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SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: P1.-F.HOFFMANN-LA ROCHE AG.-Expediente número
00-092.691.-

1. Me refiero al memorial de sustitución de poder presentado a ese Despacho el 31 de Agosto de 2004.

2. Por medio del presente, atentamente me permito manifestar a ese Despacho, que hubo un **cambio** de Representante Legal para todos los asuntos de la Propiedad Industrial en Bogotá de **F.HOFFMANN-LA ROCHE AG**, una sociedad organizada y existente de conformidad con las leyes de Suiza, domiciliada en Basilea, Suiza.

3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería, en este asunto, de conformidad con el documento de Representación Legal para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **F.HOFFMANN-LA ROCHE AG**, otorgado a favor del **SUSCRITO (GUSTAVO TAMAYO)** y/o a la doctora ALICIA LLOREDA y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ de acuerdo con la copia debidamente autenticada ante Notario Público que adjunto al presente expediente (Artículos 26 y 39 de la Decisión 486 de la Comunidad Andina de Naciones).

4. Anexo al presente acompaño fotocopia, de:

- (a) Documento que acredita al SUSCRITO y/o a la doctora ALICIA LLOREDA y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ en los términos del párrafo 1º. del Artículo 543 del Decreto-Ley 410 de 1971, como Representantes Legales en Bogotá para todos los asuntos relacionados con la propiedad industrial de la sociedad **F.HOFFMANN-LA ROCHE AG**, una sociedad organizada y existente de conformidad con las leyes de Suiza, domiciliada en Basilea, Suiza.

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abajo firmados, F.HOFFMANN-LA ROCHE AG, una sociedad organizada y existente de conformidad con las leyes de Suiza.

con domicilio en 4070 Basilea, Suiza

nombramos por el presente a ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No. 5-83, piso 6o., nuestros representantes legales y verdaderos en Bogotá, con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo 1o. del artículo 543 del decreto 410 de 1971.

Los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para representarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado; elevar solicitudes, declaraciones, reclamos, recursos y presentar desistimientos; formular descripciones, enmiendas, limitar el alcance de las solicitudes, presentar oposiciones y apelaciones; instaurar cancelaciones, renunciar total o parcialmente a los registros, abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeran conducentes al resguardo de nuestros intereses; y en caso de producirse oposición, pasando los antecedentes a los tribunales, quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a árbitros, desistir, percibir y apelar, con todas las demás facultades que resulten necesarias, y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio.

Asimismo, facultamos a los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro.

Dado y firmado

The undersigned, F.HOFFMANN-LA ROCHE AG, a corporation organized and existing under the laws of Switzerland.

domiciled at 4070 Basel, Switzerland

hereby appoint, ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ, of Bogota, Colombia, with offices in said town, Calle 72 No. 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1o. of article 543 of decree 410 of 1971.

Doctors ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ, or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps for the said end; to file petitions, declarations, claims, recourses and withdrawals, to draw up specifications; to file amendments, to limit the scope of applications, file oppositions; file cancellations total or partially waive registrations, to pay all installments and effect all other payments prescribed by law; to receive proper receipts, to comply with all other requirements and, in short, to take all those measures which they may deem fit for the protection of our interests; and in case of opposition, where the proceedings be passed over to the courts, we authorize said agents to act on our behalf, as complainants as well as defendants, before the competent judges, with full powers to make arrangements, to submit to arbitrators, to desist, to collect, to appeal and, in short, with all such further powers as may be required, and we hereby declare from now on as valid and good all that said representatives and/or the agents by any one of them appointed may do for our benefit.

We also authorize doctors ALICIA LLOREDA and/or GUSTAVO TAMAYO and/or IGNACIO SANTAMARIA and/or ENRIQUE ALVAREZ, to apply for protocolization of this document and of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property.

Given and signed this 17th day of August 2004.
F. Hoffmann-La Roche AG

Fridolin Klausner
Holder of procuration

Denise Strebel
Mandatory

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ACTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Suiza
Basilea

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Hoy de de 200 , compareció , a quien conozco y de quien me consta que firmó el anterior documento, y quien debidamente juramentado declaró y dijo que él es de F.HOFFMANN-LA ROCHE AG, la compañía nombrada en el documento que antecede, una sociedad debidamente organizada y existente conforme a las leyes de Suiza, domiciliada en la ciudad de Basilea, Suiza, legalmente constituida para un período de duración que aún no ha terminado, que ejerce su objeto social; conforme a las leyes de Suiza; que el declarante está autorizado por dicha Compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y en representación de la expresada Compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.
El suscrito Notario ha visto los Estatutos de incorporación firmados en Suiza, ciudad de Basilea, con fecha , y certifica que de conformidad con la legislación de dicho País, la anterior declaración juramentada es prueba suficiente de que los hechos sobre que ella versa son ciertos o verdaderos, de lo cual da fe.

Notary Public (Notario Público).

Switzerland
Basel

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On this 17th day of August , 2004 , personally Fridolin Klausner and Denise Strebel came both Swiss citizens and Swiss residents, to me known, and known to me to be the person who signed the foregoing instrument, who being by me duly sworn did depose and say that he is the Holder of Procuration/Mandatory of F.HOFFMANN-LA ROCHE AG, the company named within, a Corporation organized and existing under the laws of the Switzerland, domiciled at the City of Basel, legally constituted for a period of tenure not yet expired, which exercises its corporate purposes according to the laws of Switzerland; that the deponent is authorized by said Company to confer this power of attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purposes of the Company.
The undersigned Notary Public has seen the articles of Incorporation of said Corporation executed at Suiza, ciudad de Basel, under date of 19th day of June 1997 , and hereby certifies that under the laws of said Country the foregoing acknowledgment is sufficient proof that the facts therein contained are true, which he attests.

Basel, this 17-08-2004 (seventeenth day of two thousand and four)

Dr. P. Kuster
Notar

17.08.2004

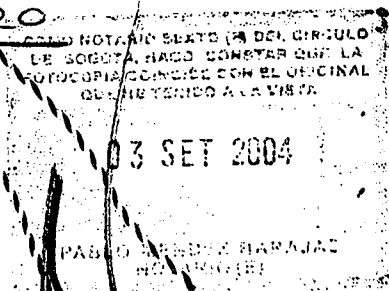
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Dr. PETER KUSTER

Allg. Prot. - 4

Nº 20

Dr. Peter Kuster
Advokat und Notar
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/42, 31/415, 31/425, 31/505, C07C 255/03, C07D 207/08, 217/18, 231/04, 263/04, 277/04, 285/12, 295/023, 413/10, 417/10		A1	(11) International Publication Number: WO 98/53817 (43) International Publication Date: 3 December 1998 (03.12.98)
(21) International Application Number: PCT/US98/10951 (22) International Filing Date: 29 May 1998 (29.05.98) (30) Priority Data: 60/047,856 29 May 1997 (29.05.97) US 9714316.8 7 July 1997 (07.07.97) GB 60/066,831 25 November 1997 (25.11.97) US 9800680.2 14 January 1998 (14.01.98) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DURETTE, Philippe, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HAGMANN, William, K. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MacCOSS, Malcolm [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MILLS, Sander, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MUMFORD, Richard, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: BIARYLALKANOIC ACIDS AS CELL ADHESION INHIBITORS			
(57) Abstract Compounds of formula (I) are antagonists of VLA-4 and/or $\alpha_4\beta_7$, and as such are useful in the inhibition or prevention of cell adhesion and cell-adhesion mediated pathologies. These compounds may be formulated into pharmaceutical compositions and are suitable for use in the treatment of asthma, allergies, inflammation, multiple sclerosis, and other inflammatory and autoimmune disorders.			

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293**TITLE OF THE INVENTION****BIARYLALKANOIC ACIDS AS CELL ADHESION INHIBITORS****SUMMARY OF THE INVENTION**

5 The compounds of the present invention are antagonists of the VLA-4 integrin ("very late antigen-4"; CD49d/CD29; or $\alpha_4\beta_1$) and/or the $\alpha_4\beta_7$ integrin (LPAM-1 and $\alpha_4\beta_p$), thereby blocking the binding of VLA-4 to its various ligands, such as VCAM-1 and regions of fibronectin and/or $\alpha_4\beta_7$ to its various ligands, such as MadCAM-1, VCAM-1 and
10 fibronectin. Thus, these antagonists are useful in inhibiting cell adhesion processes including cell activation, migration, proliferation and differentiation. These antagonists are useful in the treatment, prevention and suppression of diseases mediated by VLA-4 and/or $\alpha_4\beta_7$ binding and cell adhesion and activation, such as multiple sclerosis,
15 asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type I diabetes, organ transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory bowel disease including ulcerative colitis and Crohn's disease, certain
20 types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, and atherosclerosis.

BACKGROUND OF THE INVENTION

25 The present invention relates to biaryalkanoic acid derivatives which are useful for the inhibition and prevention of leukocyte adhesion and leukocyte adhesion-mediated pathologies. This invention also relates to compositions containing such compounds and methods of treatment using such compounds.

30 Many physiological processes require that cells come into close contact with other cells and/or extracellular matrix. Such adhesion events may be required for cell activation, migration, proliferation and differentiation. Cell-cell and cell-matrix interactions are mediated through several families of cell adhesion molecules

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(CAMs) including the selectins, integrins, cadherins and immunoglobulins. CAMs play an essential role in both normal and pathophysiological processes. Therefore, the targetting of specific and relevant CAMs in certain disease conditions without interfering with normal cellular functions is essential for an effective and safe therapeutic agent that inhibits cell-cell and cell-matrix interactions.

The integrin superfamily is made up of structurally and functionally related glycoproteins consisting of α and β heterodimeric, transmembrane receptor molecules found in various combinations on nearly every mammalian cell type. (for reviews see: E. C. Butcher, Cell, 67, 1033 (1991); T. A. Springer, Cell, 76, 301 (1994); D. Cox et al., "The Pharmacology of the Integrins." Medicinal Research Rev. 14, 195 (1994) and V. W. Engleman et al., "Cell Adhesion Integrins as Pharmaceutical Targets." in Ann. Repts. in Medicinal Chemistry, Vol. 31, J. A. Bristol, Ed.; Acad. Press, NY, 1996, p. 191).

VLA-4 ("very late antigen-4"; CD49d/CD29; or $\alpha_4\beta_1$) is an integrin expressed on all leukocytes, except platelets and mature neutrophils, including dendritic cells and macrophage-like cells and is a key mediator of the cell-cell and cell-matrix interactions of these cell types (see M. E. Hemler, "VLA Proteins in the Integrin Family: Structures, Functions, and Their Role on Leukocytes." Ann. Rev. Immunol. 8, 365 (1990)). The ligands for VLA-4 include vascular cell adhesion molecule-1 (VCAM-1) and the CS-1 domain of fibronectin (FN). VCAM-1 is a member of the Ig superfamily and is expressed *in vivo* on endothelial cells at sites of inflammation. (See R. Lobb et al. "Vascular Cell Adhesion Molecule 1." in Cellular and Molecular Mechanisms of Inflammation, C. G. Cochrane and M. A. Gimbrone, Eds.; Acad. Press, San Diego, 1993, p. 151.) VCAM-1 is produced by vascular endothelial cells in response to pro-inflammatory cytokines (See A. J. H. Gearing and W. Newman, "Circulating adhesion molecules in disease.", Immunol. Today, 14, 506 (1993)). The CS-1 domain is a 25 amino acid sequence that arises by alternative splicing within a region of fibronectin. (For a review, see R. O. Hynes "Fibronectins.", Springer-

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may be prepared from the compound of the present invention is basic, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, glutamic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantoic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used in the formula I are meant to include the salts.

It will be understood that, as used herein, references to the compounds of formula I are meant to also include the pharmaceutically acceptable salts.

Utility

The utility of the compounds of formula I and/or 0487 is demonstrated by the following examples.

Utilities

The ability of the compounds of Formula I to antagonize the action of VLA-4 and/or $\alpha 4\beta 7$ integrin makes them useful for preventing or relieving the symptoms, disorders or diseases induced by the binding of VLA-4 and/or $\alpha 4\beta 7$ to their various respective ligands. Thus, these compounds will inhibit cell adhesion processes including cell activation, cell proliferation and differentiation. Accordingly, another aspect of the present invention provides a method for the treatment of disorders or symptoms mediated by VLA-4 and/or $\alpha 4\beta 7$ binding to a mammal an effective amount of a compound of Formula I. Diseases, disorders, conditions or symptoms are for example multiple sclerosis, (2) asthma, (3) allergic rhinitis, (4) arthritis, (5) inflammatory lung diseases, (6) rheumatoid arthritis.

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30 about 0.1 mg (preferably from about 10 mg to about 100 mg) per kg of body weight per day.

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about 100 mg of a
day, preferably from
protective use from 0.1 mg
about 100 mg and more
of a compound of Formula

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/395, 31/40, 31/41, 31/415, 31/425, 31/435, 31/44, 31/445, 31/47, 31/495, 31/535, C07D 205/02, 209/04, 209/14, 209/30, 217/12, 235/02, 233/64, 241/02, 257/04, 265/30, 275/02, 277/02, 277/08, 295/08, 295/26, 401/02, 401/12, 401/14, 413/02, 413/12, 413/14, 417/02, 417/12, 417/14, 487/04, 513/04, C07F 9/02		A1	(11) International Publication Number: WO 98/53814 (43) International Publication Date: 3 December 1998 (03.12.98)
(21) International Application Number: PCT/US98/10940 (22) International Filing Date: 29 May 1998 (29.05.98) (30) Priority Data: 60/048,017 29 May 1997 (29.05.97) US 9714314.3 7 July 1997 (07.07.97) GB 60/066,525 25 November 1997 (25.11.97) US 9800686.9 14 January 1998 (14.01.98) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DURETTE, Philippe, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). HAGMANN, William, K. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MacCOSS, Malcolm		(GB/US); 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MILLS, Sander, G. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MUMFORD, Richard, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VAN RIPER, Gail, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SCHMIDT, Jack, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). KEVIN, Nancy, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: HETEROCYCLIC AMIDE COMPOUNDS AS CELL ADHESION INHIBITORS			
(57) Abstract Compounds of formula (I) are antagonists of VLA-4 and/or $\alpha_4\beta_7$, and as such are useful in the inhibition or prevention of cell adhesion and cell-adhesion mediated pathologies. These compounds may be formulated into pharmaceutical compositions and are suitable for use in the treatment of asthma, allergies, inflammation, multiple sclerosis, and other inflammatory and autoimmune disorders.			

TITLE OF THE INVENTION**HETEROCYCLIC AMIDE COMPOUNDS AS CELL ADHESION INHIBITORS****SUMMARY OF THE INVENTION**

5 The compounds of the present invention are antagonists of the VLA-4 integrin ("very late antigen-4"; CD49d/CD29; or $\alpha 4\beta 1$) and/or the $\alpha 4\beta 7$ integrin (LPAM-1 and $\alpha 4\beta p$), thereby blocking the binding of VLA-4 to its various ligands, such as VCAM-1 and regions of fibronectin and/or $\alpha 4\beta 7$ to its various ligands, such as MadCAM-1, VCAM-1 and
10 fibronectin. Thus, these antagonists are useful in inhibiting cell adhesion processes including cell activation, migration, proliferation and differentiation. These antagonists are useful in the treatment, prevention and suppression of diseases mediated by VLA-4 and/or $\alpha 4\beta 7$ binding and cell adhesion and activation, such as multiple sclerosis,
15 asthma, allergic rhinitis, allergic conjunctivitis, inflammatory lung diseases, rheumatoid arthritis, septic arthritis, type I diabetes, organ transplantation, restenosis, autologous bone marrow transplantation, inflammatory sequelae of viral infections, myocarditis, inflammatory bowel disease including ulcerative colitis and Crohn's disease, certain
20 types of toxic and immune-based nephritis, contact dermal hypersensitivity, psoriasis, tumor metastasis, and atherosclerosis.

BACKGROUND OF THE INVENTION

25 The present invention relates to heterocyclic amide derivatives which are useful for the inhibition and prevention of leukocyte adhesion and leukocyte adhesion-mediated pathologies. This invention also relates to compositions containing such compounds and methods of treatment using such compounds.

30 Many physiological processes require that cells come into close contact with other cells and/or extracellular matrix. Such adhesion events may be required for cell activation, migration, proliferation and differentiation. Cell-cell and cell-matrix interactions are mediated through several families of cell adhesion molecules

that when B and Z are each C, R², R³, R⁶, and R⁷ are each H, then R¹ is other than phenyl, 4-methylphenyl and 5-(NR^dRe)naphthyl.

In one subset of Formula Ia are compounds wherein Z is C.

In another subset of Formula Ia are compounds wherein B
5 is C, C=C, C-C or S. Preferably B is C or C=C.

In another subset of Formula Ia are compounds wherein X is C(O)OR^d.

In another subset of Formula Ia are compounds wherein R¹ is C₁₋₁₀alkyl, Cy or Cy-C₁₋₁₀alkyl wherein alkyl is optionally
10 substituted with one to two substituents independently selected from R^a, and Cy is optionally substituted with one to four substituents independently selected from R^b. For the purpose of R¹ Cy is preferably aryl optionally substituted with one to four substituents selected from R^b. More preferred R¹ is phenyl with a substituent on the 3-position and
15 optionally a second substituent; the more preferred substituents are selected from C₁₋₁₀alkoxy, halogen, cyano, and trifluoromethyl.

In another subset of Formula Ia are compounds wherein R² is H or C₁₋₆alkyl. Preferred R² is H or C₁₋₃alkyl, more preferably H or methyl.

20 In another subset of Formula Ia are compounds wherein R³ is H or C₁₋₆alkyl. Preferred R³ is H or C₁₋₃alkyl, more preferably H or methyl.

In another subset of Formula Ia are compounds wherein R⁵ is H and R⁴ is C₁₋₁₀alkyl or Cy-C₁₋₁₀alkyl, wherein alkyl is optionally
25 substituted with one to four substituents selected from phenyl and R_x, and Cy is optionally substituted with one to four substituents independently selected from R_y; or R⁴, R⁵ and the carbon to which they are attached together form a 3-7 membered mono- or bicyclic carbon only ring. For the purpose of R⁴, Cy is preferably aryl, more preferably
30 phenyl. In a preferred embodiment, R⁴ is phenyl-C₁₋₃alkyl, wherein phenyl is optionally substituted with one or two groups selected from R_y.

In one embodiment of compounds of formula Ia are compounds of formula Ib:

Formula I. Such diseases, disorders, conditions or symptoms are for example (1) multiple sclerosis, (2) asthma, (3) allergic rhinitis, (4) allergic conjunctivitis, (5) inflammatory lung diseases, (6) rheumatoid arthritis, (7) septic arthritis, (8) type I diabetes, (9) organ transplantation rejection, (10) restenosis, (11) autologous bone marrow transplantation, (12) inflammatory sequelae of viral infections, (13) myocarditis, (14) inflammatory bowel disease including ulcerative colitis and Crohn's disease, (15) certain types of toxic and immune-based nephritis, (16) contact dermal hypersensitivity, (17) psoriasis, (18) tumor metastasis, (19) atherosclerosis.

Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of Formula I per kg of body weight per day and for cytoprotective use from about 0.1 mg to about 100 mg (preferably from about 1 mg to about 100 mg and more preferably from about 1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a compound of Formula I per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg and for cytoprotective use from 0.1 mg

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N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-
((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))-phenylalanine

Step A: N-(3-Fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-
5 trimethylstannylphenylalanine, tert-butyl ester.

A solution of N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-iodophenylalanine, tert-butyl ester (1.0 gm, 1.53 mmol), hexamethylditin (411 μ L, 2.14 mmol), triphenylphosphine (8 mg, 0.03 mmol), lithium chloride (71 mg, 1.68 mmol), and
10 tetrakis(triphenylphosphine)palladium(0) (88 mg, 0.077 mmol) in 1,4-dioxane (10 mL) was heated to 95°C under a dry nitrogen atmosphere for 1.5 hr. The solution was cooled and diluted with ethyl acetate (100 mL) and successively washed with 1N sodium hydroxide solution (2X) and saturated salt solution (1X). After drying over anhydrous
15 magnesium sulfate, the solution was filtered and the solvent removed by rotoevaporation. The residue was purified by silica gel column chromatography eluted with 10% acetone in hexanes to yield N-(3-fluorobenzenesulfonyl)-(L)-prolyl-(L)-4-(trimethylstannyl)phenylalanine, tert-butyl ester (577 mg, 54% yield).
20 MS: m/e 658 (M + 18; NH_4^+).

N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-trimethylstannylphenylalanine, tert-butyl ester was prepared from N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-iodophenylalanine, tert-butyl ester by an analogous procedure.
25

Step B: N-(3,5-Dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-(5-((1H,3H)-1,3-dimethylpyrimidine-2,4-dione))-phenylalanine, tert butyl ester

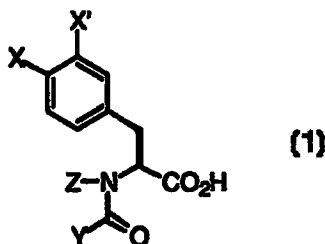
30 A solution of N-(3,5-dichlorobenzenesulfonyl)-(L)-2(S)-methyl-prolyl-(L)-4-trimethylstannylphenylalanine, tert-butyl ester (70 mg, 0.1 mmol), (1H,3H)-1,3-dimethyl-5-iodo-pyrimidine-2,4-dione (40 mg, 0.15 mmol) and tetrakis-triphenylphosphine palladium (4


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: N-ALKANOYLPHENYLALANINE DERIVATIVES



(57) Abstract

Compounds of formula (1) as well as their salts and esters are disclosed wherein X, X', Z and Y are as described in the specification and which have activity as inhibitors of binding between VCAM-1 and cells expressing VLA-4. Such compounds are useful for treating diseases whose symptoms and/or damage are related to the binding of VCAM-1 to cells expressing VLA-4.

N-ALKANOYLPHENYLALANINE DERIVATIVES

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Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin (Ig) supergene family, is expressed on activated, but not resting, endothelium. The integrin VLA-4($\alpha_4\beta_1$), which is expressed on many
10 cell types including circulating lymphocytes, eosinophils, basophils, and monocytes, but not neutrophils, is the principal receptor for VCAM-1. Antibodies to VCAM-1 or VLA-4 can block the adhesion of these mononuclear leukocytes, as well as melanoma cells, to activated endothelium *in vitro*. Antibodies to either protein have been effective at inhibiting leukocyte
15 infiltration and preventing tissue damage in several animal models of inflammation. Anti-VLA-4 monoclonal antibodies have been shown to block T-cell emigration in adjuvant-induced arthritis, prevent eosinophil accumulation and bronchoconstriction in models of asthma, and reduce paralysis and inhibit monocyte and lymphocyte infiltration in experimental autoimmune
20 encephalitis (EAE). Anti-VCAM-1 monoclonal antibodies have been shown to prolong the survival time of cardiac allografts. Recent studies have demonstrated that anti-VLA-4 mAbs can prevent insulinitis and diabetes in non-obese diabetic mice, and significantly attenuate inflammation in the cotton-top tamarin model of colitis.

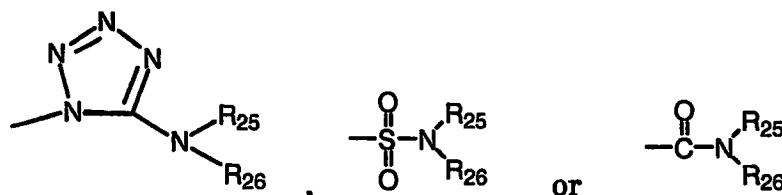
25 Thus, compounds which inhibit the interaction between α_4 -containing integrins and VCAM-1 will be useful as therapeutic agents for the treatment of chronic inflammatory diseases such as RA, multiple sclerosis (MS), asthma, and inflammatory bowel disease (IBD).

The compounds of the invention can exist as stereoisomers and diastereomers, all of which are encompassed within the scope of the present invention.

In a compound of formula 1 X' is preferably hydrogen which means that then X is a group X-6, X-7 or X-10. When Z is lower alkyl, methyl is preferred.
5 Z is preferably hydrogen.

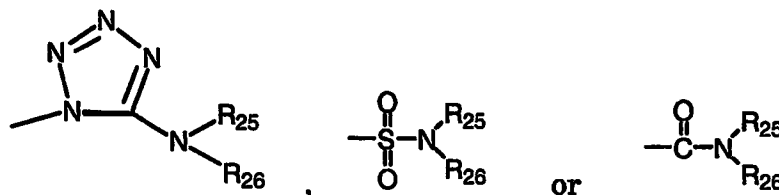
In a compound of formula 1, wherein the group is Y-1, which is preferred over Y-2, R₂₂ and R₂₃ preferably are independently hydrogen, lower alkyl, nitro, lower alkylthio, lower alkoxy, lower alkylamino, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or perfluoroalkyl wherein at
10 least one of R₂₂ and R₂₃ is not hydrogen, and

R₂₄ is hydrogen, hydroxy, lower alkyl, lower alkoxy, lower alkylsulfonyl, amino, nitro, halogen or a group of the formula:



wherein R₂₅ is aryl lower alkyl and R₂₆ is hydrogen or lower alkyl,
15 or R₂₂ and R₂₄ taken together are a fused benzene ring.

Preferably R₂₂ is hydrogen (when R₂₃ is other than hydrogen), lower alkyl or halogen. R₂₄ is preferably hydrogen, hydroxy, lower alkylsulfonyl, lower alkyl, halogen, nitro or lower alkoxy or a group of the formula:



20 wherein R₂₅ is unsubstituted or hydroxy-substituted phenyl lower alkyl, and R₂₆ is hydrogen,

or R₂₂ and R₂₄ taken together are a fused phenyl ring.

More preferred R₂₄ is hydrogen, hydroxy, amino, methyl, chloro, bromo, nitro, -OCH₃, -SO₂CH₃ and R₂₆ is H and R₂₅ is

as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and particularly in the binding of eosinophils to pulmonary endothelium which is the cause of the pulmonary inflammation which occurs in asthma. Thus, the compounds of the present invention would be useful for the treatment of
5 asthma.

In another aspect, on the basis of their capability of inhibiting binding of VCAM-1 and fibronectin to VLA-4 on circulating lymphocytes, eosinophils, basophils, and monocytes, the compounds of the invention can be used as medicament for the treatment of disorders which are known to be associated
10 with such binding. Examples of such disorders are rheumatoid arthritis, multiple sclerosis, asthma, and inflammatory bowel disease. The compounds of the invention are preferably used in the treatment of diseases which involve pulmonary inflammation, such as asthma. The pulmonary inflammation which occurs in asthma is related to eosinophil infiltration into the lungs
15 wherein the eosinophils bind to endothelium which has been activated by some asthma-triggering event or substance.

Furthermore, compounds of the invention also inhibit the binding of VCAM-1 and MadCAM to the cellular receptor alpha4-beta7, also known as LPAM, which is expressed on lymphocytes, eosinophiles and T-cells. While the
20 precise role of alpha4-beta7 interaction with various ligands in inflammatory conditions such as asthma is not completely understood, compounds of the invention which inhibit both alpha4-beta1 and alpha4-beta7 receptor binding are particularly effective in animal models of asthma. Furthermore work with monoclonal antibodies to alpha4-beta7 indicate that compounds which inhibit
25 alpha4-beta7 binding to MadCAM or VCAM are useful for the treatment of inflammatory bowel disease. They would also be useful in the treatment of other diseases in which such binding is implicated as a cause of disease damage or symptoms.

The compounds of the invention can be administered orally, rectally, or
30 parentally, e.g., intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually, or as ophthalmological preparations, or as an aerosol for the treatment of pulmonary inflammation. Capsules, tablets, suspensions or solutions for oral administration, suppositories, injection solutions, eye drops, salves or spray solutions are examples of administration
35 forms.

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

2020
Bogotá, D.C.,

Doctora
ALICIA LLOREDA RICAURTE
(Apoderado)

ASUNTO	Radicación	00092691	
	Trámite	002	
	Evento	001	
	Actuación	430	
	Oficio		2358
	Folios	032	

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:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 6 a 160) y las reivindicaciones 1 a 42 (Folios: 161 a 176).

La presente solicitud reivindica prioridad americana N° US60.169089 de 06 de diciembre de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de invención:

La presente solicitud se titula: "4-pirimidinil-N-acil-L-fenilalaninas".

El objeto de la presente solicitud se refiere a compuestos de 4-pirimidinil-N-acil-L-fenilalaninas que son inhibidores de la unión entre la molécula VCAM-1 y las células de expresión del antígeno VLA-4 y, por consiguiente, son útiles para el tratamiento de enfermedades cuyos síntomas y/o lesiones pueden atribuirse a la unión de la molécula VCAM-1 con las células de expresión del VLA-4.

Según la descripción, la molécula-1 de adhesión a células vasculares (VCAM-1), miembro de la familia de supergenes de la inmunoglobulina (Ig), se expresa en endotelio activado pero no en reposo. La integrina VLA-4, es un antígeno de aparición muy tardía que se expresa en muchos tipos de células, incluyendo los linfocitos circulantes, eosinófilos, basófilos y monocitos, pero no en neutrófilos y es el principal receptor de la VCAM-1. Los anticuerpos de ambas proteínas han sido eficaces en inhibir la infiltración de leucocitos y en evitar el daño de los tejidos de varios modelos de inflamación animal. Se ha demostrado que los anticuerpos monoclonales anti-VLA-4 bloquean la emigración de células T en caso de artritis inducida por adyuvantes, impiden la acumulación de eosinófilos y la broncoconstricción en modelos de asma, reducen la parálisis e inhiben la infiltración de monocitos y linfocitos en encefalitis autoinmune experimental (EAE). Se ha

demostrado que los anticuerpos monoclonales anti-VCAM-1 prolongan el tiempo de supervivencia de los trasplantes cardíacos homoplásticos. Los estudios recientes han demostrado que los anticuerpos monoclonales anti-VLA-4 pueden prevenir la insuficiencia renal y la diabetes de ratones diabéticos no obesos y pueden atenuar de modo significativo la inflamación en caso de modelo de colitis de monos tamarinos del algodón. Por consiguiente, los compuestos que inhiben la interacción entre integrinas que contienen $\alpha 4$ y la VCAM-1 pueden ser muy útiles como agentes terapéuticos para el tratamiento de enfermedades inflamatorias crónicas, tales como la artritis reumatoide, la esclerosis múltiple, el asma y las enfermedades intestinales inflamatorias.

Lo que se reivindica como novedoso es lo siguiente: compuestos 4-pirimidinil-N-acil-fenilalaninas de fórmula I (ver folio: 161) o sus sales farmacéuticamente aceptables.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/513, 31/198.

Claridad de la solicitud:

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción."

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

De acuerdo con lo anterior, hay grupos del compuesto de fórmula I que no están claramente definidos y, tal como están escritos, conllevan a ambigüedad, por ejemplo: "alquilo de bajo peso molecular", "cicloalquilo", "alcoxi de bajo peso molecular", "halógeno", "anillo heteroaromático", entre otros.

Asimismo, la reivindicación 37 (folios: 174 y 175) que se refieren a un compuesto de la fórmula II y que tiene los sustituyentes adicionales P1 y P2 que corresponden a un grupo protector, no es claro a qué se refiere con dicho grupo, es decir, no se dice qué es el grupo protector.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de Patente o, en su caso, de la prioridad reconocida."

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 06/12/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	WO 98/53817	Biarylalkanoic acids as cell adhesion inhibitors	3 de diciembre de 1998
2	WO 98/53814	Heterocyclic amide compounds as cell adhesion inhibitors	3 de diciembre de 1998
3	WO 99/10312	N-alkanoylphenylalanine derivatives	4 de marzo de 1999

Evaluación de los requisitos de Patentabilidad:

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

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de Nivel Inventivo:

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

La Solicitud de Patente Colombiana No. 00092691, se refiere a:

Compuestos 4-pirimidinil-N-acil-L-fenilalaninas de fórmula I (ver folio: 161) o sus sales farmacéuticamente aceptables.

La anterioridad: WO 98/53817 (folios:), se relaciona con: derivados de fenilalaninas que son antagonistas de VLA-4, y son utilizados para el tratamiento del asma, alergias, inflamación, esclerosis múltiple y otras enfermedades inflamatorias.

La anterioridad: WO98/53814 (folios:), trata sobre: compuestos de fenilalanina que también son antagonistas VLA-4 y se emplean para el tratamiento del asma, alergias, inflamación, esclerosis múltiple y otros desórdenes inflamatorios.

El documento: WO 99/10312 (folios:) menciona compuestos derivados de fenilalanina que son inhibidores de VCAM-1 y VLA-4; tales compuestos son empleados para el tratamiento de enfermedades inflamatorias crónicas tales como RA, esclerosis múltiple, asma, entre otras.

Los documentos WO 98/53817 y WO 99/10312 tienen estructura química muy semejante cuya diferencia fundamental se encuentra en los significados para los grupos que corresponden a R₁ de la presente solicitud. Además, tales documentos resuelven el mismo problema técnico referido en la presente solicitud.

El documento WO 99/10312 revela compuestos de fenilalanina cuyo grupo que corresponde a R₁ de la presente solicitud es el mismo. La diferencia estructural con respecto a la actual solicitud está en el grupo que corresponde a la pirimidina de la presente solicitud, ya que en dicha anterioridad hay otro grupo en la posición en que se encuentra dicha pirimidina. Este documento muestra el mismo grupo farmacofórico (fenilalanina) de los compuestos de la actual solicitud de patente por lo que tienen las mismas actividades farmacológicas.

Los documentos D1 y D3 y/o D2 y D3 le sugieren a una persona medianamente versada en la materia los compuestos de la presente solicitud. De igual modo, la respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de las anterioridades en mención.

Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

Evaluación de la Aplicación Industrial:

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".

El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 98/53817	1 a 42	Nivel Inventivo
2	WO 98/53814	1 a 42	Nivel Inventivo
3	WO 99/10312	1 a 42	Nivel Inventivo