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1

☒ Patente de Invención ☐ Patente Modelo de Utilidad.
☒ Capítulo I ☐ Capítulo II

2

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6

**Título (54) COMPUESTOS DE PYRIMIDINIL AMIDA QUE INHIBEN LA ADHESIÓN DE
LEUCOCITO MEDIADA POR VLA-4**

7

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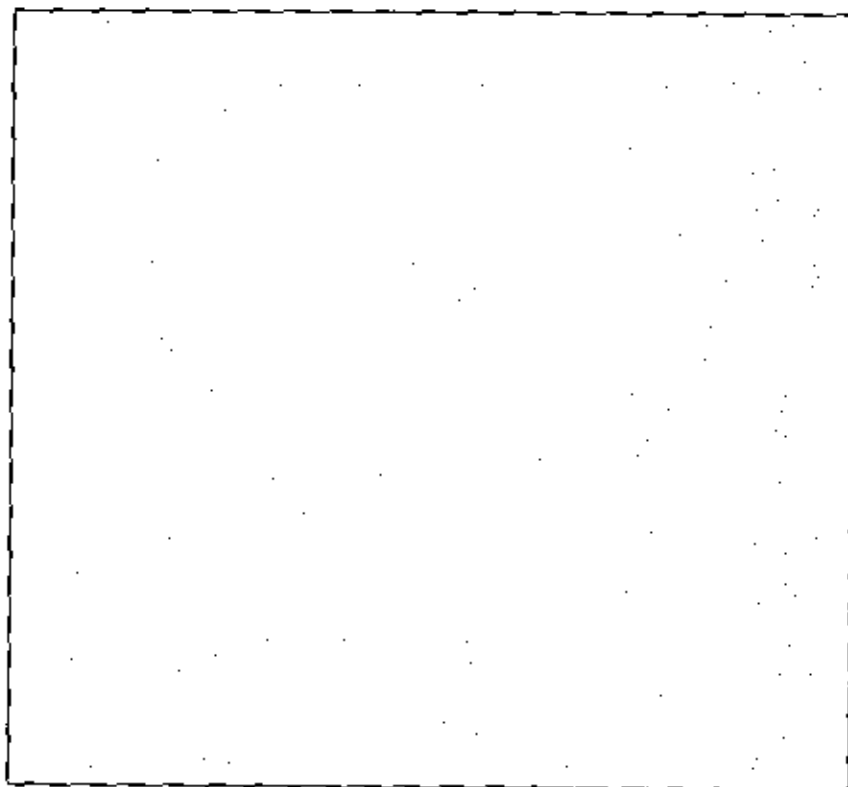
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- ☒ Comprobante de pago de la tasa de presentación de la solicitud
 - ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
 - ☐ Poderes si fuese el caso
 - ☐ Documento de cesión del inventor al solicitante o a su causante
 - ☐ Declaraciones
 - ☒ Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
 - ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
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 - ☐ Arte final 12x12.
 - ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
 - ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
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12 FIGURA CARACTERISTICA



13 Solicito la concesión de la patente,

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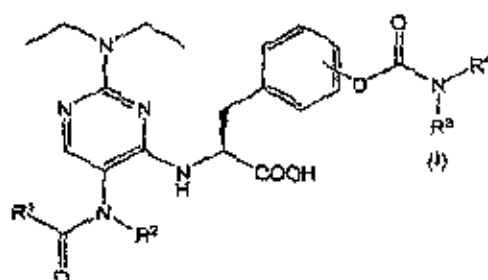
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(54) Title: PYRIMIDINYL AMIDE COMPOUNDS WHICH INHIBIT LEUKOCYTE ADHESION MEDIATED BY VLA-4



(57) Abstract: Disclosed are compounds which bind VLA-4. Certain of these compounds also inhibit leukocyte adhesion and, in particular, leukocyte adhesion mediated by VLA-4. Such compounds are useful in the treatment of inflammatory diseases in a human or animal subject such as asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tissue transplantation, tumor metastasis and myocardial ischemia. The compounds can also be administered for the treatment of inflammatory brain diseases such as multiple sclerosis (Formula I).

**PYRIMIDINYL AMIDE COMPOUNDS WHICH INHIBIT LEUKOCYTE
ADHESION MEDIATED BY VLA-4**

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 U.S.C. 119(e) to co-pending
5 provisional application U.S. Serial No. 60/722,358 filed on September 29, 2005, which
is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to compounds which inhibit leukocyte adhesion and, in
10 particular, leukocyte adhesion mediated by $\alpha 4$ integrins, where the $\alpha 4$ integrin is
preferably VLA-4. This invention also relates to pharmaceutical compositions
comprising such compounds as well as methods for treating, e.g., inflammation, using
either the compounds or the pharmaceutical compositions of this invention.

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- | | | |
|----|----|--|
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No. 330,506, published August 30, 1989 |
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| | 3 | Springer, Nature, 346:425 434 (1990) |
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- 14 Baron, et al., *J. Clin. Invest.*, 93:1700 (1994)
- 5 15 Hamann, et al., *J. Immunology*, 152:3238 (1994)
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- 26 Bao, et al., *Diff.*, 52:239 (1993)
- 27 Lauri, et al., *British J. Cancer*, 68:862 (1993)
- 28 Kawaguchi, et al., *Japanese J. Cancer Res.*, 83:1304 (1992)
- 20 29 Konradi, et al., PCT/US00/01686, filed, January 21, 2000

All of the above publications are herein incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

- 25 VLA-4 (also referred to as $\alpha 4\beta 1$ integrin and CD49d/CD29), first identified by Hemler and Takada,¹ is a member of the $\beta 1$ integrin family of cell surface receptors, each of which comprises two subunits, an α chain and a β chain. VLA-4 contains an $\alpha 4$ chain and a $\beta 1$ chain. There are at least nine $\beta 1$ integrins, all sharing the same $\beta 1$ chain and each having a distinct α chain. These nine receptors all bind a different
- 30 complement of the various cell matrix molecules, such as fibronectin, laminin, and collagen. VLA-4, for example, binds to fibronectin. VLA-4 also binds non-matrix

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molecules that are expressed by endothelial and other cells. These non-matrix molecules include VCAM-1, which is expressed on cytokine-activated human umbilical vein endothelial cells in culture. Distinct epitopes of VLA-4 are responsible for the fibronectin and VCAM-1 binding activities and each activity has been shown to be inhibited independently.²

Intercellular adhesion mediated by VLA-4 and other cell surface receptors is associated with a number of inflammatory responses. At the site of an injury or other inflammatory stimulus, activated vascular endothelial cells express molecules that are adhesive for leukocytes. The mechanics of leukocyte adhesion to endothelial cells involves, in part, the recognition and binding of cell surface receptors on leukocytes to the corresponding cell surface molecules on endothelial cells. Once bound, the leukocytes migrate across the blood vessel wall to enter the injured site and release chemical mediators to combat infection. For reviews of adhesion receptors of the immune system, see, for example, Springer³ and Osborn.⁴

Inflammatory brain disorders, such as experimental autoimmune encephalomyelitis (EAE), multiple sclerosis (MS) and meningitis, are examples of central nervous system disorders in which the endothelium/leukocyte adhesion mechanism results in destruction to otherwise healthy brain tissue. Large numbers of leukocytes migrate across the blood brain barrier (BBB) in subjects with these inflammatory diseases. The leukocytes release toxic mediators that cause extensive tissue damage resulting in impaired nerve conduction and paralysis.

In other organ systems, tissue damage also occurs via an adhesion mechanism resulting in migration or activation of leukocytes. For example, it has been shown that the initial insult following myocardial ischemia to heart tissue can be further complicated by leukocyte entry to the injured tissue causing still further insult (Vedder, et al.).⁵ Other inflammatory or medical conditions mediated by an adhesion mechanism include, by way of example, asthma,⁶⁻⁸ Alzheimer's disease, atherosclerosis,⁹⁻¹⁰ AIDS dementia,¹¹ diabetes¹²⁻¹⁴ (including acute juvenile onset diabetes), inflammatory bowel disease¹⁵ (including ulcerative colitis and Crohn's disease), multiple sclerosis,¹⁶⁻¹⁷ rheumatoid arthritis,¹⁸⁻²¹ tissue transplantation,²² tumor metastasis,²³⁻²⁸ meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

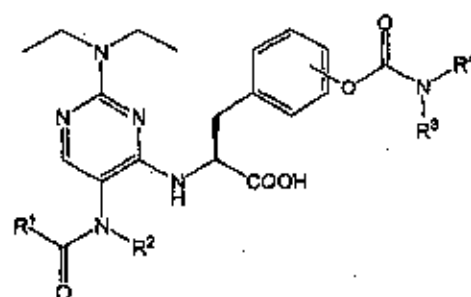
Substituted aminopyrimidines, as a class, have been disclosed as inhibiting binding of VLA-4 to VCAM-1 and, accordingly, exhibit anti-inflammatory properties.²⁹ While these compounds possess antagonist properties to such binding, enhanced bioavailability of these compounds would augment their efficacy.

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SUMMARY OF THE INVENTION

This invention provides compounds, pharmaceutically acceptable salts thereof, compositions thereof, syntheses thereof, and methods for treating VLA-4 mediated diseases.

In one embodiment, the present invention provides compounds of formula I:



10

I

wherein:

R¹ is selected from the group consisting of C₁ to C₄ alkyl, C₁ to C₄ haloalkyl, heteroaryl and -N(R⁵)(R⁶) where R⁵ and R⁶ are independently selected from the group consisting of hydrogen, C₁ to C₄ alkyl or R⁵ and R⁶ together with the nitrogen pendent thereto join to form a heterocyclic ring;

15

R² is selected from the group consisting of C₁ to C₄ alkyl, C₂ to C₄ alkenyl, and C₂ to C₄ alkynyl; and

20

R³ and R⁴ are independently C₁ to C₃ alkyl or R³, R⁴ together with the nitrogen atom pendent thereto join to form a heterocyclic ring; or a pharmaceutically acceptable salt, ester, or prodrug thereof.

carboxyl groups or groups similar thereto.

Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group.

Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

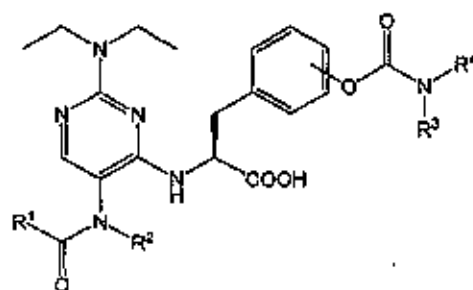
Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid,

and the like.

Integrins are a large family of homologous transmembrane linker proteins that are the principal receptors on animal cells for binding most extracellular matrix proteins, such as collagen, fibronectin, and laminin. The integrins are heterodimers comprised of an α chain and a β chain. To date, twenty different integrin heterodimers, made from 9 different α subunits and 14 different β subunits, have been identified. The term " $\alpha 4$ integrins" refers to the class of heterodimer, enzyme-linked cell-surface receptors that contain the $\alpha 4$ subunit paired with any of the β subunits. VLA-4 is an example of an $\alpha 4$ integrin, and is a heterodimer of the $\alpha 4$ and $\beta 1$ subunits, and is also referred to as $\alpha 4 \beta 1$ integrin.

This invention provides compounds, pharmaceutically acceptable salts thereof, compositions thereof, syntheses thereof, and methods for treating VLA-4 mediated diseases.

In one embodiment, the present invention provides compounds of formula I:



I

wherein:

R^1 is selected from the group consisting of C_1 to C_4 alkyl, C_1 to C_4 haloalkyl, heteroaryl and $-N(R^5)(R^6)$ where R^5 and R^6 are independently selected from the group consisting of hydrogen, C_1 to C_4 alkyl or R^5 and R^6 together with the nitrogen pendent thereto join to form a heterocyclic ring;

R^2 is selected from the group consisting of C_1 to C_4 alkyl, C_2 to C_4 alkenyl, and C_2 to C_4 alkynyl; and

R^3 and R^4 are independently C_1 to C_3 alkyl or R^3 , R^4 together with the nitrogen atom pendent thereto join to form a heterocyclic ring;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In some embodiments, the $-OC(O)NR^3R^4$ group is in the para position of the phenyl ring.

In some embodiments, R^3 and R^4 are joined to form a heterocyclic ring. In other embodiments, R^3 and R^4 are joined to form a pyrrolidinyl ring.

5 In some embodiments, R^2 is C_1 to C_4 alkyl. In other embodiments, R^2 is ethyl.

In still other embodiments, R^3 and R^4 are joined to form a heterocyclic ring and R^2 is C_1 to C_4 alkyl. In yet other embodiments, R^3 and R^4 are joined to form a pyrrolidinyl ring and R^2 is ethyl.

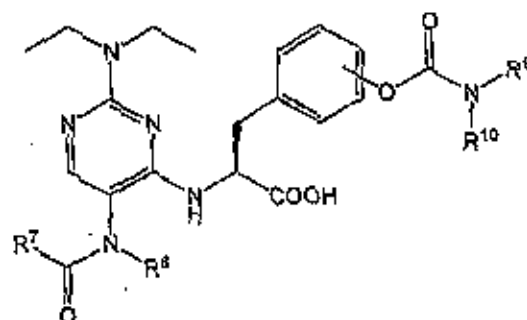
10 Examples of compounds of this invention include those having the R^1 , R^2 , R^3 , and R^4 groups recited in Table 1.

Table 1

R^1	R^2	R^3	R^4
trifluoromethyl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
iso-propyl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
t-butyl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
furan-2-yl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
piperidin-1-yl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
N-ethyl-N-iso-propylamino	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
thien-3-yl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
thien-2-yl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
furan-3-yl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	
3-thiapyrrolidin-1-yl	ethyl	R^3 and R^4 together with the pendent nitrogen form a pyrrolidine ring	

In another embodiment, the present invention provides a compound of formula

II:



II

5 wherein:

R^7 is C_1 to C_4 alkyl, C_1 to C_4 haloalkyl, or heteroaryl;

R^8 is C_1 to C_4 alkyl;

R^9 and R^{10} are independently C_1 to C_3 alkyl or R^9 , R^{10} together with the nitrogen atom pendent thereto join to form a heterocyclic ring;

10 or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In some embodiments, the $-OC(=O)NR^9R^{10}$ group is in the para position of the phenyl ring.

In some embodiments, R^9 and R^{10} are joined to form a heterocyclic ring. In other embodiments, R^9 and R^{10} are joined to form a pyrrolidiny ring.

15 In some embodiments, R^8 is C_1 to C_4 alkyl. In other embodiments, R^8 is ethyl.

In some embodiments, R^7 is C_1 to C_4 alkyl. In other embodiments, R^7 is selected from the group consisting of isopropyl and *t*-butyl.

In some embodiments, R^7 is C_1 to C_4 haloalkyl. In other embodiments R^7 is trifluoromethyl.

20 In some embodiments, R^7 is heteroaryl. In other embodiments, R^7 is selected from the group consisting of furan-2-yl, furan-3-yl, thien-2-yl, and thien-3-yl.

In some embodiments, R^9 and R^{10} are joined to form a heterocyclic ring, R^8 is C_1 to C_4 alkyl, and R^7 is heteroaryl. In other embodiments, R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring, R^8 is ethyl, and R^7 is heteroaryl.

In some embodiments, R^9 and R^{10} are joined to form a heterocyclic ring, R^8 is C_1 to C_4 alkyl, and R^7 is alkyl. In other embodiments, R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring, R^8 is ethyl, and R^7 is alkyl.

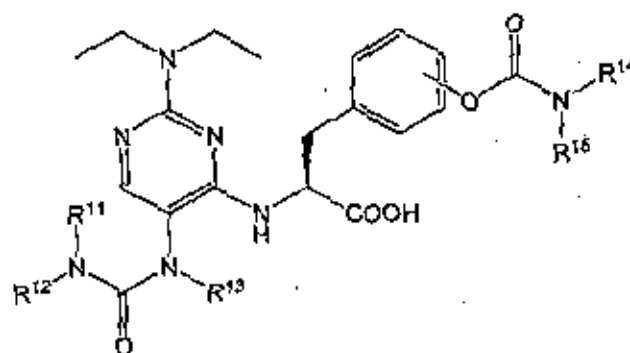
The present invention further provides the compounds of Formula II having the
5 R^7 , R^8 , R^9 , and R^{10} groups recited in Table 2.

Table 2

R^7	R^8	R^9	R^{10}
trifluoromethyl	ethyl	R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring	
iso-propyl	ethyl	R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring	
n-butyl	ethyl	R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring	
furan-2-yl	ethyl	R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring	
thien-3-yl	ethyl	R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring	
thien-2-yl	ethyl	R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring	
furan-3-yl	ethyl	R^9 and R^{10} together with the pendent nitrogen form a pyrrolidine ring	

In another embodiment, the present invention provides compounds of formula

III:



20

wherein:

R^{11} and R^{12} are independently C_1 to C_4 alkyl or R^{11} and R^{12} , together with the nitrogen atom pendent thereto, are joined to form a heterocyclic ring;

R^{13} is C_1 to C_4 alkyl; and

5 R^{14} and R^{15} are independently C_1 to C_3 alkyl or R^{14} and R^{15} together with the nitrogen atom pendent thereto join to form a heterocyclic ring;

or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In some embodiments, the $-OC(O)NR^{14}R^{15}$ group is in the para position of the phenyl ring.

10 In some embodiments, R^{14} and R^{15} are joined to form a heterocyclic ring. In other embodiments, R^{14} and R^{15} are joined to form a pyrrolidiny ring.

In some embodiments, R^{13} is C_1 to C_4 alkyl. In other embodiments, R^{13} is ethyl.

In some embodiments, R^{11} and R^{12} are independently C_1 to C_4 alkyl. In other embodiments R^{11} is ethyl and R^{12} is isopropyl.

15 In some embodiments, R^{11} and R^{12} , together with the nitrogen atom pendent thereto, are joined to form a heterocyclic ring. In other embodiments, the heterocyclic ring is selected from the group consisting of piperidin-1-yl and 3-thiapyrrolidin-1-yl.

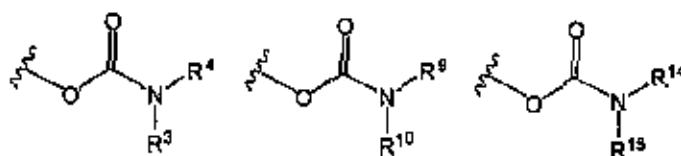
In yet other embodiments, R^{14} and R^{15} are joined to form a heterocyclic ring, R^{13} is C_1 to C_4 alkyl, and R^{11} and R^{12} , together with the nitrogen atom pendent thereto, are joined to form a heterocyclic ring.

20 The present invention further provides compounds of formula III having the R^{11} , R^{12} , R^{13} , R^{14} , and R^{15} groups recited in Table 3.

Table 3

R^{11}	R^{12}	R^{13}	R^{14}	R^{15}
R^{11} and R^{12} together with the pendent nitrogen form a piperidine ring		ethyl	R^{14} and R^{15} together with the pendent nitrogen form a pyrrolidine ring	
iso-propyl	ethyl	ethyl	R^{14} and R^{15} together with the pendent nitrogen form a pyrrolidine ring	
R^{11} and R^{12} together with the pendent nitrogen form a 3-thiapyrrolidine ring		ethyl	R^{14} and R^{15} together with the pendent nitrogen form a pyrrolidine ring	

In some embodiments, the present invention provides compounds of formula I, II, and III having the carbamyl substituents:



in their respective formulae attached to the phenyl ring at the *para* position. In still other embodiments, the compounds in Tables 1, 2, and 3 have the carbamyl substituents attached at the *para* position.

In some embodiments, the present invention also provides compounds of formula I, II, and III, including those in Tables 1, 2, and 3, having the carbamyl substituents attached at the *ortho* or *meta* positions.

The present invention also provides the compounds in Table 4.

Table 4

	Structure	Name
1		N-[2-diethylamino-5-(N-ethyl-N-(trifluoroacetyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
2		N-[2-diethylamino-5-(N-ethyl-N-(isopropylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
3		N-[2-diethylamino-5-(N-ethyl-N-(tert-butylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine

	Structure	Name
4		N-[2-diethylamino-5-(N-ethyl-N-(furan-2-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
5		N-[2-diethylamino-5-(N-ethyl-N-(piperidin-1-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
6		N-[2-diethylamino-5-(N-ethyl-N-(N-ethyl-N-isopropylaminocarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
7		N-[2-diethylamino-5-(N-ethyl-N-(thien-3-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
8		N-[2-diethylamino-5-(N-ethyl-N-(thien-2-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
9		N-[2-diethylamino-5-(N-ethyl-N-(furan-3-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine

	Structure	Name
10		N-[2-diethylamino-5-(N-ethyl-N-(3-thiapyrrolidin-1-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine
11		N-[2-diethylamino-5-(N-ethyl-N-(thien-2-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine <i>t</i> -butyl ester
12		N-[2-diethylamino-5-(N-ethyl-N-(trifluoromethylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine <i>t</i> -butyl ester
13		N-[2-diethylamino-5-(N-ethyl-N-(<i>t</i> -butylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine <i>t</i> -butyl ester
14		N-[2-diethylamino-5-(N-ethyl-N-(furan-3-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine <i>t</i> -butyl ester

In another aspect, this invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds defined herein.

In one of its method aspects, this invention is directed to a method for treating a disease mediated at least in part by $\alpha 4$ integrin, preferably VLA-4, in a patient, which method comprises administering a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of this invention. In another aspect, this invention is directed

25
to a use of a pharmaceutical composition comprising a compound of this invention for the manufacture of a medicament for treating an $\alpha 4$ integrin mediated disease.

The compounds and pharmaceutical compositions of this invention are useful for treating disease conditions mediated at least in part by $\alpha 4$ integrins, where the $\alpha 4$ integrin is preferably VLA-4 or leucocyte adhesion. Such disease conditions include, by way of example, asthma, Alzheimer's disease, atherosclerosis, AIDS dementia, diabetes (including acute juvenile onset diabetes), inflammatory bowel disease (including ulcerative colitis and Crohn's disease), multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, and
10 other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome.

Other disease conditions include, but are not limited to, inflammatory conditions such as erythema nodosum, allergic conjunctivitis, optic neuritis, uveitis,
15 allergic rhinitis, Ankylosing spondylitis, psoriatic arthritis, vasculitis, Reiter's syndrome, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis, dermatomyositis, Wegner's granulomatosis, aortitis, sarcoidosis, lymphocytopenia, temporal arteritis, pericarditis, myocarditis, congestive heart failure, polyarteritis nodosa, hypersensitivity syndromes, allergy, hypereosinophilic syndromes, Churg-
20 Strauss syndrome, chronic obstructive pulmonary disease, hypersensitivity pneumonitis, chronic active hepatitis, interstitial cystitis, autoimmune endocrine failure, primary biliary cirrhosis, autoimmune aplastic anemia, chronic persistent hepatitis and thyroiditis.

In a preferred embodiment, the disease condition mediated by $\alpha 4$ integrin is an
25 inflammatory disease.

Compounds of this invention include, by way of example, the following:

N-[2-diethylamino-5-(N-ethyl-N-(trifluoroacetyl)amino)pyrimidin-4-yl]-L-4'-
((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

30 N-[2-diethylamino-5-(N-ethyl-N-(*iso*-propylcarbonyl)amino)pyrimidin-4-yl]-
L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

N-[2-diethylamino-5-(N-ethyl-N-(*t*-butylcarbonyl)amino)pyrimidin-4-yl]-L-4'-
((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

N-[2-diethylamino-5-(N-ethyl-N-(furan-2-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

N-[2-diethylamino-5-(N-ethyl-N-(piperidin-1-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

5 N-[2-diethylamino-5-(N-ethyl-N-(N-ethyl-N-iso-propylaminocarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

N-[2-diethylamino-5-(N-ethyl-N-(thien-3-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

10 N-[2-diethylamino-5-(N-ethyl-N-(thien-2-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

N-[2-diethylamino-5-(N-ethyl-N-(furan-3-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

N-[2-diethylamino-5-(N-ethyl-N-(3-thiapyrrolidin-1-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)phenylalanine;

15 N-[2-diethylamino-5-(N-ethyl-N-(thien-2-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine *t*-butyl ester;

N-[2-diethylamino-5-(N-ethyl-N-(trifluoromethylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine *t*-butyl ester;

20 N-[2-diethylamino-5-(N-ethyl-N-(*t*-butylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine *t*-butyl ester; and

N-[2-diethylamino-5-(N-ethyl-N-furan-3-ylcarbonyl)amino)pyrimidin-4-yl]-L-4'-((pyrrolidin-1-yl)carbonyloxy)-phenylalanine *t*-butyl ester;

or the pharmaceutically acceptable salt, ester, or prodrug thereof.

Compound Preparation

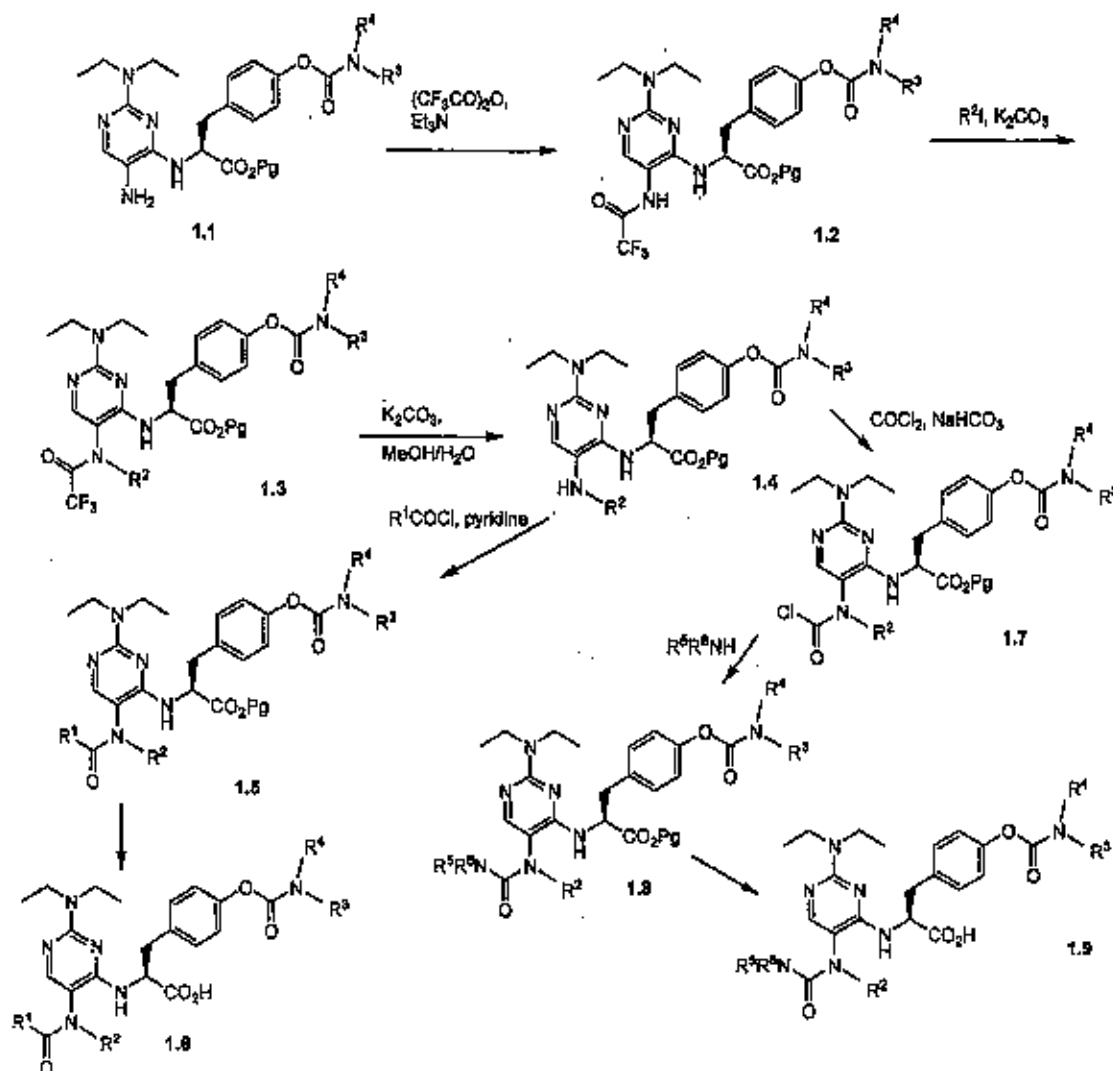
25 The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with
30 the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional
35 groups as well as suitable conditions for protecting and deprotecting particular

functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

Furthermore, the compounds of this invention will typically contain one or more
5 chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as
pure stereoisomers, *i.e.*, as individual enantiomers or diastereomers, or as stereoisomer-
enriched mixtures. All such stereoisomers (and enriched mixtures) are included within
the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched
10 mixtures) may be prepared using, for example, optically active starting materials or
stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such
compounds can be separated using, for example, chiral column chromatography, chiral
resolving agents and the like.

In one embodiment, the compounds of this invention can be prepared as described below in Scheme 1;



Scheme 1

where R¹, R², R³, R⁴, R⁵ and R⁶ are as defined above and Pg is a carboxyl protecting group such as benzyl, t-butyl, and the like.

In Scheme 1, the starting 5-aminopyrimidine intermediates, compound 1.1, are described in detail in WO 03/099809 and, for the sake of illustration only, are shown in this scheme as 4-substituted phenylalanine derivatives. It is understood, of course, that 2- and 3-substituted phenylalanine derivatives would follow a similar reaction pathway.

Specifically, in Scheme 1, 5-amino-2-diethylamino-4-substituted pyrimidine, compound 1.1 (prepared from by corresponding 5-nitro-pyrimidine by reduction with 5% Pd/C or 5% PtO₂ by weight) is converted to the corresponding trifluoroacetamide.