇, —N—OH, —N—O—alkyl, aryl, cycloalkyl, heterocyclo, and/or heteroaryl, wherein R₁₆ and R₁₇ are selected from hydrogen, alkyl, alkenyl, CO₂H, CO₂(alkyl), C₁₋₃cycloalkyl, phenyl, benzyl, phenylethyl, naphthyl, a four to seven membered heterocyclo, or a five to six membered heteroaryl, or when attached to the same nitrogen atom may join to form a heterocyclo or heteroaryl, and R₁₆ is selected from same groups as R₁₇, and R₁₇ is not hydrogen. Each group R₁₆ and R₁₇ when other than hydrogen, and each R₁₆ group optionally has up to three further substituents attached at any available carbon or nitrogen atom of R₁₆, R₁₇, and/or R₁₈, said substituent(s) being selected from the group consisting of (C₁₋₃)alkyl, (C₂₋₃)alkenyl, hydroxy, halogen, cyano, nitro, CF₃, O(C₁₋₃alkyl), OCF₃, C(=O)H, C(=O)C₁₋₃alkyl, CO₂H, CO₂(C₁₋₃alkyl), NHCO₂(C₁₋₃alkyl), —S(C₁₋₃alkyl), —NH₂, NH(C₁₋₃alkyl), N(C₁₋₃alkyl)₂, N(CH₃)₂, SO₂(C₁₋₃alkyl), C(=O)(C₁₋₃alkylene)NH₂, C(=O)(C₁₋₃alkylene)NH(alkyl), C(=O)(C₁₋₃alkylene)N(C₁₋₃alkyl)₂, C₁₋₃cycloalkyl, phenyl, benzyl, phenylethyl, phenyloxy, benzyloxy, naphthyl, a four to seven membered heterocyclo, or a five to six membered heteroaryl. When a substituted alkyl is substituted with an aryl, heterocyclo, cycloalkyl, or heteroaryl group, said ringed systems are as defined below and thus may have zero, one, two, or three substituents, also as defined below.

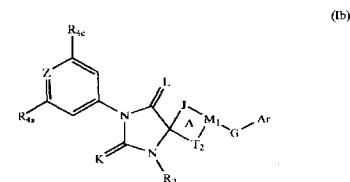
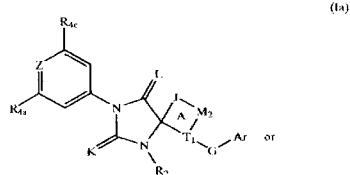
[0034] One skilled in the field will understand that, when the designation "CO₂" is used herein, this is intended to refer to the group



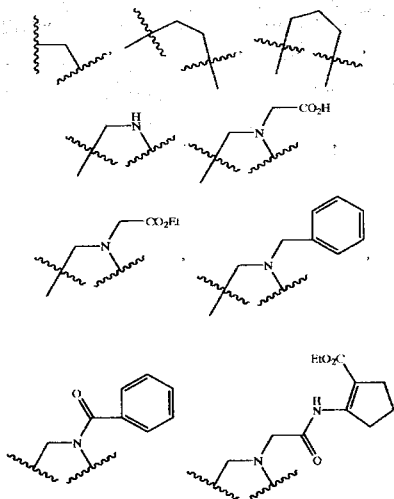
[0035] When the term "alkyl" is used together with another group, such as in "aryalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "aryalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C₀₋₂)alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, i.e., aryl(C₀)alkyl.

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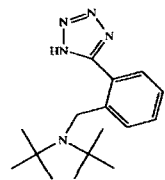
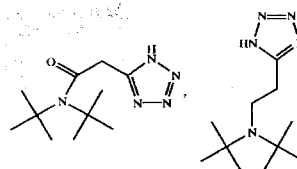
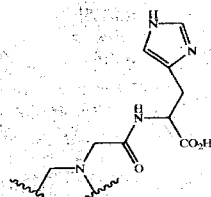
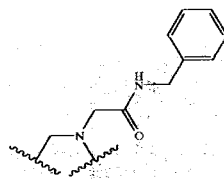
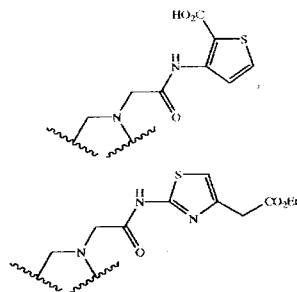
[0077] According to the foregoing definitions, the instant invention provides compounds having the formula (Ia) or (Ib):



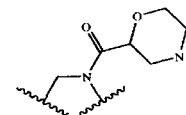
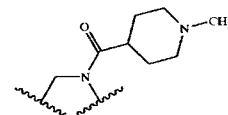
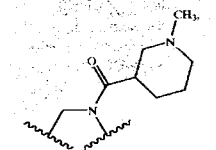
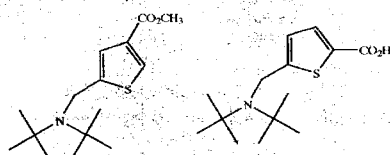
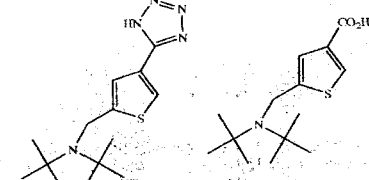
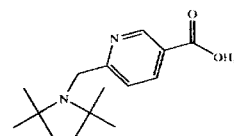
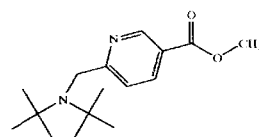
[0078] wherein the groups Ar, G, L, K, Z, T₁, M₁, T₂, M₂, R₂, R_{4a}, and R_{4c}, are as defined herein, and the group J may be selected from alkylene or heteroalkylene groups, including, without limitation, the following specific examples:



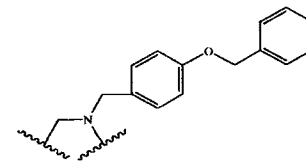
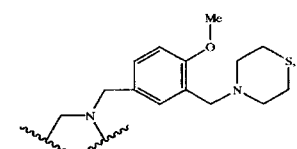
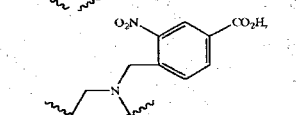
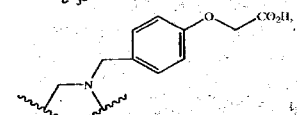
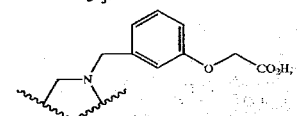
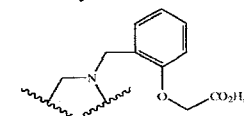
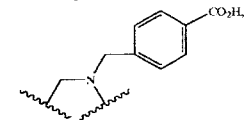
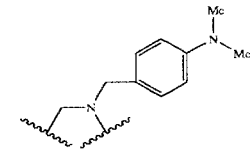
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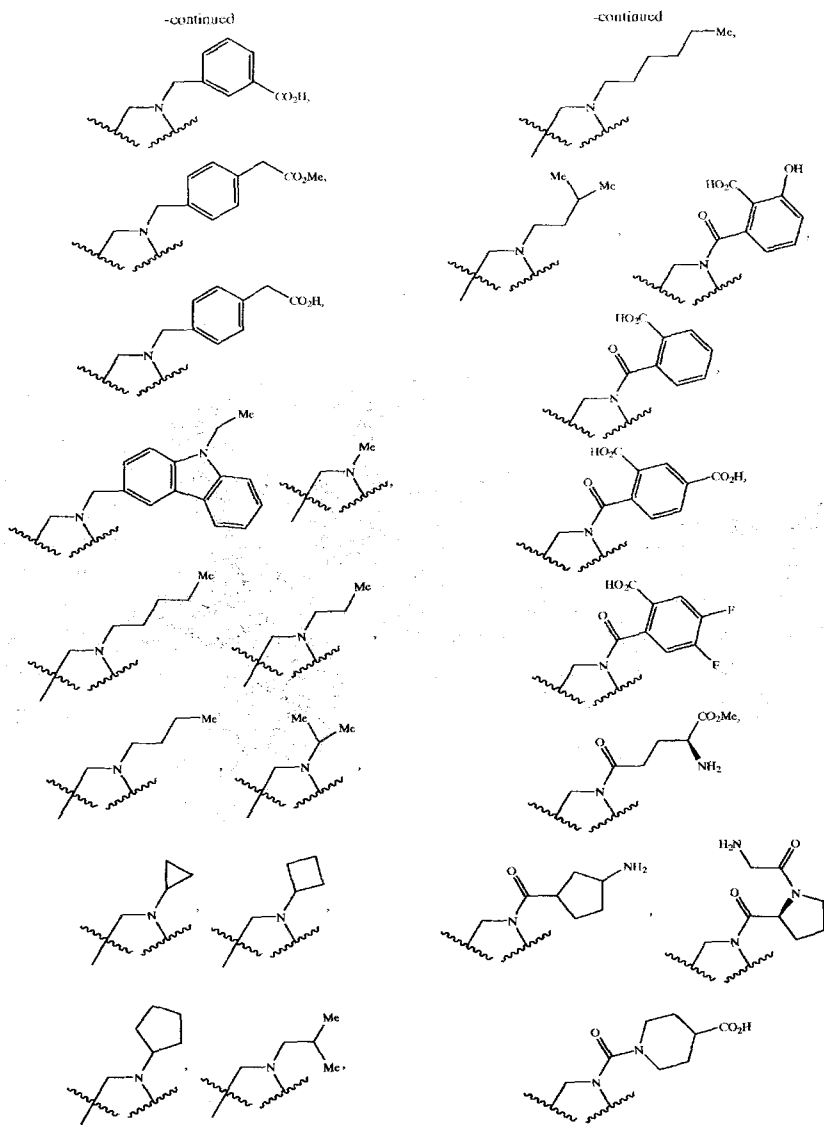
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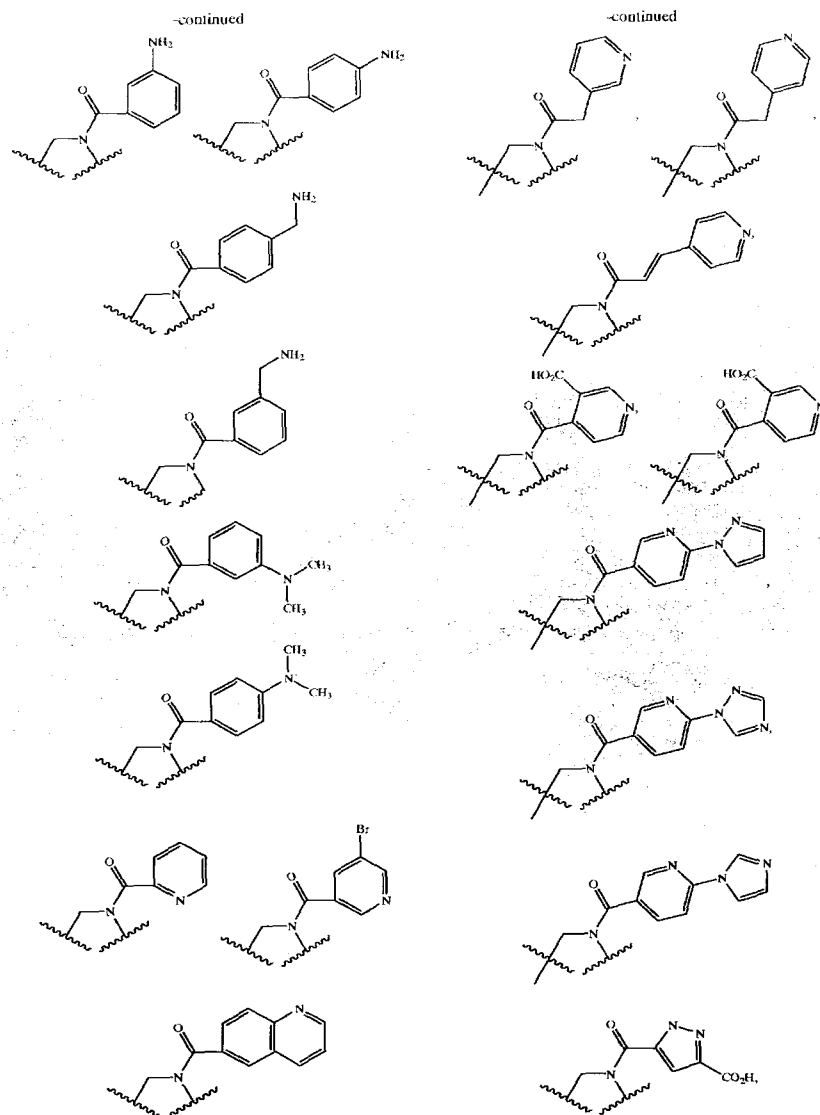
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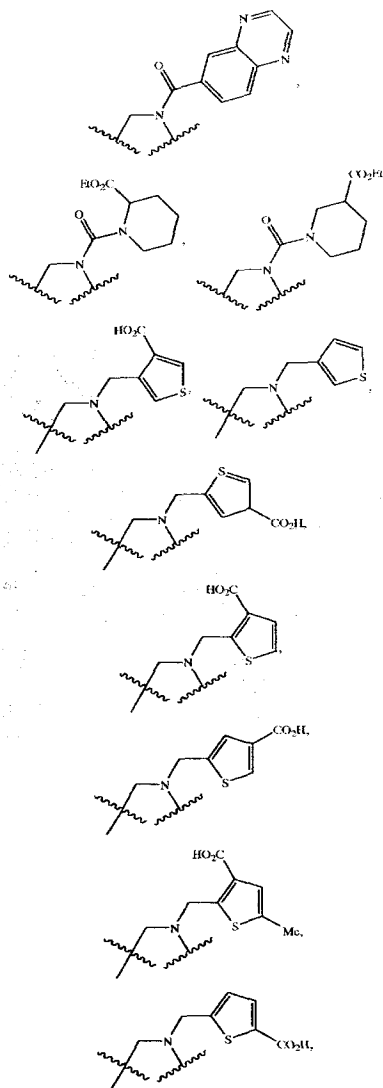


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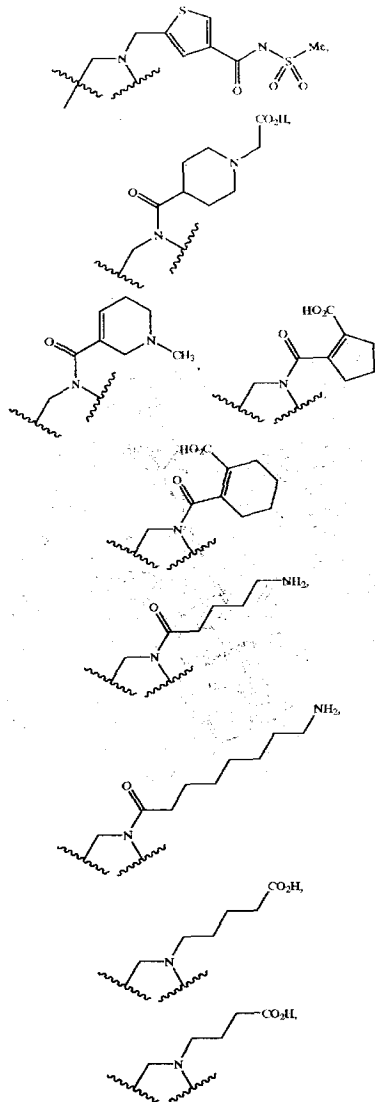


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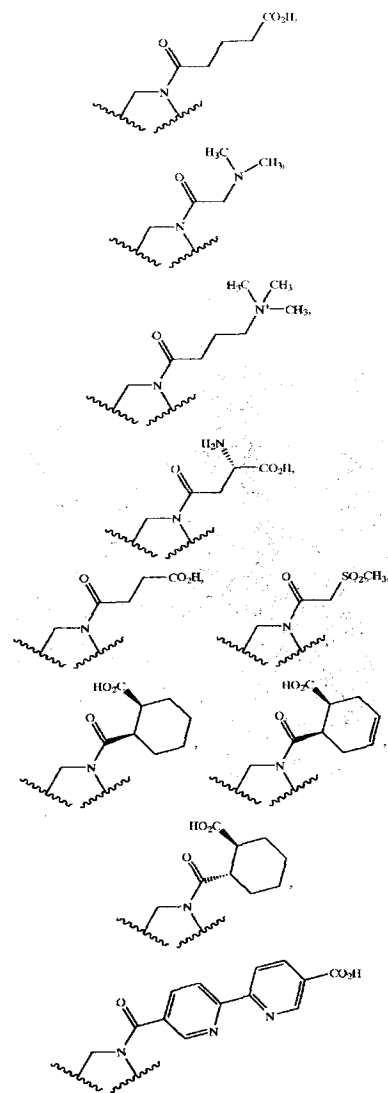
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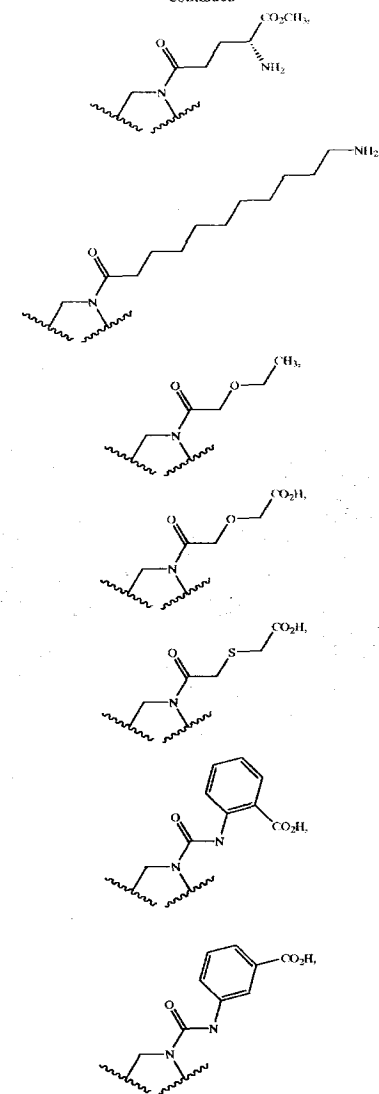
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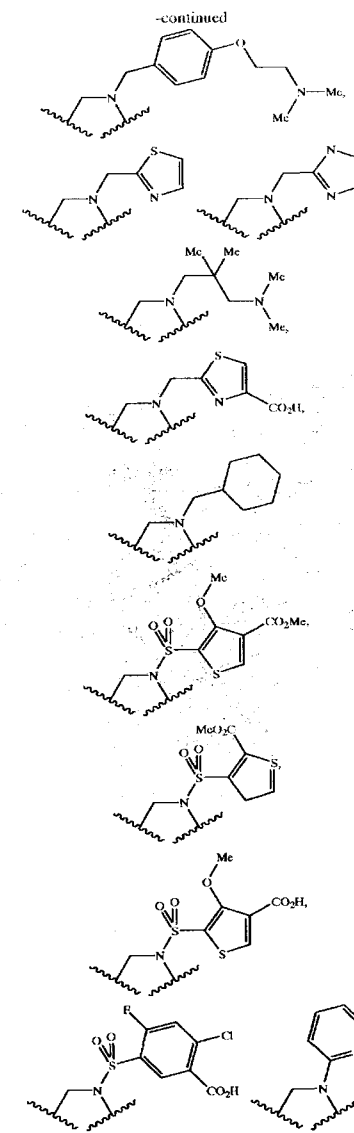
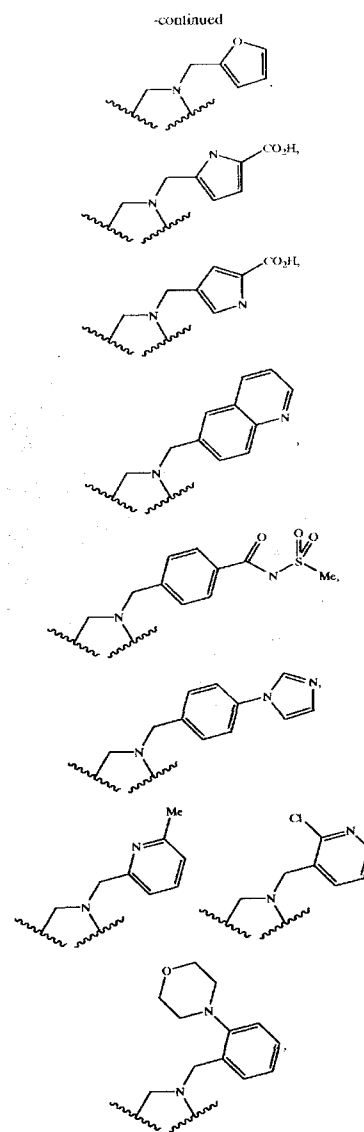
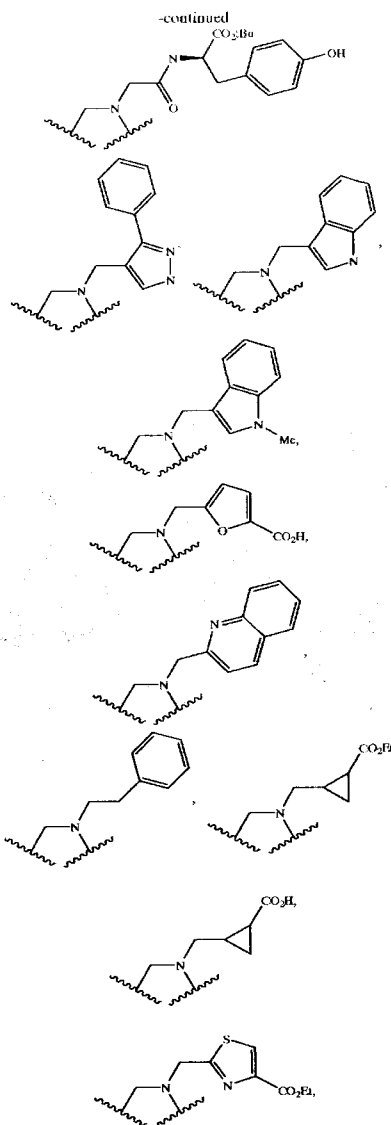
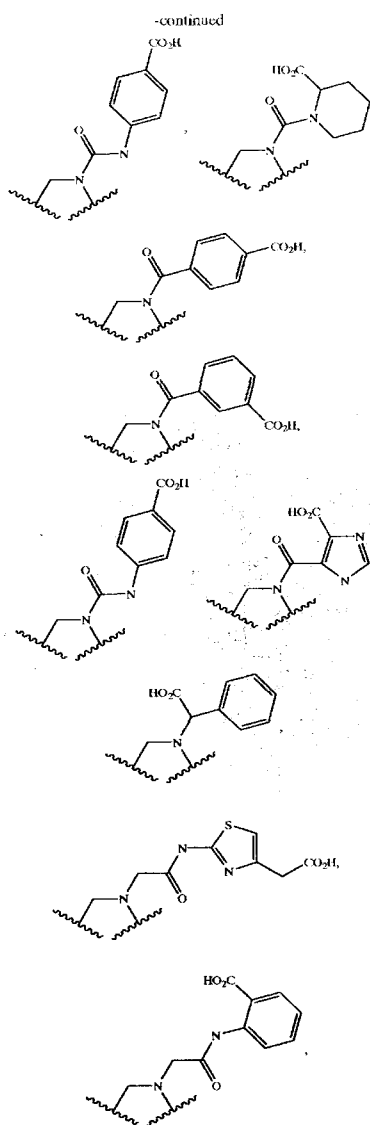


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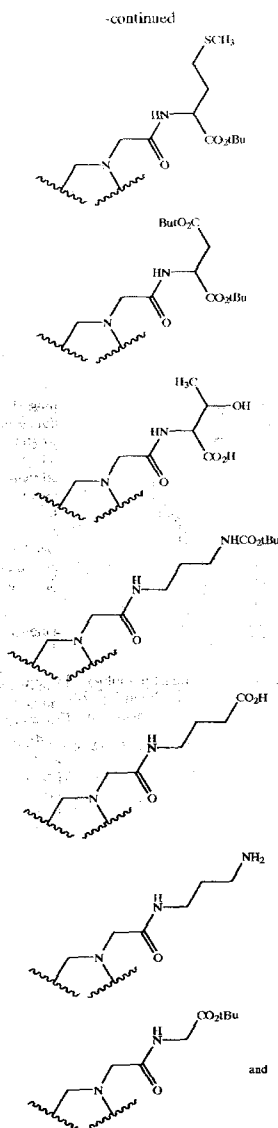
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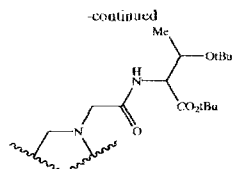
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[0079] The compounds of formula (I) can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s)" may include zwitterions (inner salts), e.g., when a compound of formula (I) contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a carboxylic acid. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, e.g., in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula (I) may be formed, for example, by reacting a compound of the formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0080] Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, malates (formed with malic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotines, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

[0081] Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-phenethylamine, N,N'-dibenzyl-ethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as



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arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others. Preferred salts include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate salts.

[0082] Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), and/or a salt and/or solvate thereof. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula (I) compounds per se. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester per se is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula (I) include C_{1-6} alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkoxyloxy- C_{1-6} alkyl, e.g. acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6} alkoxycarbonyloxy- C_{1-6} alkyl, e.g. methoxycarbonyl-oxy-methyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

[0083] Compounds of the formula (I) and salts thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that the all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have trans and cis isomers and may contain one or more chiral centers, therefore existing in enantiomeric and diastereomeric forms. The invention includes all such isomers, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers). When no specific mention is made of the configuration (cis, trans or R or S) of a compound (or of an asymmetric carbon), then any one of the isomers or a mixture of more than one isomer is intended. The processes for preparation can use racemates, enantiomers or diastereomers as starting materials. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization. The inventive compounds may be in the free or hydrate form.

[0084] Compounds of the Formula (I) may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound for formula I) is a prodrug within the scope and spirit of the invention.

[0085] Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

[0086] a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 42, pp. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

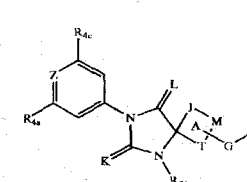
[0087] b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991); and

[0088] c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, pp. 1-38 (1992), each of which is incorporated herein by reference.

[0089] It should further be understood that solvates (e.g., hydrates) of the compounds of Formula (I) are also within the scope of the present invention. Methods of solvation are generally known in the art.

Preferred Compounds

[0090] Preferred compounds are those having formula (I),



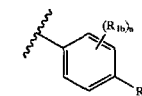
[0091] including enantiomers, diastereomers, and pharmaceutically-acceptable salts, hydrates, solvates, and prodrugs thereof, in which:

[0092] L and K, taken independently, are O or S;

[0093] Z is N or CR_{4b};

[0094] G is a bond;

[0095] Ar is directly attached to T or M and is



[0096] J is —O—, —S—, —NH—, —S(=O)—, —SO₂—, —NHSO₂—, a C_{2-3} alkylene optionally substituted with one to two R_{9a}, or a C_{2-3} alkenylene or C_{1-2} heteroalkylene optionally substituted with one to two R₉;

[0097] T is T₁ when Ar is attached to T and T₂ when Ar is attached to M;

[0098] M is M₁ when Ar is attached to M and M₂ when Ar is attached to T;

[0099] T₁ and M₁ are selected from: —N— and —CH—, and T₂ and M₂ are selected from: —O—, —S—, —NH—, —S(=O)—, —SO₂—, —NHSO₂—, —C(=O)— and —CH₂—;

[0100] provided that J, M, and T are selected to define a four to six membered saturated or partially unsaturated cycloalkyl or heterocyclo ring having from 1 to 2 heteroatoms wherein no two adjacent heteroatoms of said heterocyclo ring are simultaneously selected from —O— and —S—;

[0101] R_{1a} and R_{1b} are independently selected from halogen, C₁₋₄alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cyano, nitro, —CO₂H, —C(=O)H, —CO₂alkyl, —C(=O)alkyl, —C(=O)NH(CH₂)₂CO₂H, —C(=O)NH(CH₂)₂CO₂(alkyl), and S(O)₂alkyl; or from phenyl, benzyl, phenyloxy, benzyloxy, and heteroaryl; wherein each group R_{1a} and R_{1b} in turn is optionally substituted at any available carbon or nitrogen atom with one to two of C₁₋₄alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, cyano, nitro, —CO₂H, —C(=O)H, —CO₂alkyl, and/or —C(=O)alkyl; or alternatively, two R_{1a} groups join together with each other or one R_{1b} joins together with R_{1a} to form a fused-benzo ring;

[0102] R₂ is selected from hydrogen, alkyl, substituted alkyl, OR₁₂, NR₁₂, R₁₂, C(=O)R₁₂, CO₂R₁₂, C(=O)NR₁₂, NR₁₂, C(=O)NR₁₂, NR₁₂, C(=O)OR₁₂, SR₁₂, S(O)₂R₁₂, NR₁₂, SO₂NR₁₂, R₁₂, cycloalkyl, heterocycle, aryl, and heteroaryl;

[0103] R_{4a} and R_{4c} are halogen, alkyl, cyano, haloalkyl, haloalkoxy, or nitro;

[0104] R_{4b} is hydrogen, halogen, alkyl, substituted alkyl, nitro, cyano, hydroxy, alkoxy, haloalkoxy, phenyloxy, —CO₂H, —C(=O)H, NH(alkyl), N(alkyl)₂, CO₂alkyl, C(=O)alkyl, alkylthio, —C(=O)NH(CH₂)₂CO₂H, —C(=O)NH(CH₂)₂CO₂(alkyl), aryl, heteroaryl, or heterocycle, wherein each of the aryl, heteroaryl, and heterocycle groups are optionally substituted with one to two of halogen, C₁₋₄alkyl, OMe, CF₃, CN, OCF₃, CO₂H, —C(=O)H, CO₂alkyl, and/or C(=O)alkyl;

[0105] R₆ is —A₁—Q—A₂—R₁₆;

[0106] A₁ is a bond, C₁₋₂alkylene, or C₂₋₃alkenylene;

[0107] Q is a bond, —C(=O)—, —C(=O)NR₁₇—, —C(=S)NR₁₇—, —SO₂—, —SO₂NR₁₇—, —CO₂—, or —NR₁₇CO₂—;

[0108] A₂ is a bond, C₁₋₃alkylene, C₂₋₃alkenylene, —C₁₋₄alkylene—NR₁₇—, —C₁₋₄alkylene—NR₁₇—C(=O)—, —C₁₋₄alkylene—S—, —C₁₋₄alkylene—SO₂—, or —C₁₋₄alkylene—O—, wherein said A₂ alkylene groups are branched or straight chain and optionally substituted with a group selected from —CO₂H, —CO₂(C₁₋₄alkyl), —S(C₁₋₄alkyl), NH₂, —NH(C₁₋₄alkyl), or —N(C₁₋₄alkyl)₂;

[0109] R₁₂ and R₁₃ (i) are selected independently of each other from hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocycle; or (ii) taken together form a heteroaryl or heterocycle;

[0110] R_{13a} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocycle;

[0111] R₁₆ is selected from (i) hydrogen or a C₁₋₄alkyl or C₂₋₃alkenyl optionally substituted with up to three of OR₂₃, SR₂₃, —CO₂R₂₃, —SO₂(alkyl), and/or NR₂₃R₂₃, or from (ii) phenyl, naphthyl, five to ten membered monocyclic or bicyclic heteroaryl, four to eleven membered monocyclic or bicyclic heterocycle, and three to nine membered monocyclic or bicyclic cycloalkyl, wherein each of said R₁₆ cyclic groups in turn is optionally substituted with up to three R₁₆;

[0112] R₁₇ is selected from hydrogen, lower alkyl, and substituted lower alkyl;

[0113] R₁₈ is selected from —(CH₂)₄halogen, —(CH₂)₄nitro, —(CH₂)₄cyano, —(CH₂)₄haloalkyl, —(CH₂)₄haloalkoxy, —(CH₂)₄SR₂₄, —C₃₋₅cycloalkyl, —SO₂R₂₄, —OR₂₄, —(CH₂)₄CO₂R₂₄, (CH₂)₄NR₂₄R₂₄, —(CH₂)₄NHCO₂R₂₄, —C(=O)NH—SO₂R₂₄, C(=O)O(CH₂)₄NR₂₄R₂₄, —O(CH₂)₄NR₂₄R₂₄, —C(=O)R₂₄, —(CH₂)₄R₂₄ and —C₁₋₄alkyl or —C₂₋₃alkenyl optionally substituted with CO₂R₂₄;

[0114] R_{23a}, R_{23b}, and R_{23c} are independently selected from hydrogen and alkyl;

[0115] R₂₄ is selected from hydrogen, alkyl, phenyl, benzyl, C₃₋₅cycloalkyl, five or six membered heteroaryl, and four to seven membered heterocycle, in turn optionally substituted with one to two C₁₋₄alkyl, halogen, hydroxy, trifluoromethyl, trifluoromethoxy, —CO₂H, CO₂C₁₋₄alkyl, C₁₋₄alkoxy, —S(C₁₋₄alkyl), amino, and/or aminoC₁₋₄alkyl, provided that when R₂₄ is attached to a sulfonyl group as in —SO₂R₂₄, then R₂₄ is not hydrogen;

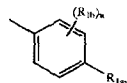
[0116] R₂₅ is selected from hydrogen and alkyl; and

[0117] n is 0, 1, or 2;

[0118] p is 1 or 2;

[0119] q is 0, 1, 2, 3, or 4; and

[0120] r is 1, 2, 3, or 4.



[0121] In compounds of formula (I), the group Ar is preferably R_{1a} wherein R_{1a} is preferably halogen, cyano, haloalkyl, haloalkoxy, or optionally substituted phenyl or heteroaryl, and R_{1b} is absent or selected from halogen, C₁₋₄alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cyano, nitro, —CO₂H, —C(=O)H, —CO₂alkyl, —C(=O)alkyl, —C(=O)NH(CH₂)₂CO₂H, and —C(=O)NH(CH₂)₂CO₂(alkyl).

4CO₂(alkyl). Alternatively, two R_{1b} groups may join together with each other or one R_{1b} may join together with R_{1a} to form a fused benzo ring.

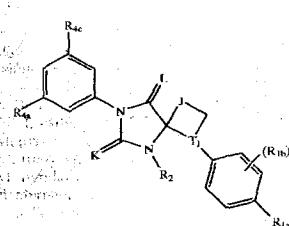
[0122] In compounds of formula (I), the groups R_{4a} and R_{4c} are preferably selected from halogen, alkyl, cyano, nitro, haloalkyl, haloalkyl, aryloxy, and arylthio, and more preferably, R_{4a} and R_{4c} are both chlorine.

[0123] In compounds of formula (I), the group G is preferably a bond; the groups I and K are preferably oxygen; and Z is preferably CH.

[0124] In compounds of formula (I), the group T is preferably T₁ and is CH, M is preferably M₂ and is CH₂, and J is preferably an optionally-substituted C₃heteroalkylene so that A is a five-membered ring, more preferably J is a group —CH₂—NR₉—.

[0125] In compounds of formula (I), the group R₂ is preferably C(=O)lower alkyl or C₁₋₄alkyl optionally substituted with CO₂H or CO₂(alkyl), more preferably R₂ is methyl.

[0126] Also preferred are compounds according to formula (Ic).



[0127] and pharmaceutically-acceptable salts, hydrates, and prodrugs thereof, in which:

[0128] I and K, taken independently, are O or S;

[0129] J is —O—, —S—, —NH—, —S(=O)—, —SO₂—, —NHSO₂—, an optionally substituted C₁₋₃alkylene, an optionally substituted C₂₋₃alkenylene, or an optionally-substituted C₁₋₂heteroalkylene;

[0130] T₁ is —N— or —CH—;

[0131] R_{1a} is halogen, cyano, or optionally-substituted phenyl or heteroaryl;

[0132] R_{1b} is selected from halogen, C₁₋₄alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cyano, nitro, —CO₂H, —C(=O)H, —CO₂alkyl, —C(=O)alkyl, —C(=O)NH(CH₂)₂CO₂H, and —C(=O)NH(CH₂)₂CO₂(alkyl); or from phenyl, benzyl, phenyloxy, benzyloxy, and heteroaryl in turn optionally substituted with one to two of C₁₋₄alkyl, halogen, hydroxy, alkoxy, haloalkyl, haloalkoxy, cyano, nitro, —CO₂H, —C(=O)H, —CO₂alkyl, and/or —C(=O)alkyl;

[0133] R₂ is selected from hydrogen, alkyl, substituted alkyl, O(C₁₋₄alkyl), amino, NH(C₁₋₄alkyl), N(alkyl)₂, C(=O)H, C(=O)alkyl, CO₂(alkyl), SO₂alkyl, C₃₋₅cycloalkyl, heterocycle, aryl, and heteroaryl;

[0134] R_{4a} and R_{4c} are halogen, alkyl, cyano, trifluoromethyl, or nitro; and

[0135] n is 0, 1, or 2.

[0136] In compounds of formula (Ic), as immediately defined above, more preferably J is —CH₂—, —CH₂—CH(R₉)—, or —CH₂—N(R₉)—, wherein:

[0137] R₉ is —A₁—Q—A₂—R₁₆;

[0138] A₁ is a bond, C₁₋₂alkylene, or C₂₋₃alkenylene;

[0139] Q is a bond, —C(=O)—, —C(=O)NR₁₇—, —SO₂—, —CO₂—, or —NR₁₇CO₂—;

[0140] A₂ is a bond, C₁₋₂alkylene, C₂₋₃alkenylene, —C₁₋₄alkylene—NR₁₇—, —C₁₋₄alkylene—NR₁₇—C(=O)—, —C₁₋₄alkylene—S—, —C₁₋₄alkylene—SO₂—, or —C₁₋₄alkylene—O—, wherein said A₂ alkylene groups are branched or straight chain and optionally substituted with a group selected from —CO₂H, —CO₂(C₁₋₄alkyl), —S(C₁₋₄alkyl), NH₂, —NH(C₁₋₄alkyl), or —N(C₁₋₄alkyl)₂;

[0141] R₁₆ is selected from (a) hydrogen and C₁₋₄alkyl or C₂₋₃alkenyl optionally substituted with one to two of OH, O(C₁₋₄alkyl), —CO₂H, —CO₂(C₁₋₄alkyl), NH₂, —NH(C₁₋₄alkyl), and/or N(C₁₋₄alkyl)₂, or from (b) furanyl, indolyl, carbazolyl, pyrazolyl, pyrrolyl, thienyl, pyridyl, pyrimidinyl, benzofuranyl, isoxazolyl, imidazolyl, triazolyl, tetrazolyl, phenyl, piperidyl, pyrrolidinyl, morpholinyl, C₃₋₅cycloalkyl, piperazinyl, thiazolyl, morpholinyl, 1,2,5,6-tetrahydropyridyl, quinoxalinyl, benzothiazolyl, benzotriazolyl, benzodioxanyl, benzoxadiazolyl, thienopyrazolyl, tetrahydroquinolyl, and quinolyl, wherein each of said cyclic R₁₆ groups in turn is optionally substituted with up to three R₁₆;

[0142] R₁₇ is selected from hydrogen, lower alkyl, and substituted lower alkyl;

[0143] R₁₈ is selected from —C₁₋₄alkyl, —S(C₁₋₄alkyl), C₃₋₅cycloalkyl, —SO₂(C₁₋₄alkyl), —O(C₁₋₄alkyl), —SO₂phenyl, halogen, hydroxy, nitro, cyano, —(CH₂)₄CO₂H, —(CH₂)₄CO₂C₁₋₄alkyl, —(CH₂)₄NH₂, —O(CH₂)₄CO₂H, —CH=CH—CO₂H, —CH=CH—CO₂(alkyl), —(CH₂)₄NH(alkyl), —(CH₂)₄NHCO₂alkyl, —C(=O)NH—SO₂alkyl, —(CH₂)₄NH(benzyl), —(CH₂)₄N(alkyl)₂, —O(CH₂)₄N(alkyl)₂, —Obenzyl, —C(=O)O(CH₂)₄NH(alkyl), —C(=O)O(CH₂)₄N(alkyl)₂, —O(CH₂)₄NH₂, —O(CH₂)₄N(alkyl)₂, —C(=O)pyridyl, —(CH₂)₄phenyl, —(CH₂)₄pyridyl, —(CH₂)₄triazolyl, —(CH₂)₄imidazolyl, —(CH₂)₄pyrazolyl, —(CH₂)₄thiamorpholinyl, —(CH₂)₄morpholinyl, —(CH₂)₄thienyl, —(CH₂)₄pyrazinyl, wherein each alkyl or cyclic

group of each R_{18} in turn is optionally substituted with one to two C_{1-4} alkyl, halogen, hydroxy, trifluoromethyl, trifluoromethoxy, $-CO_2H$, CO_2C_{1-4} alkyl, C_{1-4} alkoxy, $-S(C_{1-4}alkyl)$, amino, and/or amino C_{1-4} alkyl.

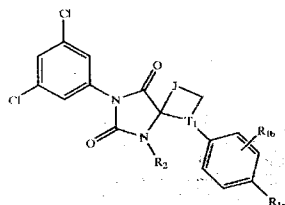
[0144] q is 0, 1, 2, 3, or 4; and

[0145] r is 1, 2, 3 or 4.

[0146] Further preferred are compounds as immediately defined above wherein R_9 is $-C_{1-4}alkylene-R_{10}$, $-C(=O)R_{10}$, or $-C(=O)C_{1-4}alkylene-R_{10}$, more preferably $-CH_2R_{10}$, and R_{10} is as immediately defined above, more preferably thienyl, phenyl, or pyridyl, optionally substituted with one to two R_{18} .

[0147] Also preferred are compounds according to formula (Id),

(Id)



[0148] and pharmaceutically-acceptable salts, hydrates, and prodrugs thereof, in which

[0149] J is $-(CR_{9a}R_{9b})_y$ or $-(CR_{9a}R_{9b})_y-NR_{9c}$, wherein x is 1, 2 or 3, y is 0, 1 or 2, and z is 0, 1 or 2, provided that y and z together are not greater than 2;

[0150] T is $-N-$ or $-CH-$;

[0151] R_{1a} is halogen, cyano, nitro, trifluoromethyl, OCF_3 , heterocyclo, or heteroaryl;

[0152] R_{1b} is hydrogen, halogen, C_{1-4} alkyl, cyano, nitro, $-CO_2H$, $-C(=O)H$, $-CO_2alkyl$, or $-C(=O)alkyl$;

[0153] R_2 is selected from hydrogen, C_{1-4} alkyl, amino, $NH(C_{1-4}alkyl)$, $N(alkyl)_2$, $C(=O)H$, $C(=O)C_{1-4}alkyl$, $CO_2(C_{1-4}alkyl)$, $SO_2C_{1-4}alkyl$, $C_3cycloalkyl$, heterocycle, aryl, and heteroaryl, or C_{1-4} alkyl substituted with one to three of amino, $NH(C_{1-4}alkyl)$, $N(alkyl)_2$, $C(=O)H$, $C(=O)C_{1-4}alkyl$, CO_2H , $CO_2(C_{1-4}alkyl)$, $SO_2C_{1-4}alkyl$, SO_3H , and/or $PO(OH)_2$;

[0154] R_{9a} and R_{9b} , at each occurrence are independently selected from hydrogen, halogen, C_{1-4} alkyl, substituted alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, cyano, nitro, $-CO_2H$, $-C(=O)H$, $-CO_2alkyl$, $-C(=O)alkyl$, $-C(=O)NH(CH_2)_1$, $-CO_2H$, and/or $-C(=O)NH(CH_2)_1CO_2alkyl$, or R_{9a} and R_{9b} together form keto $(=O)$;

[0155] R_{1c} is selected from hydrogen, C_{1-4} alkyl, substituted alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, SO_2R_{1c} , $C(=O)R_{1c}$, SO_2NR_{1c} , R_{1c} , CO_2R_{1c} , $-C(=S)NR_{1c}$, $C(=O)C(=O)R_{1c}$, $C(=O)NH(CH_2)_1CO_2H$, $-C(=O)NH(CH_2)_1CO_2(alkyl)$, phenyl, $C_3cycloalkyl$, and five to six membered heteroaryl or heterocyclo; and

[0156] R_{1d} and R_{1e} are selected from hydrogen, lower alkyl, substituted alkyl, phenyl, $C_3cycloalkyl$, five to six membered heteroaryl, five to six membered heterocyclo, or nine to ten membered aryl or heteroaryl, in turn optionally substituted with one to two of C_{1-4} alkyl, halogen, nitro, cyano, amino, C_{1-4} aminoalkyl, C_{1-4} thioalkyl, hydroxy, C_{1-4} alkoxy, $-CO_2H$, $-CO_2(alkyl)$, $-C(=O)H$, $-C(=O)alkyl$, $-C(=O)(CH_2)_1NH_2$, phenyl, $C_3cycloalkyl$, five to six membered heteroaryl, and/or five to six membered heterocyclo, provided that when R_{1d} is attached to a sulfonyl group as in $-SO_2R_{1d}$, then R_{1d} is not hydrogen; and

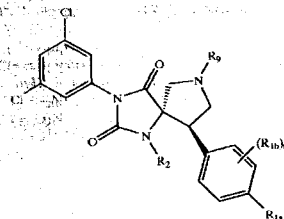
[0157] q is 0, 1 or 2.

[0158] In compounds of formula (Id) as defined above, preferably y is 1 or 2 and z is 0. T_1 is preferably $-CH-$, R_2 is preferably hydrogen or C_{1-4} alkyl, and R_{9a} and R_{9b} are preferably hydrogen.

[0159] Also preferred are compounds of formula (Id), as defined above, where R_{9a} is $-A$, Q , A_2 , and R_{10} are as defined above for compounds of formula (Ic).

[0160] According to another aspect of the invention, preferred compounds are those having the formula (Ic),

(Ic)



[0161] or an enantiomer, diastereomer, or salt thereof, in which:

[0162] R_{1a} is halogen, cyano, nitro, trifluoromethyl, OCF_3 , heteroaryl, or heterocyclo;

[0163] R_{1b} is hydrogen, halogen, C_{1-4} alkyl, cyano, nitro, $-CO_2H$, $-C(=O)H$, $-CO_2alkyl$, or $-C(=O)alkyl$;

[0164] R_2 is hydrogen or C_{1-4} alkyl;

[0165] R_9 is selected from hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, hydroxy, alkoxy, alkylthio, haloalkyl, haloalkoxy, phenyl, $C_3cycloalkyl$, phenyl, pyridyl, pyridazinyl, pyrimidinyl, $-(CH_2)_4phenyl$, $-(CH_2)_4tetrazolyl$, $-(CH_2)_4pyridyl$,

$-(CH_2)_4thienyl$, $-(CH_2)_4carbazolyl$, $-(CH_2)_4indolyl$, $-(CH_2)_4furyl$, $-(CH_2)_4quinolyl$, $-(CH_2)_4thiazolyl$, $-(CH_2)_4isoxazolyl$, $-(CH_2)_4imidazolyl$, $-(CH_2)_4benzofuryl$, $-(CH_2)_4pyrazolyl$, $-C(=O)H$, $-C(=O)alkyl$, $-C(=O)C_{1-10}alkyl$, $-C(=O)phenyl$, $-C(=O)piperidyl$, $-C(=O)morpholinyl$, $-C(=O)C_{3-6}cycloalkyl$, $-C(=O)pyrrolidinyl$, $-C(=O)quinolyl$, $-C(=O)imidazolyl$, $-C(=O)pyrazolyl$, $-C(=O)thiazolyl$, $-C(=O)quinoxalyl$, $-C(=O)pyridyl$, $-C(=O)1,2,5,6-tetrahydropyridyl$, $-C(=O)benzotriazolyl$, $-C(=O)benzodioxanyl$, $-C(=O)benzoxadiazolyl$, $-C(=O)1,2,3,4-tetrahydroquinolyl$, $-C(=O)thienopyrazolyl$, $-C(=O)(CH_2)_4tetrazolyl$, $-C(=O)(CH_2)_4pyridyl$, $-C(=O)(CH_2)_4phenyl$, $-C(=O)(CH_2)_4pyrrolidinyl$, $-C(=O)(CH_2)_4piperidyl$, $-C(=O)CH=CH(phenyl)$, $-C(=O)CH=CH(pyridyl)$, $-C(=O)CH_2O(alkyl)$, $-C(=O)CH_2S(alkyl)$, $-C(=O)CH_2S(pyridyl)$, $-C(=O)CH_2SO_2(alkyl)$, $-C(=O)CH_2SO_2(phenyl)$, $-C(=O)CH_2NH(phenyl)$, $-C(=O)CH_2NH(benzyl)$, $-C(=O)CH_2NH(thiazolyl)$, $-C(=O)CH_2NH(C(=O)pyridyl)$, $-C(=O)CH_2NH(C(=O)phenyl)$, $-(CH_2)_4SO_2(alkyl)$, $-(CH_2)_4SO_2(thienyl)$, $-(CH_2)_4SO_2(imidazolyl)$, $-(CH_2)_4SO_2(furyl)$, $-(CH_2)_4SO_2(pyrazolyl)$, $SO_2NH(phenyl)$, $-C(=S)NH_2$, $-C(=S)NH(alkyl)$, $-C(=S)NH(phenyl)$, $-(CH_2)_4C(=O)pyrrolidinyl$, $-(CH_2)_4C(=O)piperidyl$, $-(CH_2)_4C(=O)piperazinyl$, $-CO_2(alkyl)$, $-CO_2(phenyl)$, $-CO_2(benzyl)$, $-NHCO_2(alkyl)$, $-(CH_2)_4C(=O)NH(phenyl)$, $-(CH_2)_4C(=O)NH(piperidyl)$, $-(CH_2)_4C(=O)NH(thiazolyl)$, $-(CH_2)_4C(=O)NH(benzyl)$, $-(CH_2)_4C(=O)NH(C_3cycloalkyl)$, $-(CH_2)_4C(=O)NH(pyrazolyl)$, $-(CH_2)_4C(=O)NH(piperidinyl)$, $-(CH_2)_4C(=O)NH_2$, $-(CH_2)_4C(=O)NH(alkyl)$, $-(CH_2)_4C(=O)N(alkyl)_2$, $-(CH_2)_4C(=O)N(C_{1-4}alkyl)(thienyl)$, $-(CH_2)_4C(=O)N(C_{1-4}alkyl)(thiazolyl)$, $-(CH_2)_4C(=O)N(C_{1-4}alkyl)(benzyl)$, or $-(CH_2)_4C(=O)N(C_{1-4}alkyl)CO_2(alkyl)$;

[0166] wherein each alkyl, alkenyl, or cyclic group of each R_9 in turn is optionally substituted with up to three R_{18} ;

[0167] R_{18} is selected from $-C_{1-4}alkyl$, $-S(C_{1-4}alkyl)$, $C_3cycloalkyl$, $-SO_2(C_{1-4}alkyl)$, $-O(C_{1-4}alkyl)$, $-SO_2phenyl$, halogen, hydroxy, nitro, cyano, $-(CH_2)_4CO_2H$, $-(CH_2)_4CO_2C_{1-4}alkyl$, $-(CH_2)_4NH_2$, $-(CH_2)_4CO_2H$, $-CH=CH-CO_2H$, $-CH=CH-CO_2(alkyl)$, $-(CH_2)_4NH(alkyl)$, $-(CH_2)_4NH(CO_2alkyl)$, $-(C=O)NH-SO_2alkyl$, $-(CH_2)_4NH(benzyl)$,

$-(CH_2)_4N(alkyl)_2$, $-O(CH_2)_4N(alkyl)_2$, $-Obenzyl$, $-C(=O)(CH_2)_4NH_2$, $-C(=O)(CH_2)_4NH(alkyl)$, $-C(=O)(CH_2)_4N(alkyl)_2$, $-O(CH_2)_4NH_2$, $-O(CH_2)_4NH(alkyl)$, $-O(CH_2)_4N(alkyl)_2$, $-C(=O)pyridyl$, $-(CH_2)_4phenyl$, $-(CH_2)_4pyridyl$, $-(CH_2)_4tetrazolyl$, $-(CH_2)_4imidazolyl$, $-(CH_2)_4pyrazolyl$, $-(CH_2)_4thiamorpholinyl$, $-(CH_2)_4morpholinyl$, $-(CH_2)_4thienyl$, $-(CH_2)_4pyrazinyl$, wherein each alkyl or cyclic group of each R_{18} in turn is optionally substituted with one to two $C_{1-4}alkyl$, halogen, hydroxy, trifluoromethyl, trifluoromethoxy, $-CO_2H$, $CO_2C_{1-4}alkyl$, $C_{1-4}alkoxy$, $-S(C_{1-4}alkyl)$, amino, and/or amino $C_{1-4}alkyl$;

[0168] n is 0, 1 or 2;

[0169] q is 0, 1, 2, 3, or 4;

[0170] r is 1, 2, 3 or 4.

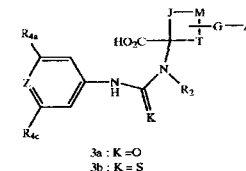
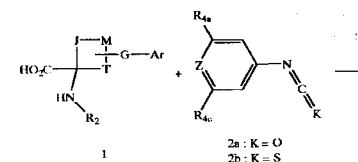
[0171] s is 1, 2, 3 or 4; and

[0172] t is 0, 1, or 2.

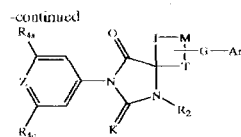
Methods of Preparation

[0173] The compounds of the invention may be prepared by the exemplary processes described in the following reaction Schemes A-K. Exemplary reagents and procedures for these reactions appear hereinafter. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art. For all of the schemes, the groups Z , K , L , Ar , J , T , M , R_1 , R_2 , R_3 , R_{4a} , R_{4b} , and R_{4c} are as described herein for a compound of formula (I), unless otherwise indicated. Groups designated generally as R , R' , X , and P as well as solvents, temperatures, pressures, starting materials having the desired groups, and other reaction conditions, may be readily selected as appropriate by one of ordinary skill in the art.

Scheme A:



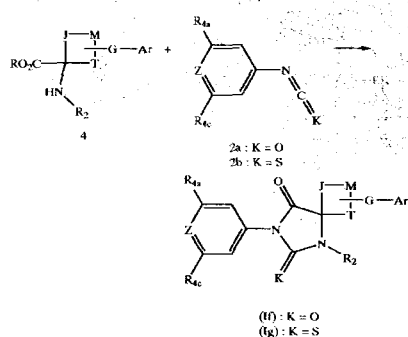
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(If): K = O
(Ig): K = S

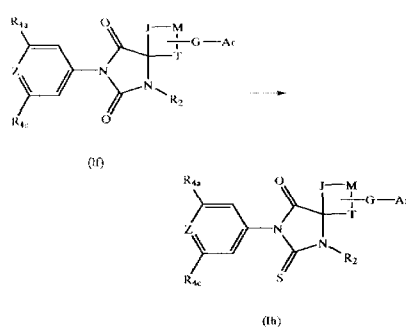
[0174] A suitably functionalized amino acid 1 is reacted with an isocyanate 2a or an isothiocyanate 2b in water in the presence of a base (such as NaOH, KOH, K_2CO_3 , $KHCO_3$, Na_2CO_3 or $NaHCO_3$), to yield after acidification the ureidoacid 3a or the thioureidoacid 3b, respectively. This intermediate product is then cyclized in an organic or aqueous solvent in the presence of a catalytic amount of acid (such as hydrochloric acid, sulfuric acid, methanesulfonic acid, or toluenesulfonic acid) to give the spirohydantoin having the formula (If) or spiro-2-thiohydantoin having the formula (Ig). See, e.g., Espada et al., *Pharmazie*, Vol. 45 (1990), at pp. 1237-1243, or Nicole et al., *Can. J. Chem.*, Vol. 40 (1962), at pp. 353-366. Alternatively, the ureido or thioureido acid can be cyclized in an organic solvent (such as DMF, THF, DCM) using a dehydrating agent (such as DCC or EDCI) in the presence of an activating agent (such as HOBT or 1-hydroxy-7-azabenzotriazole) and a non-nucleophilic base (such as TEA or DIPEA).

Scheme B:



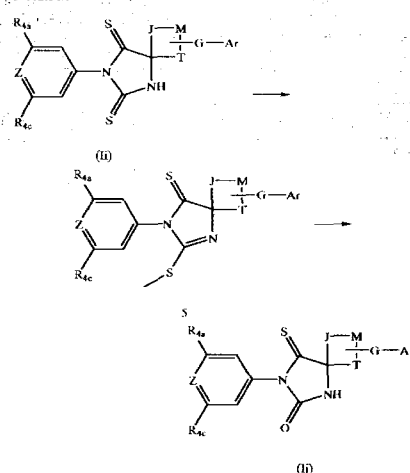
[0175] Compounds having the formula (If) or (Ig) can also be obtained in one step as depicted in Scheme B. Reaction of a suitably functionalized amino ester 4 with an isocyanate 2a or isothiocyanate 2b in an organic solvent (such as THF, methylene chloride or DMF) in the presence of a base (such as TEA, K_2CO_3 or KOH), yields the desired compound having the formula (If) or (Ig) respectively. See, e.g., Park et al., *J. Org. Chem.*, Vol. 63 (1998), at pp. 113-117; Johnson et al., *J. Am. Chem. Soc.*, Vol. 40 (1918), at p. 645; and Schöllkopf et al., *Liebigs Ann. Chem.*, (1981), at pp. 439-458.

Scheme C:



[0176] Treatment of hydantoins (If) with a reagent such as P_2S_5 or 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) in an organic solvent such as toluene or dioxane, yields the corresponding dithio-hydantoins having the formula (Ih). See, e.g., Carrington et al., *J. Chem. Soc.*, (1950), at p. 354.

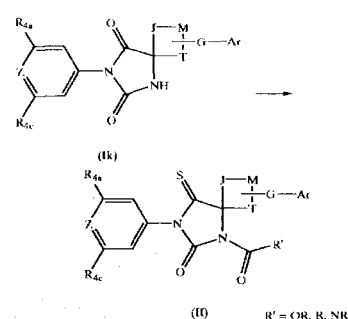
Scheme D:



[0177] Dithio-hydantoins (Ii) can be converted into 4-thio-hydantoins by S-alkylating compounds (Ij) with a reagent such as methyl iodide to give intermediate 5, which is hydrolyzed under mild acidic conditions to the 4-thio-

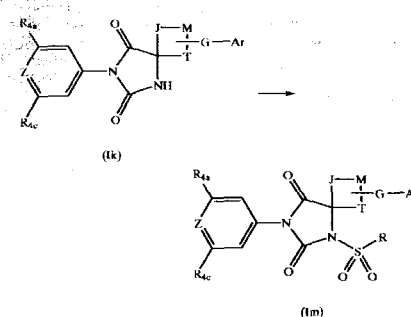
hydantoins having the formula (Ij). See, e.g., Carrington et al., *J. Chem. Soc.*, (1950), at p. 354.

Scheme E:



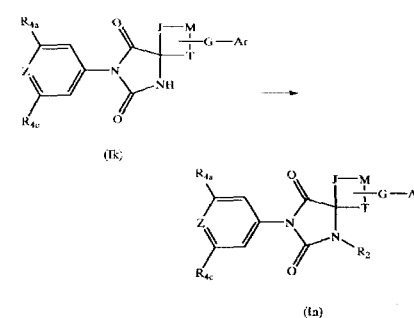
[0178] N-acylation of hydantoins having the formula (Ik) can be obtained by treatment with an acylating agent (such as an acyl chloride, an anhydride, a chloroformate or an isocyanate) in an organic solvent (such as THF or acetonitrile) in the presence of a base (such as TEA, DIPEA, DMAP or NaH) to give hydantoins having the formula (Ii). See, e.g., Link et al., *Eur. J. Med. Chem.*, Vol. 19 (1984), at pp. 261-266, and Ortin et al., *An. R. Soc. Exp. Fis. Quim. Ser. B*, (1958), at p. 69.

Scheme F:



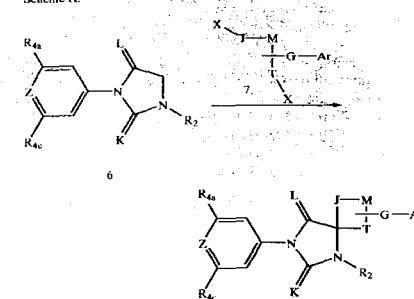
[0179] Sulfonation of hydantoins having the formula (Ik) is obtained by treatment with a sulfonyl chloride in the presence of a base (such as TEA, DIPEA, pyridine or DMAP) in an organic solvent such as toluene to give the desired compounds having the formula (Im). See, e.g., Takayama et al., *Agric. Biol. Chem.*, Vol. 51 (1987), at pp. 1547-1552.

Scheme G:



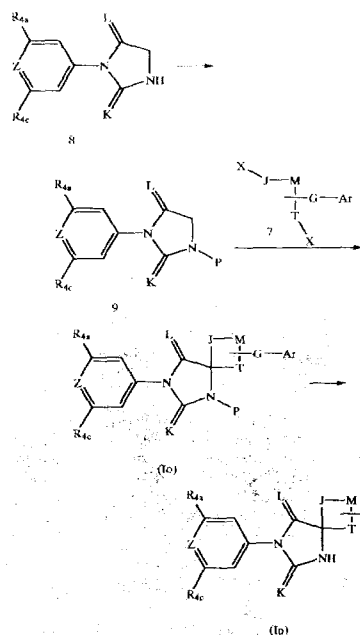
[0180] Hydantoins having the formula (Ik) can be N-alkylated in an aprotic solvent (such as DMF, THF or DMSO) by treatment with one equivalent of a base (such as NaH, NaHMDS, LDA, LiHMDS, Kt, KHMDS or tBuOK) followed by addition of a suitable alkylating agent (such as an alkyl iodide, alkyl bromide, alkyl chloride, a tosylate or a mesylate) to yield hydantoins having the formula (Ia). See, e.g., Parmec et al., *Bioorg. Med. Chem. Lett.*, Vol. 9 (1999), at pp. 749-754.

Scheme H:



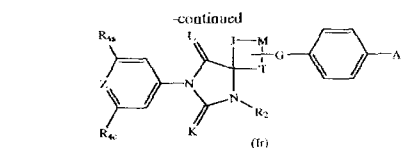
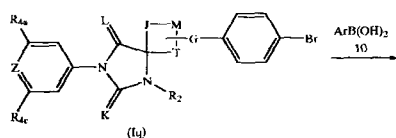
[0181] Spiro hydantoins can also be prepared as depicted in Scheme H. Hydantoin 6 is treated either sequentially or directly with two equivalents of a base (such as NaH, Kt, LiHMDS, KHMDS, LDA, tBuOK, KOH, methylmagnesium carbonate or DBU) in an organic solvent (such as THF, DMF, DMSO) and reacted with compound 7 bearing two leaving groups X (such as Cl, Br, I, OMs or OTs) to yield the desired hydantoin having the formula (I). See, e.g., Collado et al., *Tetrahedron Lett.*, Vol. 37 (1996), at pp. 6193-6196; Fujiwara et al., *J. Chem. Soc. Perkin Trans. 2*, (1980), at pp. 1573-1577; and Belzecki et al., *J. Org. Chem.*, Vol. 45 (1980), at pp. 2215-2217.

Scheme I:



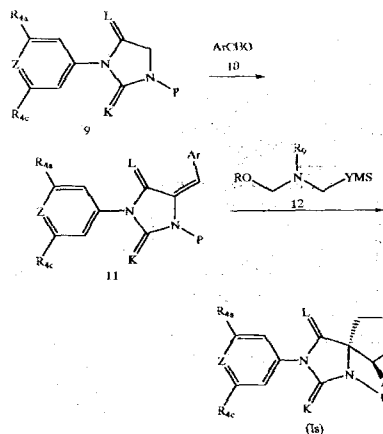
[0182] N-unsubstituted hydantoins having the formula (Ip) can be prepared using the same or similar procedure as for Scheme H, with the addition of a protection/deprotection sequence. Thus hydantoin 8 is protected on the nitrogen with a protecting group P, such as BOC (see, e.g., Nilsson et al., *J. Med. Chem.*, Vol. 35 (1992), at pp. 3270-3279) to give the intermediate 9, which is dialkylated as previously with 7 to yield the compound having the formula (Io). Deprotection gives the desired N-unsubstituted spirohydantoin having the formula (Ip).

Scheme J:



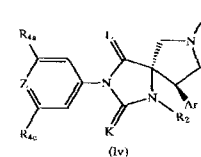
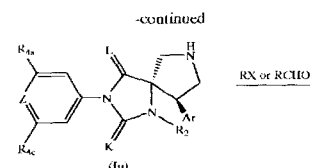
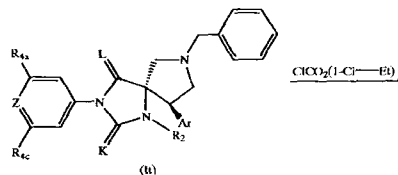
[0183] Bromo spiro hydantoins having the formula (Ir) can be transformed into biaryl compounds having the formula (Iq) by reaction with an aromatic or heteroaromatic boronic acid 10 in the presence of a palladium catalyst (such as $\text{Pd}(\text{PPh}_3)_4$) and a base (such as K_2CO_3 or Na_2CO_3) in an appropriate solvent (such as toluene, DMF, DME or water), under conventional Suzuki coupling conditions. See, e.g., Suzuki et al., *Synth. Commun.*, Vol. 11 (1981), at p. 513.

Scheme K:



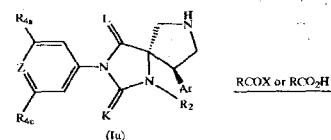
[0184] Hydantoins 9 can be submitted to a Knoevenagel condensation with an aromatic aldehyde 10 under classical conditions (e.g., sodium acetate in refluxing acetic anhydride) to obtain 11, which is then reacted with amine 12 under acidic catalysis (such as trifluoroacetic acid) to yield spiro-pyrrolo hydantoins having the formula (Is).

Scheme L:

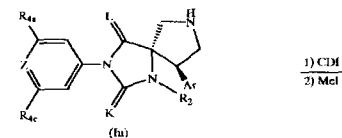


[0185] Hydantoins (It) can be debenzylated using, for example, 1-chloroethyl chloroformate in a solvent such as DCM or DCE, to yield the NH derivatives having the formula (Iu). Compounds of formula (Iu) can be alkylated by reaction with an alkyl halide RX (e.g., an alkyl iodide), in a solvent such as acetonitrile or acetone at temperature ranging from room temperature to reflux. Alternatively, alkylation can be achieved by reaction with an aldehyde in the presence of a reducing agent such as sodium triacetoxy borohydride or sodium cyanoborohydride in a solvent such as acetonitrile or DCE to yield compounds of formula (Iv).

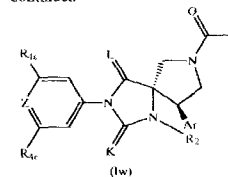
Scheme M:



Scheme O:

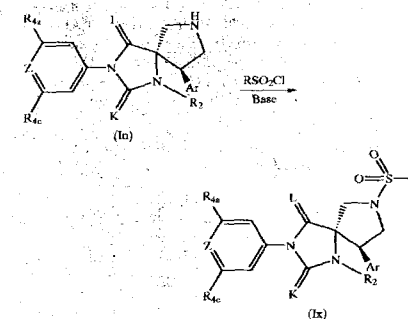


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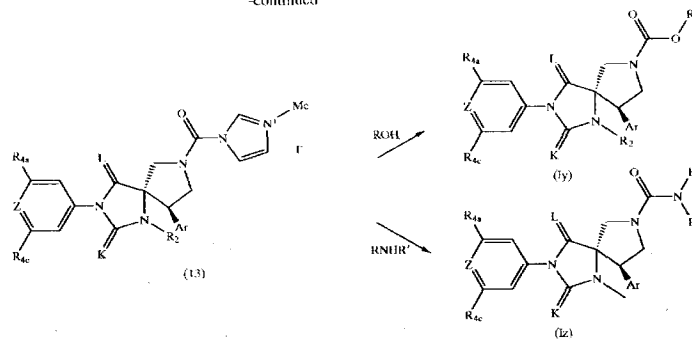
[0186] Compounds of formula (Iu) can also be acylated with an acyl halide (for example, an acyl chloride or acyl bromide) in the presence of an organic base (such as triethylamine or diisopropylethylamine) or an inorganic base (such as sodium carbonate) in a solvent such as DCM at a temperature ranging from -15°C . to room temperature to yield acylated derivatives of formula (Iw). Compounds (Iw) can also be obtained by reaction with an acid RCO_2H in the presence of a coupling agent such as dicyclohexylcarbodiimide in a solvent such as DCM.

Scheme N:



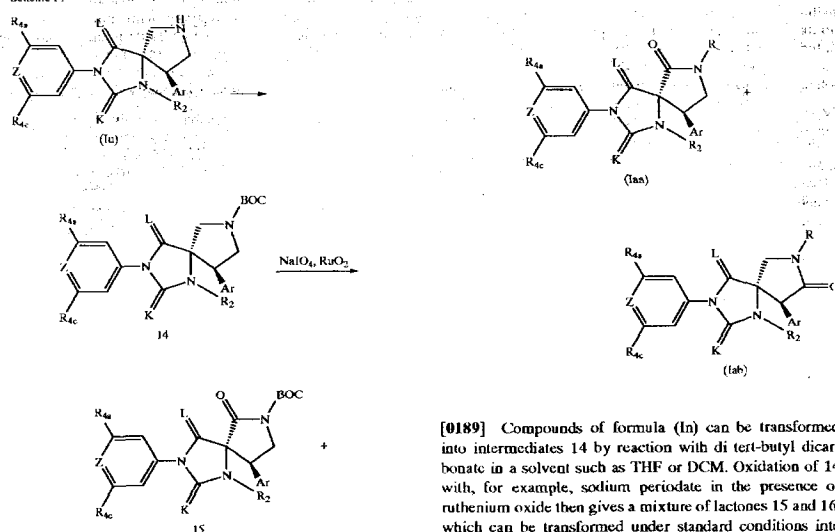
[0187] Sulfonamides of formula (Ix) can be obtained from compounds of formula (Iu) by reaction with a sulfonyl halide in the presence of a base (such as triethylamine or sodium carbonate) in a solvent such as DCM or THF at temperature ranging from -15°C . to room temperature.

-continued



[0188] Compounds of formula (Iu) can also be transformed into the activated intermediates 13 by sequential reaction with carbonyl diimidazole and methyl iodide. See R. A. Batey et al. *Tetrahedron Lett.*, Vol. 39 (1998), at p. 6267. Compounds 13 can then be reacted with either an alcohol or an amine to give carbamates of formula (1y) or ureas of formula (1z), respectively.

Scheme P:



[0189] Compounds of formula (In) can be transformed into intermediates 14 by reaction with di-tert-butyl dicarbonate in a solvent such as THF or DCM. Oxidation of 14 with, for example, sodium periodate in the presence of ruthenium oxide then gives a mixture of lactones 15 and 16, which can be transformed under standard conditions into compounds of formula (1aa) and (1ab).

Utility

[0190] The compounds and compositions of this invention are antagonists and/or inhibitors of LFA-1, Mac-1, and/or ICAMs. They are useful in treating various inflammatory diseases and disorders associated with the action of LFA-1, Mac-1, and/or ICAMs, particularly LFA-1/ICAM-1. The term "Leukointegrin/ICAM-associated condition" is used herein for ease of reference to refer to those diseases or disorders that are associated with the action or levels of LFA-1, Mac-1 and/or ICAM-1, ICAM-2, or ICAM-3. As used herein, the term "treating" includes prophylactic and therapeutic uses and thus includes the alleviation of symptoms of a Leukointegrin/ICAM-associated condition in a patient, the improvement of an ascertainable measurement associated with such a condition, or the prevention of such a condition or its symptoms. The term "patient" refers to a mammal, preferably a human.

[0191] In view of their inhibition activity, the compounds may be used to treat conditions involving the activation, co-stimulation, or infiltration of T-cells and/or leukocytes, including without limitation conditions involving the influx of leukocytes in the skin, peritoneum, synovium, lung, kidney, and heart. The inventive compounds may be used to treat conditions resulting from a response of the specific or non-specific immune system in a patient.

[0192] Leukointegrin/ICAM-associated conditions that may be treated with the inventive compounds include acute or chronic graft vs host reactions (e.g., pancreatic islet allograft); and acute or chronic transplant rejection (e.g., kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts, heterografts, and/or cells derived from such organs). Additionally, the compounds may be used to treat inflammatory conditions including, but not limited to, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, osteoporosis, diabetes (e.g., insulin dependent diabetes mellitus or juvenile onset diabetes), cystic fibrosis, inflammatory bowel disease, irritable bowel syndrome, Crohn's disease, ulcerative colitis, Alzheimer's disease, shock, ankylosing spondylitis, gastritis, conjunctivitis, pancreatitis (acute or chronic), multiple organ injury syndrome (e.g., secondary to septicemia or trauma), myocardial infarction, atherosclerosis, stroke, reperfusion injury (e.g., due to cardiopulmonary bypass or kidney dialysis), acute glomerulonephritis, vasculitis, thermal injury (i.e., sunburn), necrotizing enterocolitis, granulocyte transfusion associated syndrome, and/or Sjogren's syndrome.

[0193] The inventive compounds may be used to treat inflammatory conditions of the skin including eczema, atopic dermatitis, contact dermatitis, urticaria, scleroderma, psoriasis, and dermatosis with acute inflammatory components.

[0194] The compounds also may also be used to treat allergies and respiratory conditions, including asthma, pulmonary fibrosis, allergic rhinitis, oxygen toxicity, emphysema, chronic bronchitis, acute respiratory distress syndrome, and any chronic obstructive pulmonary disease (COPD). The compounds may be used to treat chronic hepatitis infection, including hepatitis B and hepatitis C.

[0195] Additionally, the compounds of the invention may be used to treat autoimmune diseases and/or inflammation

associated with autoimmune diseases such as organ-tissue autoimmune diseases (e.g., Raynaud's syndrome), autoimmune thyroiditis, uveitis, systemic lupus erythematosus, Addison's disease, autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), and Grave's disease.

[0196] The compounds of this invention also may be used to treat metastases or as an adjunct to minimize toxicity with cytokine therapy in the treatment of cancers.

[0197] The compounds of this invention further have utility in treating hypogonadism, frailty, sexual dysfunction, wasting, such as wasting syndromes associated with cancer and AIDS, and anemia. The compounds further have utility in treating cancers, including but not limited to cancers of the breast, brain, skin, ovary, endometrium, bladder, prostate, lung, colon, lymphatic system, liver and kidney. The inventive compounds are useful for conditions such as hirsutism, acne, seborrhea, alopecia, fibroids, hyperplasia, cachexia, polycystic ovarian syndrome, anorexia, contraception, drug withdrawal syndrome, pregnancy termination, and benign prostate hypertrophy. The compounds are further useful as antiangiogenic agents. Additionally, the compounds may be useful as inhibitors of protein prenyltransferases, particularly farnesyltransferase and the prenylation of the oncogene protein Ras. As such, the inventive compounds may potentially be useful for treating and/or preventing the diseases and disorders referred to in WO 01/45704, incorporated herein by reference.

[0198] When used as anti-inflammatory agents, the compounds may be administered prior to the onset of, at, or after the initiation of inflammation. When used prophylactically, the compounds are preferably provided in advance of any inflammatory response or symptom (for example, prior to, at, or shortly after the time of an organ or tissue transplant but in advance of any symptoms of organ rejection). Administration of the compounds may prevent or attenuate inflammatory responses or symptoms.

[0199] The present invention thus provides methods for treating such conditions as those listed above, comprising administering to a patient in need thereof an effective amount of at least one compound of formula (I) or a salt thereof. Other therapeutic agents such as those described below may be employed in combination with the compounds of formula (I). In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds.

[0200] The present invention also provides pharmaceutical compositions capable of treating the above-referenced diseases and disorders. The inventive compositions may contain other therapeutic agents and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.), according to techniques such as those well known in the art of pharmaceutical formulation.

[0201] The compounds of formula (I) may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is

generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

[0202] Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

[0203] Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginate acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, e.g., with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (e.g., GANTREZ®); and agents to control release such as polyacrylic copolymer (e.g., CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

[0204] Exemplary compositions for nasal administration via aerosol or inhalation include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

[0205] Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

[0206] Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquify and/or dissolve in the rectal cavity to release the drug.

[0207] The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a patient of from about 0.05 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and the particular condition sought to be treated and its severity. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like, subject to leukoantigen/ICAM associated conditions and/or subject to any of the above-referenced diseases and disorders.

[0208] The inventive compounds and compositions may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in treating diseases and disorders referenced above, for example, where the second drug has the same or different mechanism of action than the present compounds. Exemplary of such other therapeutic agents include anti-inflammatory agents, antibiotics, anti-viral agents, anti-oxidants, and agents used to treat respiratory conditions such as COPD and asthma.

[0209] Examples of suitable other anti-inflammatory agents with which the inventive compounds may be used include aspirin, cromolyn, nedocromil, theophylline, zileuton, zafirlukast, montelukast, pranlukast, indomethacin, and lipoxygenase inhibitors; non-steroidal antiinflammatory drugs (NSAIDs) (such as ibuprofen and naproxen); TNF- α inhibitors (such as tenidap and rapamycin or derivatives thereof), or TNF- α antagonists (e.g., infliximab, Enbrel®, D2E7, OR 1384), cytokine modulators (e.g. TNF- α converting enzyme [TACE] inhibitors, Interleukin-1 converting enzyme [ICE] inhibitors, Interleukin-1 receptor antagonists), prednisone, dexamethasone, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as Naproxen®, Celebrex®, or Vioxx®), CTLA-4-Ig agonists/antagonists (LEA29Y), CD40 ligand antagonists, IMPDH inhibitors (such as mycophenolate [CellCept®] and VX-497), methotrexate (FK506), integrin antagonists (e.g., α -4 β -1, α -V β -3), cell adhesion inhibitors, interferon gamma antagonists, prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, therapies for the treatment of irritable bowel syndrome (e.g., Zelnorm®, Zelnorm®, and Maxi-K® openers such as those disclosed in U.S. Pat. No. 6,184,231 B1), or NF- κ B inhibitors (such as calphostin, CSAIDs, and quinolines as disclosed in U.S. Pat. No. 4,200,750), disassociated steroids; chemokine receptor modulators (including

CCR1, CCR2, CCR3, CCR4, and CXCR2 receptor antagonists; secretory and cytosolic phospholipase A2 inhibitors, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; and nuclear translocation inhibitors, such as deoxyspergualin (DSG).

[0210] The inventive compounds may be used in combination with other agents used to treat respiratory conditions such as asthma, COPD, and allergic rhinitis, such as β -adrenergic agonists (such as albuterol, terbutaline, formoterol, salbutamol, salmeterol, bitolterol, pirbuterol, and fenoterol); corticosteroids (such as beclomethasone, triamcinolone, budesonide, fluticasone, flunisolide, dexamethasone, prednisone, and dexamethasone); leukotriene antagonists (e.g., Accolate [Zafirlukast®], and Singulair [Montelukast®]); Muscarinic M3 cholinergic antagonists (e.g., Spiriva®), PDE 4 inhibitors (e.g., roflumilast, cilomilast [Ariilo®], plicamylast, or roflumilast), histamine H1 antagonists, Allegra® (fexofenadine), Claritin® (loratadine), and/or Clarinex® (desloratidine).

[0211] Examples of suitable antiviral agents for use with the inventive compounds include nucleoside-based inhibitors, protease-based inhibitors, and viral-assembly inhibitors.

[0212] Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment, raloxifene, calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-1 inhibitors.

[0213] Examples of suitable anti-oxidants for use in combination with the compounds of the present invention include lipid peroxidation inhibitors such as probucol, HO-653, Vitamin A, Vitamin E, AGI-1067, and α -lipoic acid.

[0214] The inventive compounds also may be used in combination with anti-diabetic agents, such as biguanides (e.g. metformin), glucosidase inhibitors (e.g. acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g. repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (e.g., glucovance), thiazolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Ser. No. 09/519,079 filed Mar. 6, 2000 and assigned to the present assignee, glucagon-like peptide-1 (GLP-1), glucagon phosphorylase, and dipeptidyl peptidase IV (DPP4) inhibitors.

[0215] In addition, the compounds may be used with agents that increase the levels of cAMP or cGMP in cells for a therapeutic benefit. For example, the compounds of the invention may have advantageous effects when used in combination with phosphodiesterase inhibitors, including PDE1 inhibitors (such as those described in Journal of Medicinal Chemistry, Vol. 40, pp. 2196-2210 [1997]), PDE2 inhibitors, PDE3 inhibitors (such as revizinone, pimobendan, or olprinone), PDE4 inhibitors (referenced above), PDE7 inhibitors, or other PDE inhibitors such as dipyradomole, cilostazol, sildenafil, denbutyline, theophylline (1,2-dimethylxanthine), ARIFITM (i.e., cis-4-cyano-4-[3-

(cyclopentyl)oxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid), arolyline, C-11294A, CDC-801, HAY-19-8004, cipamylfylline, SCH351591, YM-976, PD-189659, mesiprom, pumafentrine, CDC-998, IC-485, and KW-4490.

[0216] In view of their usefulness in treating ischemia, the inventive compounds may be used in combination with agents for inhibiting F₁F₀-ATPase, including elarceptin, oligomycin, autoverin B, azide, and compounds described in U.S. patent application Serial No. 60/339,108, filed Dec. 10, 2001 and assigned to the present assignee; α - or β -adrenergic blockers (such as propranolol, nadolol, carvedilol, and prazosin), antianginal agents such as nitrates, for example, sodium nitrate, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, and nitrovasodilators; antiarrhythmic agents including Class I agents (such as propafenone); Class II agents (propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as diltiazem and verapamil); K⁺ channel modulators such as I_{K,ACh} inhibitors and inhibitors of the K_v subfamily of K⁺ channel openers such as I_{K,ATP} inhibitors (e.g., compounds disclosed in U.S. application Ser. No. 09/729,731, filed Dec. 5, 2000); and gap-junction modulators such as connexions; anticoagulant or antithrombotic agents including aspirin, warfarin, ximelagran, low molecular weight heparins (such as lovenox, enoxaparin, and dalteparin), anti-platelet agents such as GPIIb/IIIa blockers, (e.g., abciximab, eptifibatide, and tirofiban), thromboxane receptor antagonists (e.g., ifetroban), P2Y₁ and P2Y₁₂ antagonists (e.g., clopidogrel, ticlopidine, CS-747, and aspirin/clopidogrel combinations), and Factor Xa inhibitors (e.g., fondaparinux), and diuretics such as sodium-hydrogen exchange inhibitors, chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid, trierythralen, chlorthalidone, furosemide, musolimine, bumetanide, triamterene, and amiloride.

[0217] The inventive compounds may also be useful in combination with antiangiogenic agents, such as compounds that are inhibitors of VEGF receptors, or in conjunction with antitumor agents such as paclitaxel, adriamycin, epithilones, cisplatin, and carboplatin. Examples of anticancer and other cytotoxic agents that may be used in combination with the inventive compounds include the following: epothilone derivatives as found in German Patent No. 4138042.8; WO 97/19086, WO 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO 99/433653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253 and WO 00/00485; cyclin dependent kinase inhibitors as found in WO 99/24416; and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966.

[0218] The combination of the inventive compounds with other therapeutic agents may prove to have additive and synergistic effects. The combination may be advantageous to increase the efficacy of the administration or decrease the dosage to reduce possible side-effects.

[0219] The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts

indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds.

[0220] Compounds of formula (I), including the compounds described in the examples hereof, have been tested in assay(s) described below and have shown a measurable level of activity as inhibitors of LFA-1 and/or ICAM-1.

[0221] Assays

[0222] H1-HeLa Adhesion assay

[0223] H1-HeLa cells were released from their growth flask using versene (Gibco, Grand Island, N.Y.). Following centrifugation, the cells were resuspended in growth medium: DMEM (Gibco), 10% fetal calf serum (Hyclone, Logan, Utah), 1% Pen-Strep (Gibco), and 1% L-glutamine (Gibco) and plated for growth at 5,000 cells/well in a 96-well plate.

[0224] The next day, HSB-2 cells were divided to 2×10^5 /ml in growth medium: RPMI 1640 (Gibco), 10% FCS, 1% Pen-Strep, and 1% L-glutamine. The next day (day #3), the cells were centrifuged at $534 \times G$ for 8 minutes, washed, and resuspended in HBSS at 5×10^7 /ml. Calcein-AM, 10 μ M (Molecular Probes, Eugene, Oreg.) and 100 nM phorbol myristate acetate (SIGMA, St. Louis, Mo.) were added to the labeling and activation mix. Following incubation at 37° C. for 30 minutes, ten ml of HBSS was added and the cells centrifuged as above. The cell pellet was then resuspended and counted.

[0225] While the HSB-2 cells were labeling, the medium was aspirated from the H1-HeLa cells and the plates washed once with HBSS, followed by the addition of 50 μ l of HBSS. An additional 50 μ l of HBSS containing compound solution, DMSO, or anti-CD18 antibody was then added to each well. To the H1-HeLa cells were added 200,000 HSB-2 cells/well in 100 μ l, followed by incubation in the dark for 30 minutes. The wells were then washed three times to remove the unbound cells. A fluorescence plate reader was then used to determine the number of bound HSB-2 cells. The percent inhibition due to the compound was calculated using the vehicle control as 0% inhibition and the antibody blocked adhesion as 100% inhibition.

[0226] HUVEC Adhesion Assay

[0227] On day 1, human umbilical vein endothelial cells (HUVEC) (passage 3, Clonetics, San Diego, Calif.) were placed into a T-75 flask containing EGM bulletkit media (Clonetics) for growth.

[0228] When the HUVEC were 90% confluent (typically day 4), 96-well tissue culture plates were coated with 100 μ l/well of 2.5 μ g/ml mouse Type IV collagen (Trevigen) diluted in 0.1 M acetic acid. Following incubation for at least three hours, the collagen was removed and the plate washed three times with HBSS (Gibco). The HUVEC flask was trypsinized, and HUVEC were plated on the collagen coated wells at 1250 cells/200 μ l/well for use four days later. Twenty hours prior to use, the medium was removed and cells were stimulated with 200 μ l of 10 nM phorbol myristate acetate (PMA, Sigma, St. Louis, Mo.) in EGM. When the cells were 90% confluent (typically day 8), the PMA-containing medium was removed, the wells were

washed with HBSS, and 50 μ l of HBSS was added to the wells. An additional 50 μ l containing compound solution, DMSO or blocking anti-CD18 was then added to each well.

[0229] On day 7, HSB-2 cells were then divided to 2×10^5 /ml in RPMI 1640 (Gibco), 10% FCS (Hyclone, Logan, Utah), 1% Pen-Strep (Gibco), and 1% L-glutamine (Gibco). The following day, the cells were centrifuged at $534 \times G$ for 8 minutes, washed, and resuspended in HBSS at 5×10^7 /ml. For activation and labeling, calcein-AM, 10 μ M (Molecular Probes, Eugene, Oreg.) and 100 nM phorbol myristate acetate (Sigma, St. Louis, Mo.) were added and the cells incubated at 37° C. for 30 minutes. Following the addition of ten ml of HBSS, the cells were centrifuged, resuspended, and counted.

[0230] To the HUVEC cells were added 200,000 labeled and activated HSB-2 cells/well in 100 μ l, followed by incubation in the dark for 30 minutes. To remove unbound cells, the wells were washed three times with HBSS. A fluorescence plate reader was used to determine the number of HSB-2 cells bound. The percent inhibition due to the compound was calculated with the vehicle control set at 0% inhibition and the antibody-blocked adhesion set at 100% inhibition.

EXAMPLES

[0231] The following Examples illustrate embodiments of the inventive compounds and starting materials, and are not intended to limit the scope of the claims. For ease of reference, the following abbreviations are used herein:

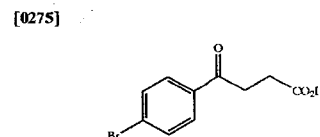
Abbreviations

- [0232] $AlCl_3$ =aluminum chloride
- [0233] Ac_2O =acetic anhydride
- [0234] $AcONa$ =sodium acetate
- [0235] bp=boiling point
- [0236] CH_3CN =acetonitrile
- [0237] DCC=dicyclohexylcarbodiimide
- [0238] DCE=dichloroethane
- [0239] DCM=dichloromethane
- [0240] DMAP=4-dimethylaminopyridine
- [0241] DIPEA or DIEA= N,N -diisopropylethylamine
- [0242] DME=1,2-dimethoxyethane
- [0243] DMF=dimethyl formamide
- [0244] $EDCl$ =1-3-dimethylaminopropyl-3-ethylcarbodiimide
- [0245] Et_2O =diethyl ether
- [0246] HOBT=1-hydroxybenzotriazole
- [0247] EtOAc=ethyl acetate
- [0248] EtOH=ethanol
- [0249] g=gram(s)
- [0250] HCl=hydrochloric acid
- [0251] KOH=potassium hydroxide

- [0252] K_2CO_3 =potassium carbonate
- [0253] l=liter
- [0254] $LiAlH_4$ =lithium aluminum hydride
- [0255] MeCN=acetonitrile
- [0256] MeOH=methanol
- [0257] $MgSO_4$ =magnesium sulfate
- [0258] NaH=sodium hydride
- [0259] Na_2SO_4 =sodium sulfate
- [0260] NaOH=sodium hydroxide
- [0261] NMP=N-methyl-2-pyrrolidinone
- [0262] PBr_3 =phosphorus tribromide
- [0263] $(Ph_3P)_4Pd$ =tetrakis(triphenylphosphine)palladium(0)
- [0264] PS=polystyrene
- [0265] $SOCl_2$ =thionyl chloride
- [0266] TEA=triethylamine
- [0267] mg=milligram(s)
- [0268] ml=milliliter
- [0269] μ l=microliter
- [0270] mmol=millimole
- [0271] μ mol=micromole
- [0272] mol=mole
- [0273] mp=melting point
- [0274] RT=room temperature

Preparation 1

4-(4-Bromophenyl)-4-oxobutanoic acid

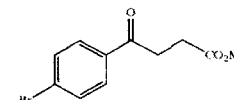


[0276] $AlCl_3$ (128.8 g, 0.97 mol) was added by portions within 20 min to a suspension of succinic anhydride (44.3 g, 0.44 mol) and bromobenzene (100 ml, 0.99 mol) in DCM (500 ml) while the reaction flask was cooled in a water bath. After 1 h 30 min at RT, the reaction mixture was refluxed for 2 h. After cooling, the reaction medium was slowly poured into a mixture of ice (1.5 l) and concentrated HCl (100 ml). The precipitate was washed twice with water, with isopropanol, and finally with pentane. After drying 4-(4-bromophenyl)-4-oxobutanoic acid was obtained as an off-white solid (86.4 g, mp=148° C.). ^1H NMR ($CDCl_3$): 7.85 (2H, d, J=8.5 Hz), 7.62 (2H, d, J=8.5 Hz), 3.28 (2H, t, J=6.5 Hz), 2.82 (2H, t, J=6.5 Hz).

Preparation 2

4-(4-Bromophenyl)-4-oxobutanoic acid methyl ester

[0277]

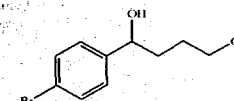


[0278] 4-(4-Bromophenyl)-4-oxobutanoic acid (86.4 g, 0.336 mol) (Preparation 1) in MeOH (1.7 l) containing H_2SO_4 (86 ml) was refluxed for 21 h. After cooling, the light precipitate was filtered off and the reaction mixture concentrated to dryness. The obtained solid was placed in water and extracted twice with EtOAc. The organic layer was washed with diluted NaOH and twice with brine, dried over Na_2SO_4 , and concentrated to yield the desired 4-(4-bromophenyl)-4-oxobutanoic acid methyl ester as a low melting point solid (87.5 g, mp=50° C.). ^1H NMR ($CDCl_3$): 7.85 (2H, d, J=8.5 Hz), 7.60 (2H, d, J=8.5 Hz), 3.71 (3H, s), 3.28 (2H, t, J=6.5 Hz), 2.76 (2H, t, J=6.5 Hz).

Preparation 3

1-(4-Bromophenyl)-butane-1,4-diol

[0279]

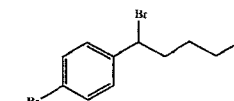


[0280] A solution of 4-(4-bromophenyl)-4-oxobutanoic acid methyl ester (19 g, 70 mmol) (Preparation 2) in anhydrous diethyl ether (100 ml) was added dropwise to a suspension of $LiAlH_4$ (5.3 g, 140 mmol) in ether (100 ml), while the temperature was kept below 5° C. with an ice bath. After 2 h at RT, the reaction mixture was refluxed for 4 h. It was then cooled to 5° C. and hydrolyzed with a saturated Na_2SO_4 solution with the temperature kept below 15° C. The suspension was filtered over celite and concentrated to yield a yellow oil (16.1 g) which was chromatographed over silica gel (eluent: DCM/MeOH 90/10) to yield 1-(4-bromophenyl)-butane-1,4-diol as an oil (15 g). ^1H NMR ($CDCl_3$): 7.40 (2H, d, J=8.4 Hz), 7.12 (2H, d, J=8.4 Hz), 4.65 (1H, br s), 4.50-4.60 (1H, m), 3.97 (1H, br s), 3.4-3.65 (2H, m), 1.6-1.85 (2H, m), 1.45-1.6 (2H, m).

Preparation 4

1-Bromo-4-(1,4-dibromobutyl)benzene

[0281]



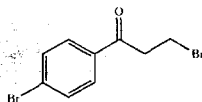
Jan. 15, 2004

[0282] PBr_3 (4 ml, 40 mmol) was added dropwise in 10 min to a solution of 1-(4-bromophenyl)butane-1,4-diol (15 g, 61 mmol) (Preparation 3) in diethyl ether (300 ml) maintained at -10°C . After 20 h at RT, the reaction mixture was cooled with an ice bath and water (100 ml) was added rapidly. The aqueous layer was extracted twice with ether. The combined organic layers were washed with a diluted aqueous Na_2CO_3 solution then three times with water until neutrality, dried over magnesium sulfate and concentrated to yield 1-bromo-4-(1,4-dibromobutyl)benzene (13 g) as a yellow oil. ^1H NMR (CDCl_3): 7.47 (2H, d, $J=8.5$ Hz), 7.26 (2H, d, $J=8.5$ Hz), 4.8-5.0 (1H, m), 3.42 (2H, t, $J=6.4$ Hz), 2.2-2.45 (2H, m), 1.8-2.2 (2H, m).

Preparation 5

3-Bromo-1-(4-bromophenyl)propan-1-one

[0283]

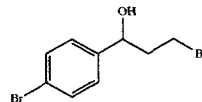


[0284] AlCl_3 (23.8 g, 178 mmol) was added by portions to bromobenzene (155 ml, 1.47 mol) at 0°C . 3-Bromopropionyl chloride (25 g, 146 mmol) was added dropwise to the red solution kept at 0°C over 30 min. After 1 h at RT, the reaction mixture was heated to 50°C for 1 h. After cooling, the mixture was poured over ice/water and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated to yield 3-bromo-1-(4-bromophenyl)propan-1-one (36 g) which was crystallized from petroleum ether ($\text{mp}=66^\circ\text{C}$). ^1H NMR (CDCl_3): 7.82 (2H, d, $J=8.5$ Hz), 7.62 (2H, d, $J=8.5$ Hz), 3.73 (2H, t, $J=6.5$ Hz), 3.55 (2H, t, $J=6.5$ Hz).

Preparation 6

3-Bromo-1-(4-bromophenyl)propan-1-ol

[0285]

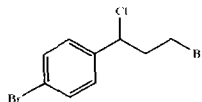


[0286] NaBH_4 (1.5 g, 39.7 mmol) was added by portions to a solution of 3-bromo-1-(4-bromophenyl)propan-1-one (11.7 g, 40 mmol) (Preparation 5) in MeOH while keeping the temperature below 10°C . After 1 h at RT, 1N aqueous hydrochloric acid was added at 5°C to pH=1 and the mixture was concentrated in vacuum. The residue was dissolved in water and extracted three times with DCM. The organic layer was dried over Na_2SO_4 and concentrated to yield 3-bromo-1-(4-bromophenyl)propan-1-ol as a yellow oil (11.1 g). ^1H NMR (CDCl_3): 7.47 (2H, d, $J=8.3$ Hz), 7.22 (2H, d, $J=8.3$ Hz), 4.87 (1H, br s), 3.50-3.62 (1H, m), 3.31-3.42 (1H, m), 2.35 (1H, OH, br s), 2-2.31 (2H, m).

Preparation 7

1-Bromo-4-(3-bromo-1-chloropropyl)benzene

[0287]

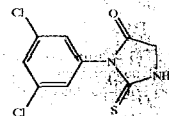


[0288] SOCl_2 (2.8 ml, 38.6 mmol) was added dropwise to a cooled (-20°C) solution of 3-bromo-1-(4-bromophenyl)propan-1-ol (11.1 g, 37.8 mmol) (Preparation 6) in a mixture of DCM (110 ml) and pyridine (3 ml, 37.6 mmol). After 2 h at -20°C , the reaction mixture was poured over a mixture of ice and 10% HCl. The organic layer was washed with water, dried over Na_2SO_4 and concentrated to yield a yellow oil (12.8 g). Distillation under reduced pressure gave 1-bromo-4-(3-bromo-1-chloropropyl)benzene as a colorless oil (5.1 g, bp=128-130 $^\circ\text{C}$ /0.5 mm Hg). ^1H NMR (CDCl_3): 7.4-7.55 (2H, m), 7.15-7.3 (2H, m), 5.07 (1H, m), 3.45-3.6 (1H, m), 3.3-3.45 (1H, m), 2.35-2.65 (2H, m).

Preparation 8

3-(3,5-Dichlorophenyl)-2-thioxoimidazolidin-4-one

[0289]

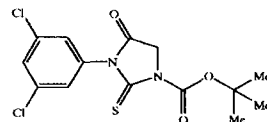


[0290] 3,5-Dichlorophenylisothiocyanate (5 g, 24.5 mmol) was added by portion to a suspension of the HCl salt of ethyl glycinate (3.4 g, 24.5 mmol) in a mixture of TEA (7.5 ml, 53.9 mmol) and dry DCM (40 ml) while cooling the flask in a water bath. After 60 h at RT, the solution was concentrated to dryness and partitioned between EtOAc and aqueous HCl. The organic layer was washed with water and concentrated. The obtained amorphous solid was washed with Et_2O to yield 3-(3,5-dichlorophenyl)-2-thioxoimidazolidin-4-one as an orange solid (5.3 g). ^1H NMR (CDCl_3): 7.45 (1H, m), 7.25 (2H, m), 4.44 (2H, s).

Preparation 9

3-(3,5-Dichlorophenyl)-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester

[0291]



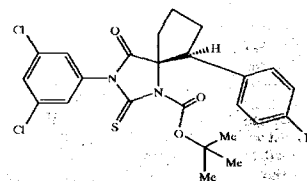
Jan. 15, 2004

[0292] A solution of di-tert-butylidicarbonate (1.04 g, 4.6 mmol) in MeCN (1 ml) was added to a suspension of 3-(3,5-dichlorophenyl)-2-thioxoimidazolidin-4-one (1.04 g, 4 mmol) (Preparation 8) and DMAP (73 mg, 0.6 mmol) in MeCN (5 ml). After 2 h at RT, the mixture was evaporated, taken into EtOAc, washed twice with aqueous KHSO_4 and once with water, and finally concentrated to yield 3-(3,5-dichlorophenyl)-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester (1.04 g) as a brown solid. ^1H NMR (CDCl_3): 7.46 (1H, m), 7.18 (2H, m), 4.54 (2H, s), 1.57 (9H, s).

Preparation 10

(SR*,6S*)-6-(4-Bromophenyl)-3-(3,5-dichlorophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]nonane-1-carboxylic acid tert-butyl ester

[0293]

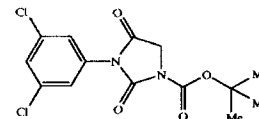


[0294] Using the same procedure as in Example 1 starting from 1-bromo-4-(1,4-dibromobutyl)benzene (423 mg, 1.1 mmol) (Preparation 4) and 3-(3,5-dichlorophenyl)-4-oxo-2-thioxoimidazolidine-1-carboxylic acid tert-butyl ester (361 mg, 1 mmol) (Preparation 9), (SR*,6S*)-6-(4-bromophenyl)-3-(3,5-dichlorophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]nonane-1-carboxylic acid tert-butyl ester was obtained (54 mg) as a white solid. ^1H NMR (CDCl_3): 7.49 (2H, d, $J=8.4$ Hz), 7.33 (1H, m), 7.09 (2H, d, $J=8.4$ Hz), 6.22 (2H, m), 4.17 (1H, dd, $J_1=13.2$ Hz, $J_2=5.4$ Hz), 2.35-2.6 (3H, m), 2-2.35 (3H, m), 1.69 (9H, s).

Preparation 11

3-(3,5-Dichlorophenyl)-2,4-dioxoimidazolidine-1-carboxylic acid tert-butyl ester

[0295]



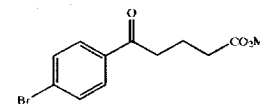
[0296] A solution of di-tert-butylidicarbonate (7.72 g, 35.4 mmol) in THF (100 ml) was added to a suspension of 3-(3,5-dichlorophenyl)-imidazolidin-2,4-dione (7.5 g, 30.6 mmol, prepared according to Fujinami et al. cited above)

and DMAP (560 mg, 4.6 mmol) in THF (150 ml). After 3 h at RT, the mixture was evaporated, taken into DCM, washed twice with 1N aqueous HCl and once with brine, and finally concentrated to yield 3-(3,5-dichlorophenyl)-2,4-dioxoimidazolidine-1-carboxylic acid tert-butyl ester (10.17 g) as a white solid. ^1H NMR (CDCl_3): 7.40 (1H, m), 7.37 (2H, m), 4.40 (2H, s), 1.58 (9H, s).

Preparation 12

5-(4-Bromophenyl)-5-oxopentanoic acid methyl ester

[0297]

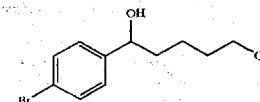


[0298] Using the procedure described in Preparations 1 and 2, the above above-titled compound was obtained from glutaric anhydride and bromobenzene. ^1H NMR (CDCl_3): 7.83 (2H, d, $J=8.5$ Hz), 7.60 (2H, d, $J=8.5$ Hz), 3.68 (3H, s), 3.03 (2H, t, $J=7.1$ Hz), 2.45 (2H, t, $J=7.1$ Hz), 2.06 (2H, m).

Preparation 13

1-(4-Bromophenyl)pentane-1,5-diol

[0299]

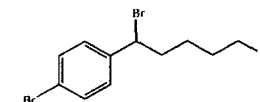


[0300] Using the procedure described in Preparation 3, 5-(4-bromophenyl)-5-oxopentanoic acid methyl ester (12.8 g, 45 mmol) (Preparation 12) was reduced with LiAlH_4 (3.4 g, 90 mmol) to yield 1-(4-bromophenyl)pentane-1,5-diol (9.4 g) as a yellow oil. ^1H NMR (CDCl_3): 7.42 (2H, d, $J=8.3$ Hz), 7.15 (2H, d, $J=8.3$ Hz), 4.56 (1H, m), 3.63 (1H, br s), 3.45-3.6 (2H, m), 2.96 (1H, m), 1.25-1.9 (6H, m).

Preparation 14

1-Bromo-4-(1,5-dibromopentyl)benzene

[0301]

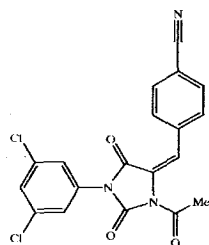


[0302] Using the procedure described in Preparation 4, 1-(4-bromophenyl)-pentane-1,5-diol (9.4 g, 36.3 mmol) (Preparation 13) was treated with PBr_3 (3.4 ml, 36.2 mmol) to yield 1-bromo-4-(1,5-dibromopentyl)benzene (6.1 g) as a yellow oil. ^1H NMR (CDCl_3): 7.47 (2H, d, $J=8.5$ Hz), 7.26 (2H, d, $J=8.5$ Hz), 4.88 (1H, t, $J=7.5$ Hz), 3.38 (2H, t, $J=6.6$ Hz), 2-2.3 (2H, m), 1.8-2.0 (2H, m), 1.55-1.8 (1H, m), 1.4-1.55 (1H, m).

Preparation 15

(E)-4-[3-Acetyl-1-(3,5-dichlorophenyl)-2,5-dioximidazolidin-4-ylidenemethyl]-benzonitrile

[0303]

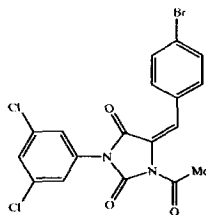


[0304] A mixture of 3-(3,5-dichlorophenyl)-2,4-dioximidazolidine-1-carboxylic acid tert-butyl ester (3.45 g, 10 mmol) (Preparation 11), 4-cyanobenzaldehyde (1.31 g, 10 mmol) and NaOAc (0.82 g, 10 mmol) was refluxed for 3 h in Ac_2O (50 ml). The solid obtained after concentration was taken into a mixture of ice/water and DCM. The organic layer was dried and concentrated to yield a solid (4.4 g) which was chromatographed over silica gel (eluent: DCM) to yield 4-[3-acetyl-1-(3,5-dichlorophenyl)-2,5-dioximidazolidin-4-ylidenemethyl]-benzonitrile as a white solid (1.25 g). mp=212° C. ^1H NMR (CDCl_3): 8.52 (1H, s), 7.6-7.75 (4H, m), 7.43 (1H, m), 7.37 (2H, m), 2.78 (3H, s).

Preparation 16

(E)-1-Acetyl-5-(4-bromobenzylidene)-3-(3,5-dichlorophenyl)-imidazolidine-2,4-dione

[0305]

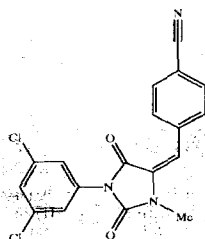


[0306] Using the same procedure as in Preparation 15, but starting with Preparation 11 (34.5 g, 0.1 mol) and 4-bromobenzaldehyde (18.5 g, 0.1 mol), the above-titled compound was obtained as a white solid (16.8 g). mp=222° C. ^1H NMR ($\text{DMSO}-d_6$): 8.23 (1H, s), 7.79 (1H, m), 7.55-7.75 (6H, m), 2.65 (3H, s).

Preparation 17

(E)-4-[(3,5-dichlorophenyl)-3-methyl-2,5-dioximidazolidin-4-ylidenemethyl]-benzonitrile

[0307]



[0308] Preparation 17 was obtained via three alternative methods:

[0309] (1). A solution of 3-(3,5-dichlorophenyl)-1-methyl-imidazole-2,4-dione (70 g, 0.27 mol), 4-cyanobenzaldehyde (53 g, 0.404 mol), and β -alanine (16.1 g, 0.181 mol) in acetic acid (1 l) was heated for 32 h at reflux. The solution was cooled and kept at 50° C. for one hour. It was then allowed to cool to 35° C., and the insoluble material was recovered by filtration to yield 35.5 g (0.095 mol) of the above-titled compound.

[0310] Yield 35%. mp=236° C.;

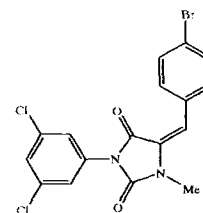
[0311] (2). A mixture of 3-(3,5-dichlorophenyl)-1-methyl-imidazole-2,4-dione (1.3 g, 5 mmol), 4-cyanobenzaldehyde (0.98 g, 7.5 mmol, 1.5 eq), pyridine (0.3 ml), anhydrous MgSO_4 (0.9 g, 1.5 eq), and EtOH (35 ml) was heated at 78° C. for eighteen hours. The reaction mixture was filtered while hot, and the solid obtained was washed with hot EtOH (2x20 mL), water (2x20 mL), EtOH (2x20 mL) and dried. Yield: 1.58 g;

[0312] (3) A mixture of 3-(3,5-dichlorophenyl)-1-methyl-imidazole-2,4-dione (1.3 g, 5 mmol), 4-cyanobenzaldehyde (0.98 g, 7.5 mmol, 1.5 eq), pyridine (0.3 ml) and EtOH (35 ml) was heated at 78° C. for eighteen hours. The reaction mixture was filtered while hot and the solid obtained was washed with hot EtOH (2x20 mL), water (2x20 mL), EtOH (2x20 mL), and dried. Yield: 2.78 g.

Preparation 18

(E)-5-(4-Bromobenzylidene)-3-(3,5-dichlorophenyl)-1-methyl-imidazolidine-2,4-dione

[0313]

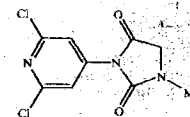


[0314] The same procedures as for Preparation 17 were followed, using 4-bromobenzaldehyde in place of 4-cyanobenzaldehyde. ^1H NMR ($\text{DMSO}-d_6$): 7.90 (2H, d), 7.72 (1H, m), 7.58 (4H, m), 6.65 (1H, s), 3.24 (3H, s).

Preparation 19

3-(2,6-Dichloropyridin-4-yl)-1-methyl-imidazolidine-2,4-dione

[0315]

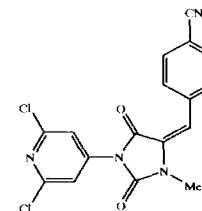


[0316] TEA (7.2 ml, 51 mmol) was added to a suspension of the HCl salt of sarcosine ethyl ester (3.4 g, 24.5 mmol) in dry DCM (80 ml). The formed triethylamine hydrochloride was filtered off and rinsed with DCM (20 ml). The filtrate was transferred into a 3-necked round bottom flask and cooled to 5° C. A solution of 2,6-dichloropyridin-4-yl isocyanate (10 g, 53 mmol) in DCM (25 ml) was added dropwise over 10 min while keeping the inner temperature below 10° C. After 96 h at RT, the reaction mixture was refluxed for 10 h. After cooling to RT, the solution was washed with brine, dried over MgSO_4 and concentrated. The obtained amorphous solid was chromatographed over silica gel (eluent: cyclohexane/EtOAc 80/20 to 50/50) to yield the above titled compound as a white solid (9.9 g). mp=134° C. ^1H NMR (CDCl_3): 7.75 (2H, s), 4.07 (2H, s), 3.10 (3H, s).

Preparation 20

(E)-4-[1-(2,6-Dichloropyridin-4-yl)-3-methyl-2,5-dioximidazolidin-4-ylidenemethyl]-benzonitrile

[0317]

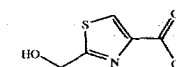


[0318] Using the third method described in Preparation 17, Preparation 19 (5 g, 19.2 mmol) was reacted with 4-cyanobenzaldehyde (3.78 g, 28.8 mmol) to yield the above-titled compound as a white solid (5.6 g). mp=230° C. ^1H NMR (CDCl_3): 7.91 (2H, d, $J=8.1$ Hz), 7.65-7.75 (4H, m), 6.40 (1H, s), 3.37 (3H, s).

Preparation 21

2-Hydroxymethyl-thiazole-5-carboxylic acid

[0319]

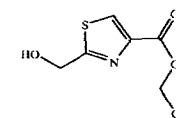


[0320] The above-titled compound was synthesized according to the procedure described in DE 2548505 to Roussel-Uclaf (1975) and Chem. Abstr., Vol. 85, #46650. ^1H NMR ($\text{DMSO}-d_6$): 8.27 (1H, s), 4.77 (2H, s).

Preparation 22

Ethyl 2-hydroxymethyl-thiazole-5-carboxylate

[0321]



[0322] A solution of crude Preparation 21 (300 mg, 1.9 mmol) and concentrated sulfuric acid (2 ml) in EtOH (30 ml) was refluxed during 5 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between aqueous Na_2CO_3 and EtOAc. The organic layer